**THE U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**CENTERS FOR DISEASE CONTROL AND PREVENTION**

convenes the

**ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES**

**VOLUME I - DAY ONE**

The verbatim transcript of the ACIP Conference commencing at 8:36 a.m. on Wednesday, June 20th, 2001, at the Marriott Century Center Hotel, Atlanta, Georgia.

# C O N T E N T S



(continued)

# P A R T I C I P A N T S

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

8:36 a.m.

**DR. MODLIN:** Good morning. If we could call the meeting to order, please.

I would like to welcome everyone to the June 2001 meeting of the CDC Advisory Committee on Immunization Practices. To begin with, I'm going to turn the floor over to Dr. Dixie Snider, who is Executive Secretary of the Committee. Dixie?

**DR. SNIDER:** Thank you, John. Good morning, and welcome everyone to this June 2001 ACIP meeting. It is a very full agenda and I would remind everybody, it goes until five tomorrow afternoon. It seems that our workload just keeps getting larger and larger, but the Committee always measures up to the task, and I am sure that you will do the same for this meeting.

We've had some changes in liaison representatives to the Committee since the last meeting. I'm pleased to welcome Dr. Gary Overturf, University of New Mexico Medical Center, who will be the liaison for the American Academy of Pediatrics, and Mr. Kevin Reilly, who is

President of Wyeth Vaccines and Nutrition, representing the Pharmaceutical Research and Manufacturers of America. We're also delighted that Dr. Larry Pickering, who most of you know, who was formerly liaison representing the AAP, is now working for the CDC National Immunization Program. And not attending today are Dr. David Salisbury from the London Department of Health and David Wilson from the American Medical Association. Also not here today is Dr. Carole Heilman, the ex officio from the National Institutes of Health, but we want to welcome Dr. Sarah Landry, who will be sitting in for Dr. Heilman.

We have three members of the Committee whose terms expire at the end of this month, June 30th, and the Charter states that these members, though, will serve until they are replaced. And because there is a hiring freeze, there is a very real possibility that we may ask these members to attend the October meeting. However, given the uncertainties of the situation, I want to take this opportunity to thank each one of them and give them this -- their certificates and a letter of appreciation from Dr. Koplan. And the first person

here is Dr. Rich Clover -- Thank you, Rick -- and Dr. David Johnson, and Dr. Chuck Helms. And we recognize that those small tokens are completely inadequate to express our sincere appreciation for all your work, but it's what we have in government.

For those of you who are not familiar with the logistics of the Committee -- And I apologize to many of you who have to listen to these things at every meeting, but we always have new people who have attended who have not been here before, and it's important for them to understand as much as they can about what's going on. So the appointed members of the Committee are at the same table that John and I are sitting at here and, in addition, we have CDC staff, in this case, Dr. Orenstein and Dr. Wharton and Dr. Mastro and, hopefully, Dr. Mawle will be joining us. At the outer table, we have our liaison representatives from a variety of organizations, including a number of professional societies, and ex officio members from our sister federal agencies.

At the last meeting, we announced the ACIP home page, which is located at www.cdc.gov/nip/acip. And

although the agenda is mailed and sent electronically, the home page is the best way to keep up with the latest version of the agenda because as new information comes in, the agenda does change as we approach the meeting time.

Our next meeting will be October 17th and 18th, 2001, and the dates for the 2002 meetings are February 20 and 21, June 19 and 20, and October 16 and 17. The Committee members will find these dates on green paper in their book. The dates -- I know I read them fast, but the dates are available on the handout table at the back of the room. Because many of the Committee members have already made dinner plans this evening -- I believe there is also a work group meeting -- we have decided that we will not have an ACIP dinner for this particular meeting. If you would like some suggestions on where you might go for dinner, places that are close by, please see Gloria or Latarsha. There is a restaurant in the lobby of this hotel. Also, I think most of you know that down this hallway there are two sets of rest rooms, one closer and one out in the lobby.

On December 14th, 2000, Dr. Koplan signed an amendment to the ACIP Charter which added three additional members to the Committee. Now, these new members are not yet appointed. The package has been prepared, but we -- again, because of the hiring freezes, we have not been able to execute getting 15 members appointed. But because of the Charter has been signed as consisting of those additional members, it means that a quorum for ACIP is now eight, according to Charter, and therefore it's important that the 12 appointed members present today return and participate in the meeting fully to assure that a quorum is present. And as I mentioned, the meeting will end at 5:15 tomorrow, and I would request that members not leave the meeting early unless it's absolutely essential.

The ACIP Charter gives me, the Executive Secretary, or my designee the authority to temporarily designate the ex officio members as voting members, but this will not take place unless there are eight appointed members not qualified to vote due to a financial conflict of interest. The ex officio members will be formally requested to vote when that is necessary. Otherwise,

they do not vote.

ACIP has always held open discussions and has reserved meeting time for official public comment. However, as I mentioned, the agenda is quite full and the Committee has restricted time in which to conduct its business. Therefore, in some limited circumstances, we've scheduled formal comment periods during the deliberation of the agenda item. However, our Chair is very good, I think, at recognizing comments from the floor that are received during open discussions, depending upon the amount of time available, and the comments need to be restricted in order to keep us within the time allotted the Committee to complete its agenda.

With added interest from individuals who want to address the Committee on individual comments on specific agenda items, we request it be requested in advance, and those members of the public who wish to address the Committee today or tomorrow should really sign up with Gloria or Latarsha so that we can arrange time for your comments. And because it is important to hear all the comments, we've set a microphone down

at each end of the tables there for the audience to use. I would appreciate anyone wishing to comment to step up to the microphone and I would appreciate that you identify yourself. We are recording this meeting and, although we may know who you are, the person doing the recording and in the transcription would not be able to identify you, perhaps. In addition, of course, speaking into the microphone allows everyone to hear your question or comment.

I also want to remind Committee members, many times we forget in our concentration on the discussion item -- we forget to identify ourselves when speaking. So I remind myself and all of us, when we're speaking, that we identify ourselves.

I think those are all the housekeeping items I had to bring up right now. John, I'll turn it back to you.

**DR. MODLIN:** Okay. Thanks, Dixie. I would like to my personal welcome to Dr. Gary Overturf and Kevin Reilly, who are joining us as liaison members, and Sara Landry from NIH, who is sitting in as an ex officio member.

In the back of your books you'll find a number of

information pieces and updates which have been published in the MMWR since our last meeting in February. This is a sort of for your interest and information and I encourage you to take a look at the work product of the Committee since the last meeting. There are several groups that are meeting today and tomorrow. The Influenza Working Group will be meeting at lunch today in the Centennial D ballroom and this evening we'll have the initial meeting of the Rotavirus Working Group, which will be an educational session, and that will be in the Magnolia Room beginning right at the end of this meeting. Is that right, Myron? Then tomorrow, the Adult Working Group will be meeting at seven a.m. in the hotel restaurant, and there will be an area in the back of the restaurant that's been set aside for the working group.

The next ACIP meeting will be October 17th and 18th here at the Marriott Century Center, and we will be announcing the locations for the 2002 meetings in the meantime.

Let me reiterate what Dixie has already mentioned, which is to ask people and members of the audience to

speak directly into the microphone so that we can hear your comments. We again ask the members of the audience in making comments to please identify themselves before speaking.

At this time, I'm going to ask the members of the Committee to identify themselves and their affiliations and, at the same, disclose any potential financial conflicts of interest. All members, regardless of conflict, may participate in discussion of all issues provided that a full disclosure of potential conflict of interest has occurred. However, persons with a direct conflict may not vote on any issue related to conflict. Only the members need to disclose their financial conflicts. Ex officio and liaison members are not required to do so, but as a courtesy, we would ask that members of the audience, in making comments, if they do have conflicts of interest, that they also -- would be willing to disclose those conflicts, although they are not required to do so.

Members of the Committee with financial conflicts of interest must abstain from voting on Vaccines for

Children resolutions. Since a conflict may also appear to be present if such a member is allowed to introduce or second a vote or VFC resolution, ACIP's policy prohibits a member with financial conflicts of interest from introducing or seconding an ACIP vote or a VFC resolution.

So I'm going to begin and ask Dr. Levin to introduce himself and disclose any potential conflicts, and we'll go around clockwise.

Myron?

**DR. LEVIN:** I'm Myron Levin, University of Colorado School of Medicine. I have research support from Merck and Glaxo SmithKline and I own stock in Glaxo SmithKline.

**DR. RENNELS:** Margaret Rennels, Center for Vaccine Development, University of Maryland. I have or have recently conducted trials supported by Wyeth Lederle, Aventis Pasteur, Glaxo SmithKline, and Merck.

**DR. BROOKS:** Dennis Brooks from Johns Hopkins School of Medicine. I have no conflict of interest.

**DR. CLOVER:** Richard Clover, University of Louisville. I or my department have a potential

conflict of interest with Merck, Wyeth Lederle, Glaxo SmithKline, Bayer, and Astra Seneca [phonetic].

**DR. WORD:** I'm Bonnie Word. I'm a pediatrician from New Jersey. I have no conflicts of interest.

**DR. TOMPKINS:** I'm Lucy Tompkins from Stanford University, and I have no conflicts.

**DR. HELMS:** Charles Helms from the University of Iowa College of Medicine, and I have no conflicts.

**DR. OFFIT:** I'm Paul Offit from the Children's Hospital, Philadelphia, and the University of Pennsylvania School of Medicine. I have one perceived conflict of interest, and that is that I am the co-inventor on a patent for a bovine human resort rotavirus vaccine, a vaccine that's being developed by Merck and Company.

**DR. JOHNSON:** David Johnson. I'm with the State Health Department in Michigan and I have no conflicts of interest.

**DR. SMITH:** Natalie Smith with the State Health Department in California and no conflicts of interest.

**DR. DESEDA:** Jaime Deseda from San Jorge Children's Hospital in Puerto Rico. I have no conflicts of

interest.

**DR. MODLIN:** John Modlin from Dartmouth Medical School, and I have no conflicts of interest. I'm going to ask to the program people to introduce themselves at the end of the table, please.

**DR. MASTRO:** Yes. I'm Tim Mastro from the Division of HIV Prevention and the National Center for HIV/STD Prevention.

**DR. ORENSTEIN:** Walt Orenstein, National Immunization Program.

**DR. WHARTON:** Melinda Wharton, National Immunization Program.

**DR. MODLIN:** Thanks, Melinda. Why don't we start with our liaison members, perhaps beginning with Dr. Marchessault, and we'll go around accordingly.

**DR. MARCHESSAULT:** Victor Marchessault, representative from the Committee -- the Committee on Immunization, and I have no conflict. I'm from Ottawa.

**DR. NAVA:** Margarita Nava from Mexico, and I represent National Immunization Council and Child Health Program.

**DR. ABRAMSON:** Jon Abramson from Wake Forest University. I'm also Chair of the Committee on Infectious Diseases for the American Academy of Pediatrics and I have no conflict of interest.

**DR. OVERTURF:** I'm Gary Overturf. I'm representing the Red Book of the American Academy of Pediatrics and I have no conflicts.

**DR. MAHONEY:** Martin Mahoney, representing the American Academy of Family Physicians. No conflicts.

**DR. JACKSON:** Rudolph Jackson from the Morehouse School of Medicine here in Atlanta, representing the National Medical Association. Thank you.

**DR. FRANCE:** Eric France from Kaiser Permanente Colorado, representing the American Association of Health Plans. I oversee vaccine trials funded by Wyeth and by Merck.

**MR. REILLY:** Kevin Reilly representing PHARMA, the manufacturers' association, and from Wyeth Lederle Vaccines.

**DR. GALL:** Stan Gall, Louisville, Kentucky, representing the American College of Obstetricians and Gynecologists, and we do vaccine trials for Merck and

Glaxo SmithKline.

**DR. KATZ:** Samuel Katz from Duke University, representing the Infectious Diseases Society of America, no conflicts.

**DR. SIEGEL:** Jane Siegel from University of Texas Southwestern Medical Center in Dallas. I'm representing the Health Care Infection Control Practices Advisory Committee, and I have no conflicts.

**DR. SCHAFFNER:** Bill Schaffner from Vanderbilt University School of Medicine in Nashville, Tennessee. I'm here on behalf of the American Hospital Association. I have no conflicts.

**DR. NEUZIL:** Kathy Neuzil from the University of Washington. I'm representing the American College of Physicians, and I've received research funding from Merck and Aventis Pasteur.

**DR. GROOM:** Amy Groom here for Dr. Jim Cheek representing the Indian Health Service. No conflicts.

**DR. DINIEGA:** Ben Diniega, DOD Health Affairs, and I own stocks in Bristol Meyers.

**DR. NICHOL:** Kristin Nichol from the University of

Minnesota and the Minneapolis VA Medical Center. I'm here representing the Department of Veterans Affairs. I have no current conflicts of interest.

**DR. GRAYDON:** Randy Graydon from the new Centers for Medicare and Medicaid Services, and I have no conflicts.

**DR. MYERS:** Martin Myers from the National Vaccine Program Office. I have no conflicts.

**DR. LANDRY:** Sara Landry representing Carole Heilman from NIH, and I have no conflicts.

**DR. MIDTHUN:** Karen Midthun, Food and Drug Administration, no conflicts.

**DR. EVANS:** Geoffrey Evans from the National Vaccine Injury Compensation Program, HRSA. I have no conflicts.

**DR. MODLIN:** Thanks, Geoff.

The first item on the agenda today is an update on tetanus and diphtheria toxoid shortage. To remind the Committee, we first briefly reviewed this topic at our October meeting last year when it was brought to our attention. And then at the February meeting, we had a rather extensive discussion about potential Td

shortages. The Committee was presented with some options and we had a broad discussion about the possible need to prioritize Td use in the event that it appeared that a shortage would be developing. The Committee did not take a vote at that time, but there was broad consensus, I would say uniform consensus, that it was reasonable that should there be a critical shortage develop that it would be reasonable for the CDC to recommend prioritization of use of Td according to indication.

Since the February meeting, it has come to the attention of the Program that the shortage has been of a concern. We'll be hearing more about it in just a second, but I wanted to let the members of the Committee know that there was some consultation between members of the program and myself and others. We did discuss whether or not it would be desirable to have -- to call an emergency meeting of the Committee, possibly by conference call. I made the decision that it was probably not necessary given the fact that the advice that the Committee provided at the February meeting was sufficiently clear that I didn't feel it was necessary

that we convene the Committee. As a result, there was an article published in the MMWR now about four weeks ago that I'm sure you have seen, with the CDC recommendation that the use of Td should be -- or Td should be used according to certain priorities, and we'll be hearing more about that now.

Dean, are you going to be leading off the discussion? Dean Mason.

**MR. MASON:** We actually probably -- you were looking for a fast ball and we've thrown you a curve. We're going to start off with DTaP supply and then the Td discussion will go uninterrupted among three people: Dr. Phil Hosbach from Aventis, Dr. Lynn Zanardi from CDC; and myself.

As discussion of the DTaP situation, we thought we should start your morning out with some good news, because the Td may not be quite as good, and the good news is with respect to DTaP vaccine.

So what's happened since the last ACIP meeting and the discussions of DTaP at that meeting. March 16th, the MMWR Notice to Readers provided an advisory that providers may experience spot shortages of DTaP

vaccine in the country. In such instances, providers were advised that prioritizing vaccines to infants to complete the primary series, doses one, two, three at two, four, and six months of age, would be the highest priority; and that should shortages occur, that the first recommendation would be to defer the fourth dose and if the shortage was more severe, to make a decision to defer the fifth dose, hopefully, with tracking systems in place by the providers such that individual children who were deferred could be called back when vaccine supply was more adequate. The decision about deferrals was basically left to the programs and to the providers based upon their individual circumstances. A comparison of DTaP vaccine backorders was presented to the -- not a comparison but information on backorders was presented to the ACIP at the last meeting. Since that time, the backorder situation, that is, the ability of the manufacturers to supply product, has considerably improved. The two -- The blue-green or turquoise -- I guess that's turquoise -- bar and the yellow bar represent the backorders of Aventis Pasteur. In February, 579,000 doses of backorder, for

our purposes, was defined as any orders placed through the CDC contracts that were over 14 days and not being filled. This represents a condition of the contract, that all orders will be filled within 14 days of receipt. So this 579,000 represents both the orders that were 15 through 29 days on backorder, as well as 30 days plus on backorder. And as you can see, from February until June, the decline has been over twofold and this represents progress in catching up with the guarantees. The red line represents the February backorders of Glaxo SmithKline, keeping in mind these are the only two companies now producing and supplying for the U.S. market DTaP vaccine. The February backorders of over 15 days duration and the CDC contract were 287,500 and the June backorders were zero. So Glaxo has upped the ante, so to speak, in terms of success in bringing product to market and actually completely catching up such that they have no backorders in place.

So, therefore, if you added the circumstances, which was of concern to the ACIP in February, our contracts represented close to 900,000 doses in backorders of

over 15 days, and that has significantly improved with the backorders now remaining only from one company. I should point out that we do have two different reporting sources for this information. We used our own CDC ordering system for the February reports and we relied on the records of the manufacturers themselves for the June reports, but in cross-checking their records with ours, the information was quite consistent.

Actions that CDC has taken in response to the DTaP vaccine shortage in accordance with the desirous recommendations of the ACIP. The National Immunization Program collects state-specific central depot inventory information. We needed to find out where the states were in terms of their present ability to handle a crisis. So we asked the states to report how many doses of DTaP each state -- each immunization project grantee had in their central inventory. It's an almost impossible situation to ask the states to report that information for all of the individual providers and the vaccines that are contained in provider refrigerators. So we kept with the central

inventory. An advisory was sent to all grantees. All DTaP vaccine orders placed through CDC's contracts would be closely monitored. This is an action that we did do and we did modify a number of state orders. Our goal, of course, was to try and ensure equitability [sic] between the states, that is, it's not necessarily a good thing when one state has a six-month supply of DTaP vaccine when another state is facing spot shortages. We also encouraged the states to downsize their central depot inventories to less than 30 days. This, of course, represents more frequent ordering on the part of the states but allows the manufacturers to be more responsive in filling the needs of the states. We considered -- In making cutbacks or allocations, if you will, to the states, we considered the population base, the number of kids served in the public sector, inventory information, how many doses they had on backorder, and special needs and special circumstances of individual states.

Of course, we gave priority to those states that were short in inventory or less than 14 days in inventory and had orders pending. We also had weekly or

every-other-week communications with both vaccine manufacturers and with the FDA. To the extent that the FDA could discuss with us lot release information, they were extremely cooperative in doing so, as were the manufacturers.

So what did the state-specific central depot inventories look like? Of course, this is not as current as we would like today. We need to do another inventory, but we needed one at that time very badly because it obviously influenced our decisions about approving vaccine orders being passed along to the manufacturers. We had at the time -- we had 20 projects that had less than a 30-day central inventory. Let me say that there are 64 grantees, of which 61 or 62 actually receive vaccine directly. The other grantees receive it -- they're large cities that receive it through the states. We had -- On the other extreme, we had four projects with over a 91-day supply of DTaP vaccine. Now, in a perfect world, we would have a closer range between grantees. And one of the things that we are going to focus on for future policy is reducing inventories at the state level when they

exceed a certain level. Probably the maximum that any state needs is 60 days. There are reasons why states build inventory. Sometimes it's funding considerations, needing to expend funds, for example, before the end of a fiscal year, but in situations where we are wanting for product, we need to assure there is an equal sharing of the pain among all the grantees to the extent possible.

The impact of the DTaP vaccine shortage, we called each of the grantees. We wanted to find out how is this is affecting their world. Now, this information obviously is about a month old but, still, it reflects that the pain was starting to be felt among the grantees only three months after the declaration of potential spot shortages. There were 48 states that -- as of May 14th, or 84 percent, that indicated that they were still able to conduct business as usual. The second question, Is current DTaP supply sufficient to maintain the five-dose series, we had 12, or 21 percent of the states that indicated that they were cutting back or were in the process -- had cut back or were in the process of cutting back in supplying product to

providers. And then eight states declared that they had formally changed their policy, which, to us, the criteria for that was that there had been written communications, advisories, notices sent out to those people affected by the state supply system. And 11 states, or 19 percent, indicated that they were aware of spot shortages within their jurisdiction as of that date.

Now, as of today, if you ask these questions, I think you would get slightly increased numbers of grantees that have been adversely affected by supply but not too much, because the supply situation, as we've shown you, is improving.

Current backorders of DTaP vaccine through CDC's contract, I've showed you earlier the improving situation. Of course, our real concern is not those that are less than 14 days -- There should be a less sign here -- because these are still within the contract conditions to be met. 155,000 doses -- 156,000 doses, really -- are the amount that are less than 14 days. What concerns us is the number of doses that are not being filled by the manufacturers because they lack

product that are either 15 to 29 days or 30 days plus. And in this situation, of course, both of these are from Aventis Pasteur, and it amounts to 268,600 doses that are on backorder as we've showed earlier. This reflects 22 orders that -- not necessarily 22 projects. You could have duplicate projects, placing orders in both categories, so that while the overall backorder is 424,500, the fact of the matter is that 155,900 of that is less than 14 days and is not a real concern. The DTaP vaccine supply estimates for the remainder of the year -- And this probably will be where most of your interest will lie -- the average need for DTaP vaccine for the four-year period 1997 to 2000 -- This is the national need, both public and private sectors combined -- was about 17.3 million doses per year or 1.44 million doses per month. One caution, of course, is that it's not an even distribution every month. States need more vaccine in July and August than they do in February because they have to gear up for school drives and so forth. But for the purposes of this discussion -- just assume that it's spread out evenly it would be about 1.44 million doses per month.

Under current circumstances, Aventis and Glaxo SmithKline project they can supply 10.4 million doses of DTaP for the remaining six months of this year, which is 1.733 million doses per month. Glaxo has stated they can increase their DTaP production and supply to the United States an additional 3.9 million doses for the same six-month period. If this DTaP increase occurs, the total supply projection for the U.S. market would be 14.3 million doses, or 2.383 million doses per month. Glaxo's commitment of an additional 3.9 million doses is contingent on the ACIP's recommendation for a return to the routine five-dose DTaP schedule before the end of this month. It is the need of the company to know if we intend to go back to a schedule that we're comfortable with because we think supply is adequate. They need to know before the end of this month because of the production issues in their plan.

So for the ACIP to consider a return to the five-dose schedule, based on the supply of 1.73 million doses per month, NIP estimates -- the National Immunization Program -- that DTaP vaccine will be sufficient for

return to the five-dose schedule for all children. There are some cautions, however, on the basis of this amount. Close monitoring of DTaP orders through CDC's contracts will continue to be necessary to ensure: equitable vaccine distribution, that states gradually, not suddenly, build up inventories, and that these inventories be kept at 30-day maximums. A return to the routine schedule is dependent on the vaccine supply being steady and in the amounts projected.

If the estimate -- adding in the 3.9 million doses that Glaxo is indicating they can provide to the market is factored in, then the available supply per month is 2.38 million doses. We estimate that DTaP vaccine will be sufficient again for a return to the five-dose schedule for all children and, also: that it would be sufficient to allow for catch-up of the children needing to be recalled for booster doses; that it would potentially eliminate existing DTaP vaccine backorders of over 15 days duration, though CDC might be in a position of having to divert some orders from one company to another to assist in overcoming the

backorders; it would better ensure sufficient quantities of product for school drives; and it would allow states to build up inventories if they so chose for a maximum of 60 versus 30 days.

And that concludes the DTaP presentation.

**DR. MODLIN:** Okay. Dean, just a quick question or comment. I am kind of curious about your language of returning to the five-dose schedule. I want to make it very clear that the Committee has never abandoned the five-dose schedule. It was just at the last meeting we provided some advice that if, in the opinion of the Program, the supplies were so critical that we might have to prioritize between the fourth and the fifth dose. We provided some guidance in that, but I don't think we've ever actually made any formal change in the schedule.

So I guess this is basically good news that probably doesn't require any formal action on the part of the Committee.

Are there questions or comments for Mr. Mason? Sam?

**DR. KATZ:** I have just a comment that I think the progress of the development of --

**DR. MODLIN:** Sam Katz.

**DR. KATZ:** This is Dr. Katz, I'm sorry. The development of registries has been rather desultory in some states and very costly, and yet when you start figuring how are you going to work with recall of children who have missed doses, this is, to me, one of the most cogent arguments for having a registry system. I don't think that it's going to be very easy to find those children who have missed doses or for whom doses have been deferred unless you have some sort of accurate computerized system.

**DR. MODLIN:** Further comments? It's my --

**DR. SNIDER:** I would just like to clarify again, I think your comments were very appropriate, John, with regard to what action ACIP took. Was the Program looking for some official statement or resolution?

**DR. ORENSTEIN:** I think we, as a Program, could very easily say we feel now that the supply is adequate to assure that five doses are available for all. We just wanted to make sure the Committee has no problems with that.

**DR. MODLIN:** Let's move on to Td.

**MR. MASON:** Right. Just one afterthought is, I don't know if Glaxo -- what specific endorsements that Glaxo is looking for in order to make a decision about supplying 3.9 million doses. I can't speak to that, but perhaps they might want to speak to that to the ACIP. There's going to be three presenters on the topic of Td availability, and I believe I'll be followed by Dr. Lynn Zanardi and then by Phil Hosbach of Aventis Pasteur.

In December 2000, Wyeth Lederle made the announcement of its intent to cease production of tetanus and diphtheria and the tetanus toxoids. Actual cessation in the public sector had occurred much earlier in 2000, and the company attributed its decision to production issues and thimerosal issues. For 1999, Wyeth Lederle provided 32 percent of all diphtheria and tetanus products for the U.S. market. That figure, or share, had dropped to 19 percent for calendar year 2000. Aventis Pasteur is now the only national producer of tetanus and diphtheria. A reminder that the University of Massachusetts Medical School does produce a small amount of tetanus and diphtheria

primarily for state residents.

The recommendations -- while the recommendations for use of Td come from the ACIP and the American Academy of Pediatrics, all decisions about Td supply now rest with the remaining manufacturer, Aventis Pasteur. If I could use an analogy to congressional process for funding, first there must be authorization for funds and, second, there must be appropriation of funds. Both must occur in order for grantees to receive funds. Well, with Td, the recommendations must be followed by supply. So that is something that is somewhat new to the supply situation. CDC does not have a contract for tetanus and diphtheria and we have no ability to make decisions about the supply of that product. There is a strict criteria that is employed by Aventis Pasteur which we will talk about briefly.

And this is the criteria. It reflects as the supply situation tightens up the -- so do the criteria for supply. Prior to the supply issues coming about, all health care providers were administering Td presumably in accordance with ACIP and AAP recommendations. January through May of this year, the first five months

of this year, the supply situation necessitated that the company establish some screening criteria and prioritize product to the extent that it could most effectively supply those in accordance with the highest priorities with the ACIP. Priority supply was given to hospitals, emergency rooms, and public clinics with the emphasis on wound management. Now, contrast that with June 11th of this year when a decision was made by the company, because of decreasing availability of product, to supply only central locations with Td, including hospitals, emergency rooms, public health departments. In the first part of the year, hospitals were limited to 50 doses a week, with increases made when justified or when appropriate. The new policy is that hospitals are limited to 300 doses per month and, again, there is an allowance with appropriate justification such as they have a greater need because of the people they serve. In the old policy, health care providers, individual practitioners, were limited to 20 doses per month. Td is no longer or for the present not being supplied to individual providers. They must refer patients to a

central location for Td. The military policies have not changed. In the previous criteria, Aventis supplied, Td boosters were not recommended, and at this time, Td boosters -- vaccine is not supplied at all for Td boosters.

The Immigration and Naturalization Service has suspended Td boosters for immigrants. That policy has not changed. Aventis keeps some product in reserve in the event of natural disasters such as floods. Product is usually shipped to a central public health inventory station such as a large local health department and they redistribute from there. The focus remains on wound management, travelers, persons with less than three doses, pregnant women without vaccination within the past 10 years.

The reflection here is the decreasing tetanus and diphtheria supply in the U.S. market. In this circumstance, what we have reported under biologic surveillance is that 15.3 million doses were distributed in '97. Our caution is that we believe reporting is underreporting and that the true distribution is something between 18 and 20 million

doses. This reporting is voluntary, so this is the data we have, but we believe this is the true reflection.

There was reasonable consistency between '97 and '98. Some decrease began in '99. 2000 was accentuated. Through May of this year, 5.2 million doses of product have been distributed. The company projects that by the end of the year 13.5 million doses will have been produced and supplied for the market. That's tantamount roughly, a little bit of an improvement over last year, about the same as '99, but still quite short of the national need and there simply is no inventory left that can overcome temporary blips in supply.

And what's the outlook for tetanus and diphtheria?

Obviously, we are where we are because the demand exceeds the supply. While Americans love a conspiracy, this situation is real, not contrived. This is not -- This is a difficult period for the company Aventis Pasteur because as the sole remaining manufacturer, the national producer of tetanus and diphtheria, tetanus diphtheria, tetanus pediatric, they are the target for the frustration being felt by

providers and consumers who cannot obtain product. Still, we must remember where we would be if Aventis Pasteur was not supplying tetanus and diphtheria. It takes about 11 months to produce this product. So what we are feeling now was the lack of information, the inability of the company to respond this time a year ago. It isn't a present reflection. They are working at full capacity to produce product. Tetanus is obviously the limiting factor in production and predictions are that improvement will not occur before early to mid-2001.

Thank you.

**DR. MODLIN:** Thanks, Dean. Why don't we go on to Lynn's presentation and then we'll have some discussion at the end.

**DR. SNIDER:** Dean, you mentioned 2002.

**MR. MASON:** 2002, sorry.

**DR. ZANARDI:** Good morning. I would like to briefly update you on the recent MMWR Notice to Readers that was published on May 25th, last month, and then the main purpose of this Notice to Readers was to recommend a delay of all booster doses of Td until vaccine supplies

are restored in 2002.

We also recommended that clinics implement a callback system so that patients whose booster dose was delayed this year can be recalled next year. And you'll hear a little bit about that later in Phil Hosbach's presentation.

The use of Td for priority indications was re-emphasized. This is travelers to diphtheria-endemic countries, wound management, completion of a primary series, and use of Td in pregnant women who are due for a booster dose. Aventis Pasteur had indicated to us that they felt there would be sufficient supply of Td this year for these priority indications.

We also took the opportunity to remind readers of the MMWR that the ACIP recommendations for wound management had not changed. We had received quite a few inquiries from practitioners about the use of DT and DTaP as a substitute for Td in wound -- particularly in wound management for persons greater than seven years of age. In particular, people were calling to ask if they could half the dose of pediatric DT and use

that in adults instead of Td. Other inquiries that we were getting that were quite common was people asking whether they could use tetanus immune globulin, or TIG, or antimicrobial therapy instead of Td in situations of wound management. So then in the Notice to Readers we re-emphasized that the recommendations have not changed and that TIG and antimicrobial therapy should not be used as a substitute for Td.

And finally, we reminded health care providers to inquire about the timing of patients' last Td in wound management situations so that unnecessary vaccinations are not given.

The current status is that there is sufficient vaccine for priority indications as has been indicated to us by Aventis Pasteur. So there's enough vaccine for all priority indications, excluding routine booster doses. Vaccine is available for natural disasters, and Td has been shipped to Houston, Texas, and I believe other areas that have recently experienced flooding.

Institutions were asked in the Notice to Readers to order vaccine for their usual anticipated need only for their priority indications and that should unusual

circumstances, such as flooding, occur, Aventis can ship very quickly, usually within 24 hours for emergency.

So those were the main messages of the last Notice to Readers, and I believe Phil Hosbach will update you on Aventis' status.

**DR. MODLIN:** Phil?

**MR. HOSBACH:** Thanks, Lynn. I just wanted to provide a little bit of an update of our situation and tell you a little bit about some of the problems and some of the solutions we have in store to get out of this situation as quickly as we possibly can.

Now, this may sound like a no-brainer to all of you. The first priority for Aventis is to produce more vaccine. With very short notice and not being able to anticipate abrupt removal of another manufacturer from this marketplace, it takes some time for us to recoup and reorganize ourselves to produce more vaccine. In fact, I believe Dean alluded to the fact that it takes about 11 months in that production cycle.

We're also -- It's very important for us to try to manage the current supply situation and there's

recommendations that were published on May 25th that will be very helpful for that. We also want to ensure for the future that we establish a back-up capacity so that this doesn't happen again.

As Lynn pointed out, we want to ensure that we have enough vaccine for critical care needs, but the success of this is really going to be dependent upon people following the prioritization and the new recommendations. Actually, they're an adjustment to the current recommendations and honing in on the priorities.

Some of the difficulties that we face with the first issuance of recommendations for priorities, where that there were six or seven priorities, and we did also again talk a little about routine Td boosters. And while we had a supply situation and Wyeth announced that they were leaving the marketplace -- I'll liken this to what happens in the northeast. If you've ever experienced a weather forecast where they say a big snowstorm is coming, everyone goes the store and buys a lot of milk and eggs and then there's no milk and eggs left. Well, that's part of what happened with Td, and

we really needed to put on the brakes and we appreciate ACIP's help in trying to do that. We appreciate greatly CDC's help in narrowing down those recommendations.

So we're really going to need a lot of your help, a lot of people around the table to help communicate what's going on. The people who most need to hear this message and understand and comply are those that currently have sufficient vaccine, and those who really believe that we can turn on a dime and replenish the supplies tomorrow -- I actually personally surveyed eight, for example, public health departments in eight states. Four of them have not yet acted on the new recommendations. I believe Dr. Atkinson encountered one situation in one of the states that he visited recently where they had not acted and they aren't sure if they're going to act on it yet, but I think we're going to get everyone to comply. We'll be sharing that information with the CDC, and our message needs to be very wide and very deep to make sure that we can meet all the critical care needs.

Now, why is this happening? Why did we suddenly rachet down? Well, right now we're in a period where we're going to have high usage for Td. We have warm weather, people out in outdoor activities. You've noticed over the past few years the weather has become a little bit more unpredictable and violent during the summertime, tornadoes, floods, those types of things. We have to be prepared for such emergencies. So we need to maintain an adequate stock to be able to address those needs rapidly. So we are continuing monitoring our supply, the demand, and you will see periodically that we will adjust our recommendations and our policies for distribution of the vaccine to ensure we can have a rapid response to any urgent need. Right now, currently, the shipping policy has been racheted down to only public health clinics and urgent care facilities such as emergency rooms. And again, we need to have vaccine available at any point in time to address any natural disasters that might occur. We are currently running 24 hours a day, seven days a week, trying to get up to speed. As you've seen, we actually had a little bit of a -- we'll realize toward

the end of the year a little bit of an increase in production. The 11-month cycle starts to kick in, and we've gone from about 12 million doses to about 13 and a half million doses. So we'll start to realize the actions that we took at the very beginning of this year. We expect that we'll be able to ease restrictions hopefully later this year, but certainly in early 2002. We're also working cooperatively with the FDA to try to obtain a license in U.S. for a Canadian Td facility and that will definitely ensure not only adequate supply for the long term but also supply of a different manufacturing facility in the event of a disaster such as a fire at our plant. We'll have the capability from Canada to supply Td to the United States, and that's very important.

What are we doing? Basically, we're making sure that we pass along the information on new recommendations to all health care providers and certainly reminding people that they're going to need to be recalling those who they are referring booster doses for. I'm going to tell you a little bit about what we're going to try to do.

I think each of ACIP members has on their -- in their packets a letter that comes from the Postgraduate Institute of Medicine. We've worked with them to create this letter and also a good summary of the current recommendations for Td, with good definitions on wound management and how to take care and address according to the current ACIP guidelines for wound management. That's going to go out to 400,000 health care providers, doctors, nurse practitioners, and school nurses. That will go out later this week, and we will be e-mailing this to the various societies so that they can -- medical societies so they can also pass out an e-mail to their members as well. We'll also be including educational materials, links, and other information on our corporate website.

One of the things that we want to plan to do to assist in the recall situation is we will also be sending out a variety of letters during the course of the summer, and within those letters to this large audience, we'll include information regarding their ability to get from us a kit that will help them in recalling their patients. That will include some reminder recall

materials, some information for their patients, as well as postcards to send to those patients where boosters were deferred. Again, we really need everyone's help around the table so that we can ensure that communication is wide and deep. We've had a slow response to the recommendations that were published late last year. We're just getting out of the gate with the adjustment to the recommendations, and certainly we need that communication to go deeply. Our principle goal is we need to restore the nation's supply of Td vaccine. It's not something that we asked for or anticipated, but it's something that we embrace wholeheartedly just like we embraced working very hard at removing thimerosal from DTaP. This is our top priority to get done. We want to ensure that we can continue to meet the critical care needs until full supply is restored. Hence, we will be adjusting our shipping and distribution policy and, hopefully, with the licensure of the Canadian facility that we'll be able to prevent shortfalls in the long-term.

Thank you.

**DR. MODLIN:** Phil, thanks. And again, just to remind

the Committee that the update that was published about a month ago was very consistent with the broad consensus that I think we had achieved during the discussion at the February meeting when we discussed most of this. And this, in many respects, is an update on the situation that was presented -- or discussed at that time.

Let's open it up and ask if there are questions or comments for any of the presenters.

Natalie?

**DR. SMITH:** Yeah. A couple of questions for Aventis. I'm just wondering -- when you say urgent care facilities and that means hospital emergency rooms, there are a lot of places where hospitals aren't too accessible in rural areas. And how do we know states if there are gaps in coverage of who has the Td vaccine, and are you shipping it to rural urgent -- like urgent care clinics, or how are you handling that?

**DR. HOSBACH:** At this point in time, we're trying to tell the people to come to the vaccine, but we now recognize that, as we talk to some of the health departments in some of the more rural areas, there may

be some needs that we need to adjust to or address. We will continue to work with the public health departments and any of the medical societies that could help us identify where there might be a problem. We will try to adjust as necessary, but at this point in time, it's serious enough that we would like the people to come to the vaccine, if possible.

**DR. SMITH:** Is there a way for states to have that information about where the vaccine is going?

**DR. HOSBACH:** Absolutely. We will provide all that information to all health departments.

**DR. SMITH:** And then I just had a brief comment on your cover letter that's going out. You say the use of Td for vaccination for those planning foreign travel, and I don't know if it's too late, but if you could add for diphtheria --

**DR. HOSBACH:** To diphtheria-endemic areas.

**DR. SMITH:** I know you say it on your additional sheet, but a lot of people may just read this letter. I've been getting lots of calls, do I need this just to go to Europe or Mexico or somewhere?

**DR. HOSBACH:** I may be a little too late. I know the

things went to the printer, but we'll see what we can do. Thank you for pointing that out to us. We'll make a try to make sure we get the message out.

**DR. SMITH:** Okay.

**DR. MODLIN:** Jon Abramson?

**DR. ABRAMSON:** Yeah. I don't know what the CDC can do about this, but North Carolina state has actively decided not just to ignore the recommendations but they made the recommendations going forward that they have enough supply, therefore they're not dropping the booster dose. So I don't know what you do about it when one state does that. Maybe Sam can comment. I am concerned about that because I think it creates the wrong setting. We have to deal with other vaccines like flu also.

**MR. MASON:** I think it points out -- One of the things I was trying to emphasize was the inequitability [sic] of inventory among different states. We're aware of North Carolina. We happen to know that communication went to them asking them to defer Td boosters and their response was "We'll think about it." We'll continue to work with them, and it doesn't seem fair. That's

for sure.

**DR. MODLIN:** Immunization policy, like all health policy, is a state's right, but it's a good point. Other comments or questions? Yes, Jaime?

**DR. DESEDA:** I have a comment. In San Juan, in metropolitan San Juan, things may not work the same everywhere, but large pediatric groups have been receiving patients from emergency rooms, which is the opposite of what should be happening. And also, if there's any consideration to increasing the supply of tetanus toxoid alone for hospitals only or emergency rooms, if this is feasible . . .

**DR. MODLIN:** Jaime, do you have information that this suggests that the hospitals actually are short of supply for wound management and kids are actually coming to their pediatrician for wound management?

**DR. DESEDA:** Well, let me just tell you the most recent one that I had just before I came here to Atlanta. I got -- a physician that had come to Puerto Rico for lectures who stepped on a sea urchin in the ocean and the emergency room didn't have any tetanus or Td. So because some of our pediatric practices are quite

large, we usually Td. So they're referring patients to us.

**DR. MODLIN:** Interesting. Thank you. Myron?

**DR. LEVIN:** Can I ask a question really at the planning level? I assume a manufacturer decides to leave the market for economic reasons and what -- what planning do we have if that should happen again, not only for this vaccine, for other vaccines? The idea of a disaster occurring in a factory was mentioned. What kind of back-up plans do we have for any of our vaccine?

**DR. MODLIN:** I think the best response to that is that NVPO and NVAC have actively been involved in studying just this issue and has a work group that is focusing on vaccine supply issues based on demand.

Marty, do you want to say anything more about that?

**DR. MYERS:** No. I think you -- There is a work group that is addressing that issue and --

**DR. MODLIN:** And they're making progress?

**DR. MYERS:** Well, the whole issue of vaccine supply is very complex, as we're hearing. It's -- There are many issues, but they have -- have taken this and they're working on this. The Secretary has specifically

directed them to get a report to him.

**DR. MODLIN:** Walt?

**DR. ORENSTEIN:** I was going to say, there is or has been a process in place in the past for dealing with short-term interruptions and that has been storage and rotation contracts for various vaccines. We made a decision in the '90's to focus those storage and rotation contracts on those vaccines that had a single manufacturer, fearing that those were the ones we were most vulnerable for. And in fact, there is a storage and rotation contract for MMR and there is a storage and rotation contract for inactivated polio vaccine given what has happened here and the disruptions when even when there are multiple manufacturers. If one leaves the market, we are seriously reconsidering that policy and discussing the potential for having stockpiles for all of the routine recommended vaccines. That will not get into whether the single last manufacturer leaves, and that's an issue we're looking to NVAC to help us with, but it certainly would help in getting through some of the -- if we had a stockpile for Td, we probably could have averted some

of the problems we're currently having.

**DR. MODLIN:** Yes?

**MS. PETERSON:** I'm Diane Peterson from the Minnesota Department of Health.

I've noticed in the previous MMWR Notices to Readers there's been recommendations for routine vaccination of persons with occupational risk, and I notice that that's not in the current letters that are going out. I'm wondering what happened to that. We do get a lot of questions on our hot line about persons particularly working in the farming industry and the need for their vaccination.

**DR. MODLIN:** Dean, did you want to respond?

**MR. MASON:** Not really.

(LAUGHTER)

**MR. MASON:** I think that the pain is being shared by a number of target groups, and I think that there's no provisions -- as it's my understanding of the policy at this time, there's no provisions for occupational considerations. That would be a broad net, as everyone knows. On the other hand, if someone in an occupation suffered wound trauma, then they would be

able to get product.

**DR. MODLIN:** Rich?

**DR. CLOVER:** Just a quick curiosity. The decreased supply of the private practitioner, what percent of the historical total distribution is not being delivered to the private docs now? Is that number known?

**DR. MODLIN:** The question is, prior to the shortage, how much was -- how much was the supply were private practitioners receiving? We did discuss that. Dean?

**MR. MASON:** It was -- For the first four or five months of this year, they were receiving up to, I believe, 20 doses a month and they could get an increased amount if they could so justify, you know, not giving Td boosters, but that was the Aventis supply policy to them. Of course, up until this year, or before this circumstance began, they were receiving it both through the public supply system as well as through their own direct ordering. Now they're not getting it at all.

**DR. CLOVER:** But how many doses is that?

**MR. MASON:** It was two vials or -- They're 10-dose

vials.

**DR. MODLIN:** What proportion of the total supply was going to private practitioners' offices? When we discussed that on the phone, I recall it was in the nature of around 10 percent. Is that correct?

**MR. MASON:** We don't have that information.

**DR. MODLIN:** Okay.

**MR. MASON:** Aventis might be able to address it.

**DR. MODLIN:** Phil?

**DR. HOSBACH:** Phil Hosbach, Aventis. I don't have those figures with me. We can get those for you. Part of the problem is that we're taking on a lot of new customers. We're no longer allowing distributors to handle the vaccine. We want to ensure that it comes directly from us, as well as we picked up another third of the business. So we don't really have those historical numbers to tell, but I could go back and get to you, Dr. Clover, the information as to what we distribute currently.

**DR. MODLIN:** Eric France?

**DR. FRANCE:** I did want to bring up sort of my local experience at Kaiser Permanente Colorado, which as an

integrated health care system that has 380,000 members in the Denver area and 500 docs, urgent care clinics, emergency rooms. I know that every month that -- I have maybe 700 doses left right now and I get 20 doses a month from the company, and I know that by October or November, we will run out of tetanus even though for the last four to six months we've been very, very tightly controlling where the doses go. So I guess I haven't really followed through whether there are other emergency departments and other places that KP members might be sent to to get the vaccine doses and maybe feel that's the way that we don't run out. But our group, of course, has been saying we're going to run out. And not only do we limit it now only to dirty wounds and not to people who have never received -- we don't give it to people who have never had a primary series, we don't give it to the pregnant women unless it's pushed on hard, but we're saying to ourselves now, which of these dirty wounds is more dirty and therefore should get the vaccine. And I wonder if this is going to come out in October or November across the country and maybe to hot spots where people just aren't getting

the vaccine and individual sites will be making individual decisions about how to prioritize within the priority scheme you already have?

**DR. HOSBACH:** Phil Hosbach from Aventis. We appreciate all that Kaiser has done and we realize that you are trying to adhere to the recommendations and we do not advise that you make decisions about whether a wound is too dirty or too clean, that you follow the recommendations as is and we'll try to work with you to make sure that you have sufficient vaccine. I think certainly give me a call or we can talk afterwards and we can make sure that we get vaccine to the right places, but we don't want people making a call on whether a wound is really dirty or a little dirty. If you need to be vaccinated -- We handed out the materials with our letter. You'll see what the definitions are for wound management from the CDC and ACIP and you need to follow those. We'll try to do what we can to help you.

**DR. MODLIN:** Thanks. Further comments or questions?

(NO RESPONSE)

**DR. MODLIN:** We have a break scheduled. It's a little

bit early, but let's go ahead and take it and we'll return at 10:15.

(BREAK FROM 9:50 A.M. TO 10:20 A.M.)

**DR. MODLIN:** Could I ask people to please take their seats so we can continue.

We're going to continue this morning talking about another vaccine or focusing on another vaccine supply issue, particularly for the influenza vaccine supply for the upcoming influenza season. I'm going to turn things over to Dr. Bonnie Word to lead the discussion. Bonnie?

**DR. WORD:** Well, I guess influenza has been -- the working group has been rather busy. I came in -- After coming on, I thought it was a rather type of -- you know, something they did once a year. I didn't know that the first thing that was going to hit me when I came on was going to be a delay or shortage, but we know it turned out to be a delay. Anyway, since we were last here, we've actually been quite busy. In May, we actually had a working group convene for a two-day workshop about live-attenuated influenza vaccine. Keiji Fukuda and I will subsequently give

you an update on that.

Other things that we're going to talk about today is -- it's a host of things, and I'm sure your packet has already given you wind of part of it. Jim Singleton actually is going to talk a little bit about vaccine use that's happened more recently, particularly in the last year or so, and previously. Dennis O'Mara will subsequently talk about vaccine supply. We have Dr. Tan from the AMA who is going to talk a little bit about the involvement from AMA and some of the communications with relationship to how -- with some of the difficulties we had last year with the season in terms of getting vaccine out. I guess most importantly -- I shouldn't say most importantly, but what happened as a forefront of what preempted things for the last several days is that as a result of ongoing discussions between FDA, CDC, as well as manufacturers, the NIP actually became informed that this year we were again going to experience a delay in influenza vaccine delivery.

Now, you all recall last year -- As I mentioned, that was my inauguration into this working group -- that

during that time, the working group had developed some alternative plans and the ACIP subsequently endorsed them and they were published in October of 2000. For the most part, it emphasized a couple of things. One was delaying initiation of major campaigns at that time; also trying to help providers focus on directing their vaccine to high-risk patients, those individuals specifically that are at risk for complication; and asking other individuals to defer their vaccine -- actually not even starting them until December, those particular individuals, particularly around the 50- to 64-year-old age group and other healthy individuals. And it seemed to work pretty well. However, there's been a lot of comments that reportedly a lot of the primary care physicians or other practitioners who are the ones who seem to deliver the majority of vaccine to high-risk individuals reportedly have been saying that they weren't getting vaccine or they didn't get vaccine until later in the season. So with that in mind, some of the things that -- in terms of looking at recommendations -- because we just published our recommendations in April -- in terms of updating it for

anticipated delay, this time is -- can you begin to have other people involved in this scenario. Before it was just focused primarily on the practitioners or the providers and also on just telling the public what to do. Perhaps, this is a time that perhaps we can involve and throw the manufacturers in as part of the solution in the early part of it. So Ben Schwartz is going to spend a great deal of time looking at this and actually we'll present some options that have been developed as well as look at some of the -- can tell you some of the rationale.

So, first, I would like to start off just trying to give a brief update of what happened at the influenza workshop. And as I said, this will be sort of a two-part person -- two-part presentation. I'll tell you a little bit about some of the things that we talked about and then Keiji is going to try to summarize most of the information.

First off, we had a couple of goals that we set for ourselves, and one was just to identify and address concerns and our issues relative to live-attenuated influenza vaccine in general and specifically in

children. Also, we wanted to review current efficacy and safety data of the inactivated influenza vaccine. The last thing is we wanted to determine what additional information, if any, would be necessary to assist the working group in formulating future options with regard to expanding the use of influenza vaccine, whether live or inactivated. And I think that's -- you know, it's been intertwined very closely because we all that that there's a live-attenuated vaccine that's sitting down at FDA looking for a review right now. But the thing is, even though it's still separate, we have to -- it is intertwined, but we have to remember, it is separate.

Essentially, the way the meeting was set up, we were able to bring in a lot of different experts with the help of the people at CDC and NIP identifying them, and we had a couple of general discussions. One was done on the impact of influenza on children. Bill Thompson and Tim Uyeki did that. And what was good about that is that they brought -- it was sort of a review to talk about pediatric infection rates, hospitalization rates, as well as some clinical complications that are

seen in children. They also looked at some mortality associated with children. Some unusual complications were presented, and one was a report that's coming out of Japan where they're having acute necrotizing encephalopathy. Now, Keiji, in his summary, will probably talk -- mention more about that.

The other thing is that everyone talks about LAIV, but one of the things that Brian Murphy did was just go back and just help review a little bit -- talk about the development of LAIV, because it's used so interchangeably. I, myself, wasn't an influenza maven, so I was just -- this was like starting from ground zero. And I think there were other people who found that particular talk beneficial.

The last thing, Kanta Subbarao presented data on effectiveness and efficacy studies of LAIV, and she did it in all the ones that were published in the pediatric data as well as healthy adult, elderly, and even high-risk adults such as cystics and individuals with asthma.

We subsequently had four subgroup presentations and we had -- originally had four -- we had four subgroups,

and each one had a subgroup leader. There were approximately about eight people in each group, and prior to coming to the meeting, they identified the articles, they were given specific questions, they identified the articles for review, and each one sort of worked a little differently, but they came with a complete presentation for the entire group. It was an extremely -- a lot of material to go through. I don't think any of the members individually could have had a chance to just read all of that material that was presented at that time, but the subgroup presentations -- the first one was on safety and effectiveness and efficacy of vaccinating young children with inactivated influenza vaccine. That particular subgroup was headed by Dr. Katherine Edwards. And what they did was -- in looking at inactivated vaccine, it was broken down into -- looking at it with that and herd immunity as well as looking at safety and immunogenicity in day care studies and also looking at it in selected high-risk populations, such as diabetics, and sicklers, and asthmatics. And lastly, just looking at overall vaccine effectiveness and

efficacy in this group.

The next subgroup presentation was on potential for reversion of LAIV vaccine strains and potential for recombination of vaccine strains with wild viruses.

The last two subgroup presentations, one was on the potential biologic issue related to co-administration of LAIV with other childhood vaccines, and it was interesting because sometimes when you begin to look at these, if you look at the immunization schedule as it is right now, it's almost every immunization that can potentially be given with it. If you start -- you know, if you draw that line down at six months, or actually in this case 12 months of age, you'll look and see -- I mean, hepatitis, DTaP, hib, IPV, Prevnar, MMR, varicella. For all children, that potentially is there. If you go to the adult population, then you have to worry about what type of co-administration in terms of pneumococcal vaccine that's there.

One of the things sometimes we found, it wasn't so much all the information that we were able to obtain, but sometimes the limited amount of information that was available for us to even review and make decisions with.

As I said, Keiji will be summarizing -- he'll just come to fine points in the topics.

The last one was the potential for adverse immunologic effects in children who were repeatedly vaccinated against influenza.

So with this in mind, we know that there are still some gaps in terms of some safety issues, some feasibility issues, as well as economic issues. Those are things that we know that we still have to deal with. We're actually planning to have a second workshop in September. It's just that some of the safety data wasn't presented, because pending the results of the FDA review, we weren't able to adequately have access to some of the material.

So right now, I would just like to turn it over to Keiji so that he can just give you a brief summary of the other points there.

**DR. FUKUDA:** Thanks, Bonnie. Just to quickly go over a couple of points about this process, because this probably was the best scientific meeting I've been to in a couple of years in terms of its coverage of the material. And I just want to show you what went into

it.

As Bonnie mentioned, there were several expert presentations made to the group and these were given by several people that you can see up here on the board. A lot of the success of the meeting really goes to the subgroup leaders. These people worked really hard to get the literature together, to get the right people, and to put it all together. I want to point out that these were Kathy Edwards, Brian Murphy, Wendy Keital, and Ruth Karron.

The subgroups -- these people convened the subgroups with help from CDC staff and, basically, each of the subgroups spent a couple of months of preparatory work. And what they did was review their relevant published literature, identify it and review it, and then there were several preconference subgroup telephone calls in which the literature was discussed and the groups decided how to present it. And then at the meeting, each of the subgroups made a presentation on their topics. And probably one of the nicest things was there was extensive time for discussions at the meeting.

Tim Uyeki and Bill Thompson reviewed the impact of flu in children, and basically, I'll just summarize some of the main points. But the attack rates in children from several different studies are higher than they are in adults, and these come from some of the community studies. In general, flu-related hospitalization rates are higher in younger children than they are in older children. And they're higher in children of high-risk conditions compared with age-matched healthy children, but they're also -- when you look at healthy children, they're clearly higher in young healthy children compared with older healthy children. And really, the complication rate is probably highest in children who are under six months of age, that group of children for whom vaccine is not approved. And then when you look at vaccination rates in high-risk children right now, they're currently pretty low, ranging somewhere between 10 to 30 percent. When you look at the complications, outpatient complications, otitis media and asthma really stand out, but there are not that many data on asthma exacerbations, and then are a variety of uncommon

complications that have been presented.

So in summarizing the impact of flu in children, the morbidity is substantial, it is higher in young children compared with older children when you're looking at healthy kids, it's probably generally underreported and underappreciated in both the medical community and in the literature. The amount of data from outpatient settings is limited. There have been recent reports of very severe influenza-associated encephalopathy reported from Japan. This was discussed both at a recent COID meeting held at AAP and our meeting, and we don't really see that same phenomenon in the United States and it's not clear quite what's going on. But the data from Japan is really becoming quite impressive.

And I think one of the outstanding questions in this group in terms of the impact is whether vaccination of mothers when they're pregnant really confers any protection to infants.

Now, the first subgroup review was held by Kathy Edwards' group and this was to look at the safety and effectiveness of trivalent vaccine -- inactivated

vaccine in vaccinating young children. And in their review, this subgroup excluded studies of whole virus vaccine because it is not recommended for young kids. They excluded studies using foreign trivalent inactivated vaccines which are not compatible with those approved for the United States and they also excluded vaccines prior to 1981 because these are vaccines with reduced antigen content compared with modern vaccines.

Several different topics were reviewed. One of them was trivalent inactivated vaccine and the possibility of herd immunity, and papers from Japan -- both older papers such as those by Walt Dowdle and more recent papers such as those by Dr. Reichert -- were reviewed, as was Arnold Monto's Tecumseh study, and then the Russian experience. Several safety immunogenicity in day care studies were reviewed by Kathy Edwards. And in general, the bulk of these studies show that the vaccine is immunogenic, the major adverse reactions are local reactions, and the vaccine is effective.

The group also reviewed the -- Bonnie reviewed the data from high-risk populations and basically looked at

populations of kids with sickle cell anemia, asthma, diabetes. In general, there are not that many data on these groups, but when you look at them, the findings are generally comparable to what you see in healthy children. And then Kathy Neuzil reviewed randomized control trials of effectiveness and efficacy and, basically, she reviewed the experience from two published studies and one study which is in press. Then, as Bonnie mentioned, both Brian Murphy and Kanta Subbarao reviewed the development of live-attenuated vaccines and the published data on their effectiveness and efficacy. And one thing that's fair to point out I don't think we have time to get into this here, but there are post-vaccination immune differences between live-attenuated vaccines and trivalent inactivated vaccines. And again, this differs depending on whether we're talking with a sero-negative population, a naive population, or a sero-positive population. So there are a lot of complexities having to do with the immune response. In general, Kanta reviewed several studies sponsored by NIH, Wyeth, and Aviron. And again, when you look

at these studies taken together, the live-attenuated vaccines clearly appear to be both effective and efficacious.

And then Brian was also the subgroup leader for a group looking at, what is the potential for live-attenuated influenza vaccine strains to revert back to wild-type strains and then what is the potential for the reassortment of vaccine strain genes with wild viruses. And basically, Brian pointed out that both A and B cold-adapted reassortant strains have been found to be genetically stable in susceptible persons. It's also clear that cold-adapted viruses can reassort, that is, they can exchange genes with other flu viruses, but they tend to do so at a lower frequency than wild-type viruses do. And again, when you look at the possible combinations of viruses out there, or virus genes, between live-attenuated virus genes and wild-type genes, there really are no unique consequences that are foreseen.

However, it's also clear that there are a couple of situations in which you would want to avoid the use of live-attenuated vaccines. One of these situations

is that you would not want to use a live-attenuated influenza vaccine bearing novel hemagglutinin or neuraminidase antigens if you thought a pandemic was coming but then that pandemic did not come, because basically, you would be releasing those antigens and genes out into the population.

A second situation in which you wouldn't want to be using live-attenuated vaccines would be in the kind of situation that we saw in Hong Kong with the H5 outbreak. If you were to use a live-attenuated vaccine bearing the normal circulating virus antigens and then those were to recombine with a H5 type of virus, then it is theoretically possible that you could end up producing a H5 virus which is more highly transmissible than the native virus. So these are two situations that you would want to avoid.

Ruth Karron's group reviewed the potential biologic issues related to the co-administration of live-attenuated vaccines and other childhood vaccines. This is a big issue. However, there are very few data on that.

Wendy Keital's group reviewed the potential for

adverse immunologic effects in children who are repeatedly vaccinated against influenza. And again, this is a very complex and difficult subject and it has engendered a lot of sort of nonspecific concerns. But what this group did is that they broke it down into two main questions. The first is, what is the risk of annually vaccinated -- what is the risk that annual vaccination of young children could adversely affect the future responses of these children to either flu vaccine or flu infection. The second question that they brought up is, what is the potential for adverse effects in children who are repeatedly vaccinated against influenza.

So in doing this, Jackie Katz provided a very nice and complete review of the immunologic response to influenza and influenza vaccines. One of the things that the group -- that this group focused on was the so-called Hoskin hypothesis, which comes out of the Hoskin studies. And basically, what this group of studies suggested was that kids who are repeatedly vaccinated would have a less good immune response against influenza. So what Wendy Keital did was

review those studies and the criticisms of those studies and then she reviewed all other studies in which more -- in which children were vaccinated more than one time. And I'll come to what her conclusions were a little bit later on.

Another major issue that came up was the discussion of the potential for unforeseen aberrant immune responses, and the example that was brought up was, for example, the immune response to the early RSV vaccines.

So the summary findings of this group were that repeat immunizations in children and adults with both trivalent inactivated vaccine and live-attenuated vaccine appear to be both safe and well-tolerated. No aberrant immune responses have been identified, but more data are needed, particularly in young, unprimed children. Another major conclusion -- another major summary is that theoretical risks -- there are theoretical risks associated with repeat immunizations. For example, there could be some sort of risk associated with repeated exposure to egg proteins, but these risks have not been identified. These remain theoretical risks.

So what is felt to be necessary is continued evaluation of the safety, tolerability, and efficacy of both trivalent, inactivated, and live-attenuated influenza vaccines in young children. And another thought was that if either of the vaccines is recommended for routine use in young children, especially the live-attenuated vaccine, then Phase IV studies are definitely indicated to assess the potential for adverse events.

So just to quickly summarize the major findings again, you know, influenza clearly can lead to serious complications in children, and the rates of these complications are higher in younger children than they are in older, healthy children. However, more data are needed, particularly from outpatient settings. I think more data on the relationship to asthma and those sorts of things would be welcomed. It would be useful to have more data related to influenza and encephalopathy and other things, such as meningococcal infections. There was a suggestion that there may be some relationship between influenza and an increase in meningococcal infections.

Trivalent inactivated vaccine appears to be both safe and efficacious. However, again, more data would be welcome in the youngest age groups and also both high-risk and healthy children. In particular, what would be welcomed are some dose-ranging studies. These really have not been done for a couple of decades. And then one of the outstanding questions here is whether maternal vaccination with trivalent inactivated vaccine confers any protection to their infants.

Published studies suggest that live-attenuated influenza vaccines are immunogenic and efficacious, but more data are needed in young children. And again, remembering, this review was done without looking at the Aviron data. We have not -- We did not examine those data in this meeting.

Now, there are some concerns about live-attenuated vaccine strains reassorting with wild-type strains but, in general, these are really limited to a few specific situations involving the possibility of pandemic viruses or potential pandemic viruses. Clearly, there's a paucity of data on the

co-administration of flu vaccines with other vaccines and more data are needed. There have been several studies published since the Hoskin studies and, in general, many of those data are quite good and they really cast out that the -- on the veracity of the Hoskin's hypothesis.

Aberrant immune responses are theoretically possible. However, there are no data to suggest that they exist for flu vaccines.

So a number of studies would be desirable, and some of the main ones which the group highlighted were: dose-ranging studies would really be very welcome in all age groups. Again, one of the big questions is whether maternal vaccination can protect infants, and that's a high priority question. Clearly, more live-attenuated data in young children would be welcome. For both vaccines, further studies on vaccine safety would be welcome.

So, basically, these are the steps over the next couple of months. I think that most of you know that VRPAC is planning to review the Aviron live-attenuated product in July, and then the ACIP flu working group

is planning to meet in the fall time. The tentative dates are September 10th and 11th. I think that the point person for this meeting will probably be Jim Singleton at CDC. And at this meeting, several things will be reviewed. One is, depending on how the VRPAC meeting goes, we hope to be able to review the unpublished Aviron safety data. And then are a number of outstanding important issues which have not been examined with the same care, and these include the economics of annually vaccinating the children, the logistical and feasibility issues for pediatricians and other providers in meanings after recommendation, and then what the potential impact would be on programs and funding of programs, and then the crowding of the vaccine schedule. So these are the issues that we hope to be discussing in the next few months.

I think that unless there are any questions at this point, we'll segue into the next major --

**DR. MODLIN:** Keiji, why don't we take a couple of minutes and see. Obviously, we're going to be discussing influenza immunization in children in great detail over the next couple of meetings, if not longer.

But if there are specific questions or comments at this stage, particularly that might help guide the working group . . .

Eric?

**DR. FRANCE:** Dr. Eric France.

I did just want to make one addition to Keiji's comments regarding the work group, specifically around the safety questions of the trivalent inactivated vaccine. Kathy Neuzil, in her presentation, mentioned that the largest study of the safety and efficacy of the trivalent in its most current form really involved only 200 families. So there isn't some large body of experience with thousands of children being reviewed looking for any rare adverse events that might be associated with trivalent inactivated vaccine, and I'm mentioning that because the VSD program is looking at their data sets to look to see if there's anything unusual with the hopes of having that done by September or October of this year.

**DR. MODLIN:** Myron?

**DR. LEVIN:** Two questions. Is there a document from that meeting that is available for us to read, is one;

and the second is, did you discuss the use of either of these vaccines in immunocompromised individuals other than the sicklers and the asthmatics?

**DR. FUKUDA:** Yeah. The answer to both of those is yes. There are actually fairly extensive notes which are being compiled from the meeting and we can make those available to the Committee. I think that actually Marie over here took the notes and they have to be edited, but we'll make those available to the Committee. And they'll really be helpful because this is just compressing a very large --

**DR. LEVIN:** Yeah.

**DR. FUKUDA:** -- number of very complicated issues, and there are many more things which fell out of the meeting than I've been able to cover here.

Then there was discussion about the -- some discussion about the effects of the vaccines in HIV-infected and other immunocompromised kids, but the focus of the meeting was on healthy kids. It wasn't on high-risk kids, and there aren't all that many data. And of the data which are there, many of them are unpublished right now. So we did touch upon it, but there wasn't

extensive discussions on it.

**DR. LEVIN:** I mean, that question -- the reason for raising it is to think about what studies might be useful in that area.

**DR. FUKUDA:** Yeah. When you see the document, there are many other studies which would clearly be useful, and a lot of these fall out again into the safety and effectiveness arena in specific groups, specific high-risk groups, and in young kids in general. But I think that more studies in HIV-infected and other immunocompromised kids would definitely be welcome. And you know, one of the big questions is whether live-attenuated flu vaccines pose a risk for that group, in particular. And I think this is one of the issues that will be revisiting back -- when we come back in September and we get to look at some of the other safety data.

**DR. MODLIN:** Questions?

(NO RESPONSE)

**DR. MODLIN:** Thanks. Keiji, why don't we go onto supply?

**DR. FUKUDA:** Okay. Well, I'm going to bow out of this

and just turn this over to Ben Schwartz, but let me just segue into this whole discussion that we're going to embark upon now.

As all of you know, we had a severe flu delay -- flu vaccine delay last year for the 2000-2001 season, and in response to that situation, ACIP issued supplemental recommendations, both on July 14th and on October 6th in two separate MMWR issues. I think that one of the things we've been trying to do at CDC, both at the National Immunization Program and at NCID, is to look at what the effect of those recommendations were. Right now we're not certain. I do want to point out that, in a big sense, we did dodge a bullet last year because it was a mild season. And as you know, we can't prognosticate what the upcoming season is going to be, but it was a mild season last year.

Nonetheless, this issue engendered a firestorm of comment, both from physicians, from other -- from vaccine recipients. There was a GAO investigation. There have been many congressional inquiries and so on. So what we're hoping to do in the next hour or so, hour and a half, is to get an update on what the supply

situation looks like for this year and then to lunge into a discussion on some potential recommendations. So I'll stop there.

**DR. MODLIN:** Ben, are you leading off or --

**DR. SINGLETON:** I'm going to lead off with an update on influenza vaccine utilization, showing some of data from last year and what updates we have since then and some early data from what happened last year. And that will be followed by Dennis O'Mara with an update on the supply situation and then L.J. Tan from the AMA, and then Ben Schwartz will talk about the draft document and recommendations.

We're going to talk about vaccine coverage trends through the 1999-00 season, preliminary coverage data from last year, an update on reported places of vaccination, and then I'll summarized.

This graph I showed last year just basically shows the vaccine coverage trends in different age groups. The red is people 65 and over; the blue is people 50 to 64; and the green is people 18 to 49. There's two different surveys, the Behavioral Risk Factor Surveillance System and the National Health Interview

Survey, represented here. They give similar results. The updated data is in that dotted line up to the red. That's from the National Health Interview Survey. It's the dotted lines up to the top right. The preliminary data from the National Health Interview Survey for interviews conducted January through June for the years 1997 through 2000 were released by the National Center for Health Statistics. And the vaccine coverage rate in 2000 among older people was 68 percent and was about 23 percent in people 18 to 64. I didn't break that data into high-risk groups, but we do have that for 1998. It's not on this graph, but it was published in the April ACIP recs. And vaccine coverage was 43 percent for high-risk people age 50 to 64 and 23 percent for those at high risk, age 18 to 49. This trend in data through 2000 in older people indicates a possible plateauing. Between 1989 and 1995, vaccine coverage basically doubled; whereas, from 1997 to 2000, it's increasing gradually at about one percent per year, indicating that there may be a plateauing that happened through that time period. And because of the 12-month recall period where people

asked, each survey year's data represents primarily vaccinations received in the prior flu season.

This is another graph I showed last year and I've added a line. This basically shows the number of influenza vaccine doses produced. And what I want you to focus on is the dark-blue line, the third one down, which is an estimate of the net doses distributed in the U.S., reported by the manufacturers. And then the light-blue line is an estimated number of total adult doses. That's based on the survey data taking the coverage times, the population. And so in 1999, we estimate about 60,000 -- 60 million adults got vaccinated. Now, it tracks fairly well with the net doses distributed when you take into account that the data in those light-blue lines does not include doses that went to children, military, or institutionalized populations.

I'm going to switch now to some preliminary influenza coverage data from last year. Some data was kindly provided by Dr. Steve Black at Northern California Kaiser, preliminary analysis of the Food Net Survey which is being led by Carolyn Bridges and Scott Harper

of the Influenza Branch at CDC, and data from the Behavioral Risk Factor Surveillance System. We took interviews of people in December, reflecting vaccines received in the few past months and compared to earlier years.

This is data from Northern California Kaiser. This is for target members age 65 and over. It compares the last season to the season before that. On the far right, the vaccine coverage rate dropped from 70 percent to about 60 percent. This is data that includes vaccinations documented by the health plan from September through March. It does not include vaccinations that may have been received outside of the health systems, which may make that difference in coverage not as great. One thing to note is that the number of target members 65 and over did increase by about 30,000 approximately, and that was due to aging of the cohort and recruitment of new members.

This is a similar table for high-risk children, and the coverage rate here dropped from 31.5 percent to about 29 percent. But notice that the number of high-risk children that were targeted also dropped from 38,000

to about 19,000 and that was a deliberate effort of the health plan to target the higher-risk children and to focus more on the older adults. So they did achieve about the same coverage, but they narrowed the focus of who they're targeting. And I see for both of these -- There were similar results found for high-risk adults under age 65.

What Kaiser did do -- A lot of their vaccine clinics were delayed because of the vaccine supply. And what they did to try to maximize vaccination of high-risk persons of all ages was sending reminder brochures in late October and they did automated phone calls in November and early December to target members who had not received vaccine prior to that.

I'll switch now to the second data source that has been analyzed. This is the Food Net Survey. In 2000, influenza vaccine questions were added. This is an ongoing monthly telephone survey. It accesses the rate of self-reported diarrhea and risk factors for food-borne illnesses and it has randomly-selected individuals of all ages included in this sample. And the catchment area covers about 11 percent of the U.S.

population. Influenza vaccine were added relating to receipt and timing for vaccination and reasons for not being vaccinated. What I'm going to show here is just some preliminary, unweighted analysis from data from December and January, 2001 interviews and it only includes persons with complete data.

There's a lot of information on this. I'll walk you through it.

This is the preliminary unweighted results. The first bullet shows that there were 2,011 persons with complete data, and among that group, the reported influenza vaccination rates ranged from 60 percent in people 65 and over to 28 percent in high-risk people under age 65 and 12 percent in non-high-risk persons.

Now, among the 447 reported vaccine recipients, about 60 percent were aged 65 and over or reported high-risk and were a younger age. That percent varied from 67 percent among those vaccinated before December to 74 and a half percent among those vaccinated in December.

I just need to point out that this is unweighted data and the age distribution of this unweighted sample may not reflect the actual age distribution in the target

population. So these need to be viewed with caution. In addition, those statistical tests of significance were performed because the data was unweighted at this point.

Looking at the month of vaccination reported by vaccinees, 71 percent of the people who reported vaccination for last season were vaccinated in November or December.

Some preliminary conclusions are that a large of proportion of vaccine received in November and December was received in November and December. That's consistent with what we know about the supply. A higher proportion of doses were received by those at high risk in December compared to the earlier year. There's various explanations of that. This is a preliminary finding, so we shouldn't read too much into it at this point. It's unclear whether high-risk persons received a higher proportion of all vaccines administered compared to prior years. There's not data for earlier years in the Food Net to compare at this point.

I want to shift now to the Behavioral Risk Factor

Surveillance System. What I did was take persons who were interviewed in December 2000 and compare that to persons interviewed in December of 1999. This is in 18 states that did ask about flu vaccination in their 2000 survey. And what I've shown here is broken out in different age and risk groups and just show the vaccine coverage in 2000 compared to 1999 and then relative percent change between '99 and 2000. So, for example, in people 65 and over, coverage dropped from about 67 percent to 62 percent. The last two rows show people who were either 65 or over or had diabetes and then other people. We couldn't identify other risk conditions other than diabetes. So this is not a real clean comparison here, but just looking at the relative percent change, there was a larger drop among the people who are under 65 without diabetes compared to the known high-risk people.

Sort of the bottom line, though, is what percent of vaccine went to high-risk people, what impact did the ACIP recommendations have. This data just shows December interview data from '95, '97, '99, and 2000. And 45 percent of those in 2000 were in the two high-risk

groups we could identify compared to 38 percent in the prior year, but in years before that, it was a similar ratio, 43 to 44 percent.

The final data I'm going to share -- this was shown last year. This shows where people reported receiving their flu shots related to the 1998-99 flu season. Just to refresh your memory, in people 65 and over, about 63 percent reported receiving the vaccine in a doctor's office and about 33 percent of people 18 to 49 reported receiving it at their workplace. Some new data since last year, we analyzed people with diabetes. This shows the 18- to 49-year-olds with and without diabetes, and the proportion of those vaccinated at a doctor's office or workplace, and what you see is that people with diabetes in this age group were more likely to receive vaccine at a doctor's office and less likely to receive it at the workplace.

What I did here is just take the vaccination coverage rates by age group and multiply it by the census data to estimate how many doses were received overall, about 80 million, and then broken out by where those were received based on the previous data. What you see is

that about 46 or 47 percent of vaccine doses received among adults were received in doctors' offices and about 19 percent in the workplace and then a scattering in other places. The dark-blue lines represent the doses estimated to have been received by people age 65 and over, and you see that half of those doses received in doctors' offices were among the elderly, whereas only less than three percent of doses received in the workplace went to the elderly. And about a third of doses received in health departments, other clinics, and stores were received by elderly.

It's possible that in subsequent seasons increasing number of vaccines have been delivered in stores and work places and other sort of nontraditional settings, and we're going to be able to look at that in the 2000 BRFSS and selected states asked this question again about where people receive their vaccine. And in 2002, we'll have that data for all states.

For the 2000-01 season, there are examples where a larger proportion of high-risk persons were vaccinated in store settings than in previous years in response to ACIP recommendations. One large national

commercial provider conducted a random sample of its influenza vaccination clinics that it conducted in retail settings, and they found that 64 percent of the persons they vaccinated in these retail settings were age 65 and over and another 23 percent were age 50 to 64. And they feel that the majority of the younger people vaccinated had high-risk conditions, although they don't have data collected to verify that.

Just to summarize, before the 2000-01 season: there's a possible plateau in vaccine coverage among the elderly; there's been a steady increase in the total number of adults vaccinated; and up to one in five flu shots going to adults went to adults under 65 in the workplace.

For 2000-01, this is a very preliminary summary, but there is evidence from the Food Net that later vaccination did occur. There may have been a moderately lower coverage among high-risk. This needs to be verified with additional data from people interviewed later in the year -- later in 2001. And maybe a small shift in the ratio of doses that went to high-risk versus healthy, but this data is preliminary

and hard to interpret at this point.

So that's a wrap-up on the influenza utilization. So Dennis O'Mara is going to next talk to us about the possible influenza vaccine supply for this year. Any questions quickly while Dennis is coming up?

**DR. MODLIN:** Why don't we hold the questions, if we can, until we've completed the presentations.

**DR. O'MARA:** Good morning. My name is Dennis O'Mara. I'm a public health advisor with the National Immunization Program. I work in the Immunization Services Division where I am the Associate Director for Adult Immunization. And for about the past 10 months or so, I've been working almost exclusively on issues related to vaccine production, distribution, and administration -- influenza vaccination production, distribution, and administration. Here on my cover slide is a list of colleagues who have assisted in collecting and pulling together the information and data that I'll be sharing with you this morning.

Before we talk about -- and I'll be talking about preparations that we and our partners are making to prepare for the upcoming season, but before we do that,

I want to take a couple of minutes and review some of the lessons that we learned last year.

First of all, we learned that the vaccine supply is fragile. Whereas, prior to last year, there were four manufacturers making influenza vaccine, this year, as we know, there are now -- last year there were only three and this year there will only be three. And the vaccine production process is very complex and involves passing through and achieving many milestones and problems or failures at any one of those milestones can greatly reduce or totally jeopardize the production. The companies are faced with the challenge of essentially producing a new vaccine every year. So, again, the production part of the process is complex, and the companies have to adhere to a variety of regulatory issues and to also comply with the FDA's Good Manufacturing Practices. And it turns out that making flu vaccine is nearly, from what the companies tell us, a year-round process. And when they finish one year's production, it's virtually time to turn attention to the next year's effort.

Making flu vaccine, at least at this point in the U.S.

for the U.S. market, is an egg-based type of system and that adds even more challenge, difficulty, and complexity to the process. And of course, the FDA also faces a lot of challenges in doing all of the testing and developing the potency reagents and so forth that they have to do.

The vaccine distribution process is also complex. It's primarily a private sector process. It involves not only the vaccine companies, but distributors and other types of resellers. And distribution, as we know, is subject to a lot of market forces, sort of supply and demand, but that supply and demand process does not always match up with public health needs as we have seen recently.

And the public sector is involved in distribution -- purchasing, distribution, and administration only to a limited extent, so that, unlike in childhood vaccine, the public sector is not in a great position to be the gap-filler when there are problems at the local level.

We know that targeting vaccine to high-risk individuals is challenging as well. We learned that, if we didn't already know it. We know that in order

for that to work, vaccine providers and recipients sort of need to change their approaches, their behaviors. Providers need to be willing to focus almost exclusively in the early going to provide vaccine to individuals with medical conditions that place them in high-risk complications from influenza and to defer patients who are coming to them seeking vaccine who do not have these high-risk conditions. And that is asking them to perhaps do something that is not necessarily in keeping with their -- with their desire to serve every patient as well as they can. Recipients or those seeking vaccine also need to perhaps change the way they approach things. We certainly want the high-risk individuals to come forward early in the process and seek out vaccination and not wait; and at the same time, those without risk conditions, we want them to defer until later in the vaccination season when vaccine is usually more plentiful.

State and local public health departments are -- have tried and are trying and will try again this year to assist in the targeting process, but they have limited infrastructure to do so. So that is also a bit

of a challenge for us. And then reminder systems, we think, are important, especially to try to target those with risk factors and a lot of providers don't have those reminder recall systems in place.

The supply and demand we say is difficult to match up sometimes. There's uneven distribution, probably in most years, that occurs, but the duration of the unevenness varies from year to year. And of course, last year it was extensive and when that happened, it sort of threw the whole system into some chaos. Companies produce and distribute vaccine at different rates, as we know. So when providers receive their vaccine supply will depend, to a great extent, on which company or distributor is providing it.

We also learned that communications are essential, and the feedback we got last year from at least some providers is that at the operating level, at the individual patient -- I'm sorry, provider office level, many doctors weren't getting the information and the messages that we were trying to send out about what was happening and what we recommended. So we are obviously going to be working on that much more

extensively this year.

So to try to address some of those issues and make use of the lessons we learned last year, we are intending this year trying to develop voluntary approaches throughout the entire system of production, distribution, and administration to target high-risk patients early in the vaccination season. So we want to try to work to get vaccine shipments directed to providers who are seeing high-risk patients. One possible way to do that is for companies, vaccine companies, and distributors to try to collect information from their customers about the extent to which they are serving high-risk patients and to try to then triage orders accordingly. That is fraught with some difficulties and we are going to be talking with distributors and the companies more about that. That's one option.

Aventis Pasteur announced early on that what they were going to do this year, starting in September, is to fill each customer's order to 25 percent -- I'm sorry, to at least 25 percent of each customer's order, thereby giving each of their customers a quantity of vaccine

early on that they could use to begin vaccinating their high-risk patients, and that sort of addresses the presumption that many share, that most providers do see and serve at least high-risk patients.

Another thing we can do is to work with the operators of mass clinics to tighten up their operations and to get them to follow our best practices, which we have already redone this year and distributed widely. And we also have a patient self-screening form that we will redo and distribute as soon as this meeting over after we learn about the results of your deliberations today, so that in the end, these mass clinic operations will focus -- will also focus almost exclusively in the early going on vaccinating high-risk patients, and I think we can work with these operators and get them to do that. We've asked the states, as they develop their plans, to put in some -- to put together as part of the plan some criteria by which they and the local public health colleagues can work out a way to serve -- help redistribute vaccine where it's appropriate and possible to do so where there are areas with uneven distribution, where some

providers may have excess vaccine and could share that with others who have very little or none, especially in the early going. So, again, focus could be maintain on reaching the high-risk.

And finally, we would like to try to provide a little bit more explicit recommendations and some of that. Again, we got some feedback that some of the -- some of the providers, that they would like to see some clearer types of recommendations. Dr. Ben Schwartz is going to talk about that in a few minutes.

So what have we been doing to prepare for the upcoming season? We've been trying to firm up our existing partnerships and to make new ones where it's appropriate, and we have done that. Having those partners has really helped us to do a better job of planning. And in turn, the planning has informed our efforts to communicate. We know a lot more now about what to communicate and with whom to communicate, and we're then monitoring the whole process, the whole system, to try to keep track of what's happening and to further adjust our efforts.

In the partnering arena, here's a partial list, at

least, of the types of groups and organizations that we've been working with and they have all been very responsive in my view, very positive, very willing to work with us and with each other, and I think, as a result, we're much further along this year than we were last.

In terms of planning, as you probably know, AMA sponsored a meeting in March, March 27th, where representatives from most of those categories of groups and organizations attended. It was, in my view, a very positive meeting, a very useful meeting, and Dr. L.J. Tan from the American Medical Association is here and will talk in a few minutes about that meeting and what went on there. I'll just say that we're talking about having a second meeting in August right before the vaccination season kicks off to make sure that all of our plans are in place.

We've asked the health departments, the state health departments, to develop contingency plans and they are doing that. We discussed these with them at the National Immunization Conference last month and I think they're all making good progress in that regard.

Every year, CDC develops vaccine contracts through which state and local health departments can purchase vaccine. Last year, we had a contract that allowed the states to purchase up to two million doses. This year, we've increased that to try to put a little bit more vaccine into the hands of public health in case we did have a delay or shortage so that we could -- so that they actually could attempt to fill gaps to a greater degree than last year.

We are having discussions and are planning meetings with both the distributors' trade organizations -- there are two of them, HIDA and HDMA -- and discussions and meetings planned also with the vaccination contractors. These are the companies that have popped up all over the country that contract with commercial concerns like grocery stores and drugstores and the like to put on community-based mass clinics.

In terms of communication, Walt Orenstein wrote a letter to providers which went out last month. It was widely distributed. We developed a chain of mechanisms to -- working with our partners to distribute information and we are now working on a

letter, a similar letter, to pharmacists. We are preparing and distributing biweekly bulletins to partners, and in all this material, we are asking our partners to re-distribute to make sure that these messages and this information gets into the hands of their colleagues, their members, and their constituents. We have a website now at NIP where we will post a lot of useful information. I'll give you that address at the end. We continue to have ongoing calls and meetings with partners. Some of those are scheduled on a regular basis, some are ad hoc as needed, and our office communications is developing a mass media campaign through which we will attempt to reach the general public once again.

And in terms of monitoring, we are in frequent communication with the vaccine manufacturers, with the FDA. We're going to review the state plans and hopefully be able to give them some useful feedback. It's no longer HICFA now. It's the Center for Medicare and Medicaid Services. We're talking with them, working with them. We have been for years. We're trying to promote the vaccination of elderly

individuals. We're getting feedback from our partners and we're trying to incorporate that into our thinking and planning. And our office communications tracks news media coverage of stories about vaccine supply, availability, and so forth so that we can make sure that we're doing a good job communicating with the public and, if we're not, we can adjust our communications accordingly.

Now what I want to do is turn to sort of the centerpiece of my presentation, which to share with you some data and information that the vaccine companies have shared with us and are authorizing us to talk about in the aggregate. We're going to talk about 1999 which we'll call our benchmark year. I have been cautioned by my colleagues at FDA and elsewhere that no single year is actually an usual or average year when it comes to producing influenza vaccine. Every year has its own unique set of challenges, difficulties, and circumstances. We'll use '99 as the benchmark for this discussion. The figures from '99 and 2000 are aggregate monthly distribution of influenza vaccine and the figures for 2001 are projections.

Now, we should caution that you can use these figures as a rough guide, but they are, indeed, projections. They're current as of late last week, but they could change substantially as the production process and distribution progress.

So my segue on this was going to be that I have good news and bad news, and normally the person bearing good news and bad news gives the audience the option of which they would like to have first. I'm not going to give you that option. In fact, you've already heard the bad news first, which is that, unfortunately, we're going to have to expect a delay again this year in the distribution of the influenza vaccine supply. The good news, however, is that according to the data we've collected so far, the delay should not be as extensive as it was in 2000. There's more total vaccine projected to be produced in the coming year than in 2000 or 1999, some 84 million doses total projected, right now at least. And I think that, as I've just been trying to describe to you, we and our partners are in much better shape, we're much better prepared to deal with this in the coming year than we were last year.

So here is monthly projected vaccine distribution for the coming year. You can see that July and August and in December, a little bit of vaccine is coming out. The peak months for distribution are going to be September, October, and November, and the peak of those is October by a slight margin. Here we see the same data as cumulative percentages. So, for example, in October, the companies estimate that approximately 64 percent of the total production will be distributed. And here we are looking at '99, 2000, and 2001 data. The '99 data in gold, the 2000 data in light blue, and the 2001 in dark blue, and as you can see, the 2001 projections sort of track partway between '99 and 2000. So, for example, in October, we would expect that slightly more than half the vaccine will have been distributed -- I'm sorry, 53.5 million doses will have been distributed compared to about 75-plus in '99, and only 26 million last year.

And here are the cumulative percentages: again looking at October, slightly more than a third came out in October last year; virtually all of the supply came out -- was out by October of '99; and this coming year,

not quite two-thirds is anticipated to be out in October.

So what are the some of the potential problems that we could encounter with this delay that we know anticipate? First of all, even before we get to the point of distributing vaccine, we could, or the companies could, encounter, unfortunately, production difficulties. And as I said, a problem or a failure at any one of the milestones could seriously jeopardize the supply. Also, there could be uneven distribution of vaccine, and as I said before, there probably is every year, but the longer that unevenness exists, the more difficulty and problems that it causes and the attention that it gets. We will try and the state and local departments will try -- all of our partners will try to minimize the unevenness. There could be some early vaccination of young healthy individuals. Of course, all of our effort and focus and messages will be -- will be trying to encourage providers to vaccinate high-risk individuals first and both seeking vaccine to come forward early if they have high-risk conditions or wait if they don't.

And hopefully, our efforts will minimize the number of healthy individuals being vaccinated early.

Although, one can imagine that probably in some places at some times that will happen. If it does, we and our partners will try to deal with that and also try to keep it in perspective because I think that this year we will see some change and some movement towards a better focus on high-risk vaccination early in the season. And then there could be some price speculation as happened last year and not -- this is a free-market-type of operation. I don't know that there's a whole lot that we can do about it. Hopefully, with a minimum delay in distribution, we won't see a price -- we won't see price speculation or it will not happen extensively and will be limited in duration.

So, in summary, we've projected a delay in distribution of the issue of vaccine. It shouldn't be as severe as last year. More vaccine should be available than in the previous two years, and we and our partners think are going to be better prepared to deal with it. We're proposing actually a series of voluntary approaches throughout the system to try to ensure that flu vaccine

gets directly to high-risk individuals early in the season and we and our partners will continue to work together, to plan, to communicate, and to monitor the whole process.

Here is the address for the CDC website. That is effective actually tomorrow. I would be pleased to answer any questions -- or I guess we're going to hold questions.

**DR. MODLIN:** Mr. O'Mara, thank you. Why don't we Ben, are you --

**DR. SCHWARTZ:** It's going to be Dr. Tan.

**DR. MODLIN:** Okay. Dr. Tan from AMA.

**DR. TAN:** Now, on behalf of the American Medical Association, I appreciate the opportunity to present this to this prestigious body here.

I also have some breaking news from the AMA House of Delegates meeting that I'm going to present at the end of this just to highlight the importance of this issue and also the stringent attention that's being placed on this issue by our physician members outside.

The AMA represents about 300,000 physicians and physicians-in-training, and on their interim House of

Delegates meeting in December 2000, the AMA passed a Substitute Resolution 416. These are some of the results that came out of that resolution, the first being "that our AMA work all with appropriate agencies and organizations, including vaccine manufacturers, to prioritize the distribution channels for influenza vaccine to assure the vaccine is available to patients in accordance with CDC guidelines for high-risk patients." That's one recommendation.

Another one was "that our AMA explore options for appropriate oversight of the supply, distribution, and marketing of flu vaccines by appropriate agencies." As a result of that, the AMA and the CDC's National Immunization Program co-sponsored a meeting on March 27th that Dennis has already referred to, and we invited participants -- almost all stakeholders that are involved in either the production, the distribution, and/or the administration of the flu vaccines. These participants included manufacturers, all of them, many distributors, many contractors, state and local public health departments, the pharmacy practice, state medical societies, national specialty medical

societies such as the ACP, AAP, AFP, immunization managers, as well as government agencies, of course, the CDC, the FDA, and the now newly-renamed CMMS.

The idea of this meeting was to provide an opportunity, and in fact, a fairly unique one, for participants to understand influenza vaccine supply, distribution, administration, and the circumstances that led to delays in the flu vaccine availability in 2000-2001.

The AMA felt that this was extremely important because we obviously felt that a lot of the problems that resulted in that substitute resolution coming to the House floor was due to a lack of understanding about the vaccine and its distribution and its manufacture.

And also, by bringing all these stakeholders together, we felt that this would be a very unique way to discuss opportunities to work together to prevent further delays from happening -- and as I have just found out, I guess that's not going to happen -- and to minimize any public health impact in the event that another delay or shortage occurs.

So this is some of the perspectives from our physicians on the ground regarding the 2000-2001 delay and this

came out in our meeting. And the wonderful thing is that the NIP has been very good at addressing a lot of these perspectives that our physicians provided. One of the major ones that our physicians were very upset about was that providers serving general populations were receiving vaccine while the physicians serving high-risk populations were not. Physicians, as I've just mentioned, have little understanding about the ordering and distribution process and I regret to say they still don't. Physicians do not normally order influenza vaccine until the season has arrived and physicians were caught between the distributors' delay in shipment and their patients' demands for vaccines. It was extremely painful for a lot of our physicians to have to refer their patients to the Giant down the street or the grocery store down the street or the Walgreen's down the street which had vaccine when they did not.

Physicians also believe -- and this, of course, I realize is a very difficult issue -- that they should be prioritized first to receive shipments of the vaccine. Based on some of the studies that have been

presented today, physicians do administer most of the -- I think 60 percent of high-risk populations are served by physicians in physicians' office, and this, again, as Dennis alluded to, physicians felt that they were notified too late about the revised ACIP recommendations. And it was not just the revised ACIP recommendations, physicians felt generally that they were totally out of the loop in terms of communications regarding the vaccine. They felt they had no idea the delays were happening. They felt that the way they found out information was when they read in the press and there was never an opportunity to provide a heads-up to the docs out there. And as such, they were caught with, quote, unquote, "their pants down" when their patients came in for their vaccinations.

The third point down was a major issue for a lot of our physicians. They felt that other providers were not vaccinating high-risk persons first and they also felt that despite the release of the best practices late last season, that there was still a lot of providers who were not abiding by those best practices and still vaccinating the lower-risk populations first.

And finally, the physicians felt that terminology used in communicating the problem was ambiguous, and this goes to back to that whole conspiracy theory that has been brought up several times. When you use terminology that's ambiguous, people think conspiracy. When you say "delay," what it actually translates to regionally and to our physicians is a shortage. And so the question here -- you know, physicians start saying, well, I don't have the vaccine, so it really doesn't matter if it is a delay, it really is a shortage. And when you start getting the conspiracy theories out there, then you get escalating paranoia and then you get these resolutions hitting our House floor, which then we have to act on. Some of the findings from this meeting, I think, most of you are fairly aware of. I have generalized them. They are specific points. This meeting was wonderful in that they were very specific points that were brought up that can be addressed, but I'm not going to go through all those because it was a six-page list. But I have summarized them in terms of a general statement here. The most important finding, I think, that we are trying

to communicate out there to our physicians is that when vaccine supply is sufficient -- and this is critical, is sufficient -- the current production and distribution system, while it's not perfect, is adequate. Practical solutions, however, are needed to assure that adequate supplies are available, and there were very specific ideas mentioned such as, for example, providing manufacturers, quote, unquote, "incentives" for when there's over-ordering, improving reimbursement for vaccinations. Because if there's improved reimbursement, you might be able to get more physicians administering it and you get more people coming into the market to make the vaccine, things like that. An appropriate contingency plan, however, is needed when the vaccine supply is delayed or insufficient. And we at the AMA agree with the CDC that this should be a voluntary plan that's executed by all the stakeholders in both public and private sectors. So we highly agree with the CDC in the sense that we must all collaborate at both the public and private levels to build and implement this voluntary plan.

This is critical, the first point here, that improved communication is necessary among all stakeholders involved with influenza vaccine production, distribution, and delivery. And in fact, while this communication is improving, a problem has already arisen this season and that has actually led to some of the actions that was taken by the AMA yesterday on the House floor that I'll quickly talk about at the end of this. All information must be made available to providers and other stakeholders as quickly as possible. Now, I understand, and this came out at our meeting on March 27th, that there is a priority data that's involved in this and that, therefore, it is difficult for sometimes the manufacturers to divulge their production as time goes on. However, the AMA does want to urge that whenever and as soon as possible this information is available, it needs to get out there to everybody so that the messages can be coordinated and provided to the public and to the providers. And in this regard, we felt that the CDC is best suited to collect and disseminate information when a problem in vaccine production or distribution occurs and to

implement this contingency plan.

As a result of this meeting, the AMA prepared a Board of Trustees Report Number 36 yesterday. The initial recommendations on this Board of Trustees are as follows -- and I'll just quickly read through them -- that the AMA will continue to work with the CDC to organize a second roundtable meeting of influenza vaccine -- Dennis has already alluded to this and we're hoping that this will occur in the third week of August; that the AMA will communicate current ACIP recommendations and whatever is pending from this body on the flu vaccine to physicians and to assist the CDC in disseminating its informational letters and bulletins. We have already developed a website is, as you can see, up there, that is updated on almost a daily basis. Whenever anything comes out, it goes up and it also goes out to our physicians. The AMA has very strong communication vehicles to reach our member physicians as well as to our members of our Federation, our Federation being all of the national and state and local medical specialty societies. We have e-mail blast fax that goes out to them. In fact, Dr.

Orenstein's letter from May 18th, the flu bulletin from May 29th, all went out on the day that we received them. So we are working very closely and we enjoy working very closely with the CDC on trying to get this information out to our providers.

The AMA will monitor progress in developing this contingency plan and also in developing a plan to respond to an influenza pandemic in the United States. The AMA and its physicians feel that the docs are going to be on the front line in a pandemic and that the docs should therefore be involved as closely as possible in the preparation of a pandemic plan. I think the delayed, quote, "shortage" from last season exposed a lot of gaps in pandemic planning, and the AMA sincerely hopes that that will be addressed in future planning of the pandemics.

And the fourth and final, as of two days ago, recommendation was that the AMA will support mechanisms to include influenza vaccine supply to ensure goals of Healthy People 2010 are achieved. This is extremely important to the AMA, and one of the reasons for this was that we have now been getting a

lot of reports from our physicians on the ground that the cost of vaccine -- the flu vaccine has gone up and the reimbursement levels have not. A lot of our physicians have now told us that it is now a loss for them to administer the flu vaccine, and many of them have said that they're not going to do it. And what they will do is now refer patients -- healthy patients to public health departments. This is, of course, something we don't want to see happening. So very primary on our list of things to address at this August meeting as well will be issues of reimbursement for the vaccine from Medicare or from the CMMS.

Unfortunately, when this report went to the House Floor yesterday evening, there was about 30 minutes of very angry testimony from the floor and this had to do with the communications issue. The May 18th letter from Dr. Orenstein was sent out to all our providers who then abided by the instructions to go ahead and order vaccine early. So they then, following receipt -- reception of the letter, called their manufacturers and asked to order vaccines, whereupon, they were then told that preorders had been closed for several weeks now and that

they could no longer order vaccine. There was a lot of testimony on the floor regarding this issue, that, again, it goes back to this conspiracy theory. You know, there's a letter going out telling us to order vaccine. We call the manufacturers and they tell us, oh, no, the preorders are closed because we sold everything we have. And this, again, for the physicians smacks of, unfortunately, conspiracy. And as a result of that and a couple of other little issues, the House added a fifth recommendation that I will now read to you. I don't have that available because I only just got this morning, and the recommendation is that our American Medical Association will immediately investigate issues, including cost, reimbursement, availability, and distribution, which may adversely affect the ability of physicians to provide flu vaccine to their patients in the upcoming 2001-2002 flu season. Unfortunately, what that means is that that puts -- it may put our Washington office into effect, and we're trying very hard to work with the CDC and, hopefully, we'll be able to continue to work on this issue at a voluntary level and not have any kind of additional

action that may be putting a sledge hammer to, hopefully, what's just a small mole hill.

Again, thank you very much for hearing us, and I appreciate the opportunity to present.

**DR. MODLIN:** Thanks, Dr. Tan. Members of the Committee are being supplement our recommendations from February and specifically to supplement them along the lines of developing more specific guidance regarding vaccine distribution and administration we've done in the past.

Ben is going to take us through the proposed supplementary language, and then we will open it up for comments or questions and discussion at that time.

**DR. SCHWARTZ:** We've had a good introduction to the issues that need to be discussed this year in order to deal with the projected delay of flu vaccine distribution. And what I would like to do in the next few minutes is to describe the draft recommendations that have been worked on by a group of us. The group consists of folks at the National Immunization Program, from the Influenza Branch and the National Center for Infectious Diseases, from the CDC Office of

the Director, most notably Dixie Snider and Dave Fleming, who is the Deputy Director, but still hasn't totally put aside his ACIP hat, and also, we've received input from the Food and Drug Administration and have had input from Bonnie Word from ACIP and from the Flu Working Group.

Before going through the specific recommendations that we've drafted and that we would like to put out for your consideration, I would like to very briefly review last year's recommendations so that we can see where we have been and then where we're going and how the two are a little bit different.

I've abstracted the recommendations from the October 6th, 2000 MMWR and I've reordered them to characterize the recommendations as a numbered focused on medical care providers, which include focusing on high-risk patients and health care workers, determining local priorities so that available supply can be matched with those local needs, continuing vaccination through December and beyond to begin vaccinating those who are not at high risk in December, providing pneumococcal vaccine and not forgetting about high-risk children.

For campaign organizers, there were two recommendations dealing with scheduling of those campaigns and focusing them on those at high risk. And for health care organizations, to use proven effective techniques in order to increase vaccination of high-risk persons.

Just like Dennis characterized the programmatic lessons learned in his presentation, I would like to focus on some of the observations and lessons learned related to the recommendation process, but before doing so, I would like to issue a caveat, and that caveat is: first, that we have little data that have yet been analyzed to look at how vaccine was used in the last season; and secondly, that there's no experience from which one can't derive the wrong lessons.

But with those caveats, I think it's been clear from our experience and from the things that Dr. Tan said as well that there's a need to make stronger recommendations, more definitive recommendations earlier in the season. And clearly, publishing recommendations from the ACIP in October is not optimal in terms of leading to modifications of practice.

Secondly, providers' ability to focus vaccine toward high-risk individuals may be limited. It may be difficult for providers to turn patients away who seek vaccination while many vaccine doses that were used in the past have gone to settings where they are primarily given to lower-risk individuals, and Jim provided this information in his presentation on work site vaccination, particular.

Third, some providers last year had vaccine early while others had none, leading to complaints that high-risk patients could not be vaccinated, as well as concerns by professional societies and Congress. And these concerns have led to some proposals for a greater government role, including legislation that has been proposed for Congress.

Redistribution of vaccine, which we've already talked about a little bit this morning, between providers or health departments appeared to be uncommon last year. We pilot-tested a CDC website which could be used to facilitate communication between those who had vaccine and those who needed vaccine, and I think the CDC experience was that that was not entire successful.

And finally, while vaccination in November and December was increased compared with prior years, the data particularly for Northern California Kaiser suggested that overall coverage dropped and little vaccine was ordered for December delivery. The CDC guaranteed nine million doses of vaccine that was made available for distribution in December; and from those doses, only about one and a half million were actually distributed.

With these observations and lessons in mind, I'd like to describe the approach that we took to developing draft recommendations for your consideration this year, and this process occurred pretty much over the past week. So it was fairly rapid.

We state in the draft recommendations an explicit goal, and explicit goal is to create a prioritized system where persons who are greater than or equal to 65 years old and who have chronic illnesses and the medical personnel who care for them receive vaccine that is available early. In addition to this explicit goal, there are several implicit goals which are important, both for the short-term, for this particular influenza

season, but also for the longer term as well. Those goals are to maximize coverage of those at greatest risk for severe influenza complications and to increase coverage in high-risk and targeted groups in order to achieve the Healthy People 2010 goals. And I think it's important that even in a year of vaccine delay that we don't forget those goals which involve increasing our vaccine coverage markedly, and as Jim points out, with the increase having appeared to plateau over the past couple of years, this is particularly important that we not forget our longer-term priorities.

The approach that we are taking in formulating recommendations for this year is to consider the influenza vaccination system, where our goals are most likely to be met if providers, the public, manufacturers, distributors, and vendors, and health departments all work together to achieve common immunization objectives. Whereas, last year, our recommendations were focused primarily to providers, with several recommendations for those who organize mass campaigns. This year, we feel that we can most effectively accomplish our objectives if we include

all the players in the system, and Dr. Tan has very well stated the belief from AMA that that is the correct approach.

The draft statement which has been formulated has been passed out to members of the ACIP, as well to the liaisons, and I would like to very briefly review the format and the contents of that because I'm not going to go through the whole draft statement but to focus on the recommendations.

The statement begins with an introduction and a summary of the recommendations for those who may not wish to read through the entire article. There's a very brief background of the delay that was experienced in the 2000-2001 season and several of the manufacturing issues have been highlighted, including the need to make a new vaccine each year.

The projections for 2001-2002 that Dennis presented are included, along with some of the data that Jim has shared with us earlier today from Food Net and from the Behavioral Risk Factor Surveillance Survey. A brief discussion is provided and then, following that, the explicit goal of increasing early vaccination of those

who are at high risk and health care providers who take care of them and then the recommendations. I'd like to now move specifically to those recommendations. As I've indicated, the recommendations are divided into recommendations specific for the various participants in the immunization system, and the first group of recommendations focus on those for health care providers. They are that: "Providers should actively target vaccine available in September and October to persons at increased risk of influenza complications and to medical people who care for them," and there is a table included in the draft statement defining those high-risk conditions.

The text following this recommendation goes on to suggest that reminder recall systems may be an effective way of actively identifying and bringing in high-risk individuals for vaccination and indicates that there are now data from a national survey suggesting that the majority of providers have the capacity to do reminder and recall, although many do not choose to do so.

The second recommendation is that: "Providers should

continue vaccinating patients, especially those at high risk and in other target groups, through December and later as long as vaccine is available." The text under that includes definitions of those targeted groups, including those who are 50 to 64 years of age. It mentions that vaccination in December or later will provide substantial protection based on data from the last 19 years would show that 79 percent of the time the influenza season peaked in January or later, and it also encourages health care organizations to assess provider influenza vaccination practices and to provide feedback on coverage, which is a proven effective technique in increasing vaccine coverage. The second group of recommendations are designed for the public, and they state that "Persons who are at high risk, including those who are greater than or equal to 65 years of age or less than 65 who have underlying chronic illnesses, should seek vaccination in September and October or as soon as vaccination is available with their provider." It comments that because vaccine will be distributed to providers at different times, communication is important and that

unvaccinated high-risk people continue to seek vaccination throughout the season.

The second recommendation is specifically to those who are not at high risk and indicates that "Persons who are not at high risk are encouraged to defer seeking influenza vaccine until November and later when additional supply will become available," and this is something new. Last year, we did not discourage those who were not a high risk from coming early and we feel that this year such a recommendation would be warranted. We suggest that people who are unsure of their risk status should contact their provider in order to determine if they should come in early, that others should defer seeking vaccination, and that, again, additional vaccine will be available later, and that providers should develop a system whereby reminders can be sent to those who choose to defer vaccination until later in the season.

The third group of recommendations are focused toward manufacturers, distributors, and vendors. And again, this is something new. This is something that was not included in the prior years' recommendations, but we

recognize the importance of vaccine distribution in being able to achieve our coverage goals, both the early vaccination goal as well as the other goals that I mentioned.

The first recommendation for these groups is that "Distribution of vaccine to work sites should be delayed until November." And we have specifically focused on work site vaccination because, as Jim presented in his data, the vaccine delivered in work sites is less likely to go to those who are at high risk or who are elderly.

Therefore, the recommendations state that delaying distribution of vaccine to work sites other than hospitals or chronic care facilities would make substantially more vaccine available early to providers of high-risk patients and it provides the recommendation then that manufacturers attempt to identify those work site orders which may not identified by the company named but rather by the name of the doctor who is placing the order or that those who are ordering for work sites self-identify and communicate with the manufacturer or distributor

indicating their willingness to receive vaccine later. In addition, because planning these campaigns often occurs early before information may be fully available about production, we think that this may be a reasonable recommendation to make for every year rather than only being a special recommendation for the upcoming flu season.

Secondly, we recommend that vaccine that is available early in the season be apportioned so that some vaccine is distributed to all providers who have placed orders. And I think Dr. Tan stated very well that last year many providers who had high-risk patients were unable to get vaccine early and could not vaccinate those patients. This recommendation would assure that that does not occur.

And finally, we suggest that manufacturers, distributors, and vendors should inform providers of the amount of vaccine and the date of shipment which will allow them to then use strategies such as reminder and recall to bring in those patients who are at high risk rather than just opportunistically vaccinating whatever patient happens to come into the office during

the period of time that vaccine is available.

A fourth group of recommendations, or in this case, a single recommendation, would be focused toward health departments and other organizations, and that is that "Groups that provide influenza vaccine services should develop contingency plans responding to a delay in vaccine distribution," emphasizing particularly the importance of communication among partner organizations and the potential for redirection of vaccine to high-risk persons in the community.

One additional recommendation that I would like to share for your consideration -- and this is not included in the draft that you received yesterday but which we've put together as we accepted comments from the Influenza Branch and also based on discussions with folks this morning, highlighting the importance -- is to add an additional section on recommendations for mass vaccinators. And that recommendation may be that organizers of mass immunization campaigns not in work places -- in other words, at senior centers, clinics, or retail stores -- should make special efforts to vaccinate the elderly and those at high risk of

influenza complications and that informational materials defining the high-risk groups and presenting a rationale for a tiered approach, as well as screening forms that could be used in a campaign, are available from CDC.

So from that brief description of the draft recommendations, I would be interested in your thoughts and comments.

**DR. MODLIN:** Normally, I like to inform the Committee when we have important decisions to make ahead of time. Sorry. I just wasn't able to do so in this instance. We had a lot of information presented to us and we actually have a relatively short period of time in which to deal with it, but we do need -- would like to focus the Committee's attention on the recommendations that we're being asked to discuss and to vote on. But let's open things up now for questions, comments, first of all, from Committee members, and then we'll go around and we'll start with Natalie.

**DR. SMITH:** Yeah. I had several comments, but I'll just start with a couple of them.

One is, I'm afraid you're advising patients to seek

vaccination in September, and I understand why you're doing that. I don't want them to think they have to get it in September -- I mean, obviously, we know the flu season starts much later -- and I'm worried about the pressure on providers and health departments who want it. I notice there's nothing -- what was really helpful last year for states, I think, was that they got the message to delay their mass campaigns till mid-October, because nothing is worse than having to cancel clinics you've already scheduled. And there's nothing in here about -- you know, I know you -- about delaying those clinics or anything referring to that sort of situation. So I think if we're making comprehensive recommendations, we might want to include that, because that was a strong message that we've been putting out already this year.

**DR. SCHWARTZ:** Let me respond to those two concerns. Specifically, with respect to when high-risk individuals seek vaccination, underneath the italicized recommendation is the comment that because vaccine will be distributed at different times, these high-risk folks should communicate with providers

about availability.

I don't know if you think that's sufficient to take care of the concern that people will just show up at the office when vaccine is not available.

With respect to delaying mass vaccination campaigns, I think that for those who are organizing campaigns, a recommendation to wait before publicizing the campaign to assure that vaccine will be available is very reasonable. And Eric France was telling me this morning how last year Kaiser had to keep delaying their campaign and then put out another notice saying we're going to have it these dates and delay it again. So, clearly, that's a problem. However, at the same time, when a mass vaccinator does receive vaccine, I don't believe there's any necessary reason to delay further. So, for example, saying that mass campaigns should defer until November may not make sense if they do receive vaccine earlier than November. There's no particular reason for them to hold the vaccine without administering it.

So I think the recommendation that I propose might be reasonable would be one that focuses on how these mass

vaccinators can target the higher-risk patients when they have vaccine to do so. But I would certainly be open to suggestions and modifications to --

**DR. SMITH:** I mean, at least in the parentheses, you want to include health departments and HMO's and that kind of thing.

**DR. SCHWARTZ:** Sure, yes.

**DR. MODLIN:** Paul?

**DR. OFFIT:** John, I had just one non-recommendation-related question. It's for the group that presented.

Could someone summarize for me why it is this year that we have a delay in distribution of vaccine? My understanding last year was that the problem was primarily in scale-up from seed stocks, growing the vaccine. Is that still a problem?

**DR. MODLIN:** Ben, do you want to respond to that?

**DR. SCHWARTZ:** I think it may be most appropriate if representatives from the company could share some of those issues with us.

**MR. REILLY:** Kevin Reilly, liaison.

I think this year the quantities have been increased.

We also have three manufacturers only where in '99 and prior -- everyone was using '99 as the benchmark year. So you're comparing to a year where there was four suppliers. So the time patent this year is a little bit delayed. There is also release concerns. The yield issue has been overcome and I think we're -- at this stage, we're confident that, as we can be at this stage, delivering the full quantity. I think just so -- and in addition to answering the question, maybe I could take two minutes to step back and pick up on some of the comments about the complexity of influenza manufacture and distribution that have been made. To tie back to the opening speaker on CDC -- from CDC, influenza vaccine manufacture and distribution each year is a very complex activity. We have to realize that this is a new vaccine each year. We start off virtually with new strains from FDA at the beginning of the year. It takes us six to eight months to manufacture the product and, ideally, every single person wants vaccine from mid-August to the first of September. Frankly, that's an impossible task. The typical task that we do achieve is that from mid-August

to the end of October, all of the vaccine is distributed. Clearly, last year we had a major shock on the system in terms of the compounding of a number of factors, the yield factor, the exit of one manufacturer. Frankly, Wyeth Lederle had delays in their manufacture also. So I think we saw a very severe shock last year. I don't think we're fully recovered yet, but we -- each manufacturer is adding more capacity and building more volume into their systems. So I think the overall system is recovering and you can see the improvement already in this year's supply patent.

**DR. MODLIN:** Phil Hosbach, did you want to respond as well?

**DR. HOSBACH:** I defer to Dr. Rubin.

**DR. MODLIN:** Pardon. I just wonder if Dr. Rubin could respond for Aventis.

**DR. RUBIN:** Yes. Fred Rubin from Aventis Pasteur. We fully support these recommendations as a prudent measure to be taken at this time. I would suggest, though, that the term "delays" in the title of the recommendations sort of implies that this is another

bad year or something, and I agree with what was just said, that we do have vaccine -- as of now, we're projecting that the vaccine supply is going to be good. In the text where it's used, I think the term "delays" is okay because you want to get people to move it out, but the recommendations do suggest that we're moving the immunization season an additional two weeks out. So I think to put it in the title, that this is a delay, implies that everything has to relate back to 1999, and I don't think that -- I think it's time to move away from that. Tell them what to do, but don't tell them in the title that it's a bad -- it's another bad year. So . . .

**DR. MODLIN:** Okay. Further -- Let's continue on this point if there are other points to be made about the question of delay or causes.

Jon?

**DR. ABRAMSON:** Yeah. If we're going to use the word "delay," then we need to put the reasons -- I'm sorry. If we're going to use the word "delay," we're going to need to put the reasons in. Otherwise, it looks like we're trying to cover up something that we're not trying

to cover up. So I feel fairly strongly that, if we're going to use that word -- if we're setting a new framework for timing, because that's what reality is, then we need to put that in and not use the word "delay."

**DR. MODLIN:** That's a good point. Dr. Jackson?

**DR. JACKSON:** Jackson, AMA.

My comments are much like those made before me. I listened fairly intently to the discussions, but there was no real indication as to what exactly was causing the delay this year. Last year we knew that one manufacturer dropped out, the yield from other processes much lower than expected, and perhaps the identification of the strains might have been late in being given to the manufacturers, but I haven't heard this year what it is that may cause for the quote, unquote, "delay," specifically.

**DR. MODLIN:** Thanks. Yes?

**DR. McKIVEN:** Hi. Linda McKiven from CDC, Office of Health Care Partnerships, and I had just a couple of questions.

One was, did the group consider making recommendations specifically for managed care organizations? Because

I felt that some of the recommendations spread across the different groups and weren't really focused on managed care. There was a recommendation for health departments and a recommendation for providers. So I just had that question.

And then the second question was for provider recommendations, what about standing orders programs? I think the main difference between provider reminder recall and standing orders is the need for physicians' exams according to the ACIP. So I wonder why that couldn't also be included.

**DR. MODLIN:** Perhaps I could respond in that I think that many of those issues are already addressed in the recommendations that we did publish in February, almost certainly are. The question is, do they need to be addressed in this update?

**DR. SCHWARTZ:** I think the standing orders issue is specifically addressed in earlier ACIP publications. With respect to specific recommendations for managed care organizations, some of them may come under the recommendation for mass immunizers as was relative to Kaiser. Also, as I stated, there is a recommendation

for assessment and feedback, which is something that managed care organizations are well situated to do. So that could also looked at as a recommendation for managed care organizations.

I would like to also, just very briefly, comment on the information that came from Wyeth and from Aventis, and that is that, as both companies point out, it's important in the long run that we do increase influenza vaccine supply. And to increase supply, it's likely that we'll need to extend production over a longer period of time and we'll need to administer vaccine over a longer period of time. And the only way that we'll be able to reach our HP 2010 goals is by doing so. I actually liked Dr. Abramson's suggestion that we consider this a new framework for timing, and it's consistent with what was published by the ACIP in the April 20th MMWR, where the optimal period for influenza vaccination has been extended through the end of November. So that may be a very reasonable way to look at things.

**DR. MODLIN:** Dr. Nichol?

**DR. NICHOL:** Just a few quick comments.

We have talked repeatedly this morning about the critical nature of the timing as well as content of communication. I think it is urgent for us to get these recommendations out as quickly as we can. I would agree that we might frame these recommendations, indeed, as a new framework or paradigm for the delivery of influenza vaccinations becoming a new norm rather than a contingency plan or a single season model.

A couple of additional specific comments regarding recommendation number three, the issue of work sites is not just an issue of distribution of vaccine to work sites. Most of the people who bring the vaccine to the work sites are also vendors or providers who provide vaccine to high-risk people, I would guess. So you may also want to include in that recommendation a comment that that also includes providers who are planning programs. Many providers plan programs for work sites as well as high-risk groups.

Under recommendation number four, I think strengthening the language here about the importance of local initiatives to bring the stakeholders and groups together to make vaccine delivery work when

there is uneven availability of vaccine is very important, and I would urge consideration of something going beyond just asking the local health departments to come up with a contingency plan. They really need standing groups of the stakeholders in order to make this work and vaccine delivery is a local issue. The CDC and the state health departments really can't make that work at a local level.

And finally, you might consider putting in some language here or on the website or something about how people order vaccine, when they should order vaccine, getting back to Dr. Tan's comments and other comments, as well as perhaps some information on how we can redistribute vaccine, in particular the legal authority under which providers can actually redistribute vaccine.

**DR. SCHWARTZ:** If you've written down some of your specific comments on recommendation three, I would be interested in getting those comments from you, Kristin.

**DR. MODLIN:** Lucy Tompkins?

**DR. TOMPKINS:** Lucy Tompkins.

In regards to essentially forming this document -- reformulating this document to essentially be generic recommendations for every year, the simplest thing to do would be to change your title, Ben, which is just eliminate the words "projected delay" and just entitle this influenza supply distribution, vaccine distribution, or something like that.

**DR. MODLIN:** Or supplementary recommendations. All right. Yes, Rick Zimmerman?

**DR. ZIMMERMAN:** One of my questions -- I guess my comments is, is this going to be just an issue with 2001 or are we going to see the next several years this issue? My concern is that there are a number of outbreaks a year that have occurred in December, and it obviously varies by region. And if we're saying we're changing not just from October to November as the most recent ACIP influenza recs say, we're now shifting the time from October through December. That's a shift that's going to leave some years when there's an influenza outbreak early. So I think this issue, is this a delay or is this a time shift, or is it both, really needs to be thought through, because if we're saying -- are

we really saying we're going to extend the season routinely through December or are we going to -- is this a one-time thing? Where are we at?

**DR. SCHWARTZ:** I think you asked part of the question. I would like to raise the question a little bit differently in that extending the season, extending the vaccination season, I think is a recommendation that is valuable for every year. Because, again, to vaccinate a higher proportion of elderly and high-risk patients, I think we need to continue vaccinating for a longer period of time, and the data that the Influenza Branch has generated suggests that, in the vast majority, it appears the influenza season peaks in January or after that.

I think the other issue that you raised is very important is that if vaccine is available early in the year, is it necessary that we recommend patients who are not at high risk always defer vaccination until later, or could there be a setting where there is so much vaccine available early that the Committee would want to basically open up the recommendations?

So I think your point about trying to get information

from manufacturers about whether this will become the norm or whether in subsequent years we would expect a larger volume of vaccine to be available early is an important issue.

**DR. MODLIN:** Phil, do you want to address that?

**DR. HOSBACH:** Yes. Phil Hosbach from Aventis Pasteur. Just to follow up on Dr. Abramson's comments and Dr. Nichol.

We really feel, at least at Aventis Pasteur, that this would be more of a normal year and a normal distribution. We could easily get vaccine out in July or August, but that created some of the uneven distribution that's being talked about. It comes out in dribs and drabs. It's the early part of our process. What we're doing is a managed distribution process, to allow more vaccine to hit the market on a regular basis. So this is going to become more of the norm of what we try to do at Aventis and we would encourage the other manufacturers to do so as well.

**UNIDENTIFIED SPEAKER:** Could we hear from the other manufacturers?

**DR. MODLIN:** Yes. Mr. Reilly?

**MR. REILLY:** Maybe I -- Kevin Reilly, Wyeth. Maybe I could add to that also.

In terms of the longer-term perspective of whether this is going to be -- the current situation is the norm or will we overcome it, I think as companies are able to respond by building capacity, it will become a lot easier. It was mentioned about extending the time of manufacture. There is actually very limited ability to do that because we take -- we cannot start the manufacture until we get the strains, which is usually January. So this manufacture takes place between January and July or August. What we can do is expand our capacity and make more vaccine during that time period which will help both the total supply and the time profile within the four months of that supply becoming available.

But I do agree with Ben, as a general policy, opening up that time period of when we recommend immunization and vaccination. I think it's good for the whole system.

**DR. MODLIN:** Yes?

**DR. NOLAND:** I'm Pat Noland from the State of Rhode

Island.

One of the lessons that we learned really follows up on some of the comments from the AMA. The communication with physician offices was extremely erratic, and the real problem turned out to be often at the vendor and distributor level, not at the manufacturer or the public health level. One of your recommendations -- and I couldn't memorize them that fast -- talks about physicians doing reminder recalls and then patients calling physician offices. From both this and my experience with meningococcal vaccine, asking patients to call physician offices sometimes creates disasters. I think you want to be very careful how we craft the public message. It implies that the physician has some control over what's happened and they, in fact, feel they don't.

And I would like to raise one other vendor problem, which you may be very familiar with, but just to be sure, we actually tried to redistribute vaccine in Rhode Island. We had some work sites who said, we'll be happy to contribute our vaccine in October to distribute to places that are treating high-risk and

we'll work out something for later in the season. In one instance, the distributor took back the vaccine because they felt this was an inappropriate use of their product. I don't know what the negotiated price issues were in that, but the distributors were not very supportive at all of redistributing vaccine to get it to high-risk providers. We did have individual practices who shared when they got a shipment, but the informal market was very difficult because of that fact.

**DR. MODLIN:** Thank you, Dr. Noland. Chuck Helms?

**DR. HELMS:** Like Kristin, I've got some concerns that we've got to act fairly quickly on the document before us. At the same time, the discussion of, if you will, the wisdom of a long-term commitment to an approach like this based on the time frame offered is something we can discuss later on. It would be one thing, I think, if we were stepping back from where we were last year or doing the same thing as last year. We're moving forward to a better distribution this year than last, and we have no hard data at all that the thing we've established as standard practice really is the best

practice to begin with.

So my argument would be that we've got a decision to make about this document before us now and that a discussion about the plan, if you will, the long-term plan, is something that could be discussed rationally over the next year.

I have a couple of questions about just wording here that I don't want to go into great detail on now, but maybe you would want to continue with this . . .

**DR. MODLIN:** Further questions and discussion? Yes, Dr. Overturf?

**DR. OVERTURF:** Just one question about the issue of household contacts, which is in the section under recommendations for the public.

I'm little concerned where that sentence is because it really maybe should appear at the -- under the persons at high risk, and the concern that's specific to pediatrics actually is the issue about beginning vaccinations in November for children since children may require two doses. You really will not have immunity for some of those children. And actually, they are kind of a hot spot for introducing influenza

into the family from day care centers and other places. So you may want to consider putting -- either adding a note about that specifically for young children or perhaps moving that up the issue with high-risk -- high-risk individuals who come in in September could identify who else is in the family.

**DR. MODLIN:** Gary, that actually is addressed in some detail in the regular statement, and I guess the question is, do you feel that it is of sufficient importance that we need to address that again here in the supplementary statement?

**DR. OVERTURF:** Well, I think it is because something that is going to come up before this Committee very shortly is influenza immunization in children in general. I think to begin to lay down some of the rules and to also to introduce them as important components of influenza epidemiology, particularly for high-risk patients, it is probably important to readdress it.

**DR. SCHWARTZ:** Let me ask you a question, Gary. If the -- We specifically discussed whether household contacts should be included in this group for earliest vaccination, and the feeling was that this represents

such a large number of individuals, that to encourage them to get vaccinated early would likely have the effect of decreasing the vaccination of those who themselves are at highest risk. The question I would ask you is whether you feel that there should be a recommendation specifically for household contacts of high-risk children where the size factor may not be as large or whether you think that all contacts of those of high-risk should be vaccinated early?

**DR. OVERTURF:** Well, I personally think all contacts of high-risk should be, but if you were going to supplement a group out there, I would say children should come first because of the logistics problems in trying to get children immunized with two doses.

**DR. MODLIN:** Walt?

**DR. ORENSTEIN:** I would just like to come back to the issue of delay again, because, in some senses, this is certainly a delay from what people's expectations normally are. And if we avoid it in the title -- I'm concerned that we need to get the attention of people. I think one of the issues is the attention wasn't there until fairly late last time. I think we really want

to get people's attention now to change their practices. It may be, as Chuck said, in the future this will be the norm and we can get prepared for it, but I think the key message to people is this year's season is not going to be at the preconceived notions which might be with 1999 and earlier. And I would argue that the word "delay" is important to get out because it is a major change in what their expectations would be.

**DR. MODLIN:** And that perhaps this can be incorporated in the future statements beginning next year as we begin to lay down some expectations.

Rick Zimmerman?

**DR. ZIMMERMAN:** In the ACIP -- in the back of the booklets is the ACIP flu recs. On page 13, it's table 2, and that's the proportion of cases that occur by month -- the months of peak influenza activity, and it's 21 percent for December. So you've got a fifth of the season peaking in the December, and I just think that's a sobering thing if you're -- I guess I'm speaking in favor of Walt's suggestion of the delay, but until we may do some decision analyses to see the real benefits,

where you've gotten pros for extending to December, Healthy People 2010 goals, you've got a pro, more doses out the door and effectively given -- so those are pros -- and the con, you have the potential for 21 percent of the seasons not getting all the vaccine out and into people before the season hits, I think you'll almost need a decision analysis on that to see what's happening. We can't do that today, but I guess, because of that, I speak of delay being maybe appropriate this year and maybe next year we change the time frame where we can actually look at decision analysis-type data.

**DR. MODLIN:** Dr. Cox?

**DR. COX:** Yes. I would just like to reinforce that view. I think while we talk about peak activity, peak influenza activity occurring only four of the last, whatever, 23 of 19 seasons in December, we have to realize that there's a lot of sporadic and regional activity and even outbreaks in nursing homes that are occurring earlier. And we have to remember that as good as it is to extend the vaccination season and make sure that everyone that can be immunized is, there is

an optimal time to vaccinate.

**DR. MODLIN:** Just -- Dixie, go ahead.

**DR. SNIDER:** Oh, thank you. Dixie Snider. One other factor that hasn't been mentioned in the context of this discussion is also the live-attenuated vaccine which also will come into play, presumably, sometime in the near future and would impact. So I just would bring that to people's attention as another factor in thinking long-term. It seems to me, again, it's important to try to focus on deriving solutions for the problems for the near term -- for the coming year. And as been mentioned -- I think everybody appreciates -- the sensitivities that were raised last year have now thrown this issue not only to this Committee but have thrown it into the political process, as we heard from Dr. Tan, and we fully anticipate that we'll have to be convincing leadership in the Administration and perhaps in Congress that we've done all that we can possibly do. And when I say we, I'm talking about not only this Committee but the manufacturers and the regulators and the distributors and everybody to deal with this effectively in the

context of the free market system and so forth. So I would hate for us to get too far afield and try and think about too many things at once and too many years in advance about how we deal with this issue.

**DR. MODLIN:** Dr. France?

**DR. FRANCE:** I'm very pleased to see that you've got section on the mass vaccinations and I think it would be important for you to review again what Dr. Oxenstein's letter was saying around those. Specifically, in his letter, he was asking for a delay or recommending potentially the delay of mass vaccination programs in the latter half of October and potentially in November. So I am a little concerned about the wording in the sense that we should have them seeking out vaccine in September and October when the other letter from the CDC said delay mass vaccinations until the need of October.

**DR. SCHWARTZ:** The draft recommendation doesn't state a specific date for those campaigns, but in order to make it consistent with what Walt had sent out earlier, perhaps we should add that.

**DR. SMITH:** I think that would be helpful. I mean,

that was what I was trying to say earlier. Because these clinics are already being scheduled right now.

**DR. MODLIN:** Okay. We're going to need to bring some closure to this pretty quickly. One last comment, Dr. Jackson.

**DR. JACKSON:** Yeah. I want to go back to my comment once again. Last year I think we were able to convince the public and others why this, quote, unquote, "delay" occurred last year. And it was brought out again, one company dropped out and there were problems with the yield. What is the cause for this coming year, which is not clear to me. I know that there may have been an increase in production possibilities, but it still isn't clear and we've already got the, quote, unquote, "conspiracy theory" floating around and the AMA has already brought that out. Something has to be said as to why we're making these recommendations again and legitimize to those who think there may be a conspiracy or some other electricity problem going on here.

**DR. MODLIN:** Dr. Baylor, do you want to address Dr. Jackson's question?

**DR. JACKSON:** Yeah, I'll address that.

I think it's important if we go with -- as Walt had suggested, if we used the language "delay." I mean, as the manufacturers have indicated, I think it's important to realize that the '99 benchmark that we're using that we're mentioning the article, that was sort of the norm back then. There were four manufacturers. There are three manufacturers now. Those manufacturers are trying to build capacity so that they can increase the supply. You can't do that overnight. There are a number of issues involved in increasing that capacity. So there will be more -- they're projecting more vaccine for this year, but they're also -- there are going to be some shifts in timing because they're building up the capacity. I think that's critical. So the reasoning for the, quote, "delay," if you will, is to build that capacity, it's going to take a while. I think the manufacturers have spelled that out pretty good.

**DR. MODLIN:** Norm, that's a good point. Perhaps we are trying to, quote, "explain" the reasons for the delay, we might include just such a sentence --

**DR. BAYLOR:** And I would agree with that.

**DR. MODLIN:** -- relating to the fact that this is something that's being addressed --

**DR. SMITH:** John, can I address that?

**DR. MODLIN:** Yeah, Natalie?

**DR. SMITH:** I think it would be helpful -- The issue about this is compared to 1999 and all that is buried much later in the editorial note. And I think if you're going to have a title that includes the word "delay," you need to put -- define what you mean by "delay" and say it's not going to be as extensive as last year and put that right up front.

**DR. MODLIN:** That's good. I'm going to have to ask that we bring some closure to this, and we're already running a few minutes late. Let me ask the voting members of the Committee if they are comfortable voting now on changes that have been suggested -- first of all, comfortable with voting on the statement now and, secondly, with the -- with the proviso that we include the changes that have been suggested. It sounds to me like the major changes, if I've got them correctly here, are: one, defining what "delay" means and explaining that and putting that into context; secondly,

addressing the issue of those patients who may seek vaccine early in September and October; and then, thirdly, Dr. Overturf and Dr. Abramson's issues regarding including children as contacts of high-risk individuals and the specific language regarding that. Are there other issues? Those are kind of the major ones that I picked up. Dr. Brooks?

**DR. BROOKS:** I think if we're -- we're talking about a whole shift in paradigm.

**DR. MODLIN:** Yes.

**DR. BROOKS:** I was wondering if we should say something in the statement that ACIP is considering changing the recommendations across the board. Because there was and still is a lot of confusion regarding influenza. We're going to come with another set of recommendations. Although I think it's good to come out with a statement early. I'm just wondering since there's been a lot of discussion about the fact that we may want to just shift the whole paradigm, should we say something in the text?

**DR. MODLIN:** Add something to the effect that this will be included -- likely be included in next year's

statement, obviously this is a work-in-progress. It's a shift. I think it's everybody's intent that this would be included in the influenza recommendations for next year. I don't think there will be any doubt about that.

Let me ask how members feel about that. Would they like to see the new language before we vote on this or would you be comfortable voting now? I think most people are saying, yes, they would like to see it. Then if that's the case, why don't we revisit this at eight in the morning tomorrow. Do you think that would be appropriate?

**DR. SCHWARTZ:** That would fine.

**DR. MODLIN:** We will have an additional 10 or 15 minutes for discussion and take a vote at that time. Okay. We will break for lunch. We will be back at 1:15 on the dot. Thank you.

(LUNCH RECESS FROM 12:40 P.M. TO 1:40 P.M.)

**DR. MODLIN:** Could I ask people to take their seats, please.

The next item on the agenda will be a continuation of the discussion of the hepatitis B statement. We have

been working on the hepatitis B statement for sometime. It is a document that has reached a considerable stage of maturity. Hal Margolis has been working on it, focusing on it, since the last meeting and has had a bit of assistance from Bill Schaffner and Jane Siegel. We're going to review the hep statement -- the hepatitis B statement now and some additional information. I'm going to turn things over to Hal. Hal?

**DR. MARGOLIS:** What we wanted to do first is to give this Committee an update. It has actually been almost three years since we've talked about probably the thorniest part of hepatitis B immunization which is adult high-risk immunization. So we would like to present both some epidemiologic and some implementation data. Susan Goldstein from our group and Cindy Weinbaum are going to give that presentation. I will kind of them talk about where we are kind of in a policy issue with adult immunization and then we'll go into the statement.

Susan?

**DR. GOLDSTEIN:** Okay. I'm going to review some of the changing epidemiology of hepatitis B over the past two

decades and we're going to follow this discussion with some of the new strategies to vaccinate high-risk adults in the United States.

Our current strategy for preventing transmission of hepatitis B consists of prevention of perinatal transmission which includes routine screening of all pregnant women and vaccination of newborns born to hepatitis B surface-antigen mother -- antigen-positive mothers with vaccine; routine vaccination of routine; more recently routine vaccination of adolescents; and since 1982, we've had a recommendation for selective vaccination of children, adolescents, and adults at increased risk for infection.

Well, who are these high-risk adults? This group includes injecting drug users, sexually active homosexual and bisexual men, and heterosexual men and women who have reported more than one partner in the previous six months, previous treatment for another sexually-transmitted disease, and commercial sex workers. I also want to point out that in the 1991 MMWR, it states -- and this is a quote -- "Most patients

seen in STD clinics should be considered candidates for vaccination."

High-risk adults also include inmates of long-term correctional facilities. And for most of the rest of the presentation, we're going to be focusing on these four groups, but just for completeness, I just want to go over the other high-risk adults. They include household and sex contacts of persons with chronic HBV infection, persons with occupational exposure to HBV, clients and staff of institutions for the developmentally disabled, chronic hemodialysis patients, and certain international travelers, those being persons who are going to have potential exposure to blood or persons who will be travelling for greater than six months.

Now I want to talk a little bit about what has happened to the epidemiology of hepatitis B over the last two decades. This slide shows the reported incidence of acute hepatitis B from 1982 to 1998. The incidence of disease has decreased from 13.8 per 100,000 in 1987 to 3.3 per 100,000 in 1998. Overall, a 76 percent decline in incidence has been seen. That's the good news.

The bad news is also evident on this slide, and that is, since the mid-1990's, the decline in incidence has plateaued and we've seen no further decline. And the incidence of this vaccine-preventable disease has remained stable.

Now, when we looked at the reported incidence of hepatitis B by age group, we see -- and you'll see this in a second; Hal assured me that this would work -- that the trend by age group paralleled the overall trend. In pink, we first see the incidence in the younger age group, 10- to 19-year-olds, and in this group, the incidence of disease decreased by 73 percent. And we think we can attribute this to the effects of hepatitis B vaccination.

In the next older age group, the 20- to 29-year-olds, there was a similarly high decrease in incidence, 71 percent. Now, the decline in this age group is probably a combination of hepatitis B vaccination and behavioral changes. And by that, I mean changes in injection and sex practices, safer injection and safer sex practices.

In the next age group, the 30- to 39-year-olds, we see

a decline, though less, and in that age group it was about 53 percent. And in the older age group -- and I'm getting close to 40, so I hesitate calling it the older age group -- there was even less of a decline, and that was about 38 percent.

But what we do see on this slide, while there was a decline in incidence in all age groups, in all age groups also, there's been this plateau since the mid-1990's. So we've done well, but we need to do better.

I'm going to walk you slowly through this rather busy slide. It shows the reported risk factors for acute hepatitis B in the 1980's on the left and in the 1990's on the right. Now, although there's been a decline in number of cases in each of the major risk groups -- and when I say major risk groups, I'm referring to heterosexuals, men who have sex with men (MSM), and injecting drug users (IDU). Although there's been a decline in all three of these major risk groups, there's been a shift in the epidemiology.

In the 1980's, 21 percent of all cases were attributable to heterosexual activity. This proportion increased

significantly, and in the 1990's, it accounts for 38 percent of all cases. In contrast, the proportion of cases associated with MSM decreased from 15 to 12 percent and injecting drug users, from 20 to 14 percent. I think the take-home message from this slide is that from the 1990's, heterosexual activity has emerged as the predominant mode of transmission of hepatitis B virus in the United States, and we really need to stop thinking of this disease as a disease occurring only among MSM and injecting drug users, but a disease occurring among the whole population.

This graph shows trends in age for acute hepatitis B by risk group, heterosexuals on the left, MSM in the middle, and injecting drug users on the right. What we see here is that there has been an increase in the median age of cases with acute hepatitis B from about 25 years old in the early '80's -- and that's 1982 to 1988 -- to 30 or 32 years old in the period 1994 to 1998. Well, this is actually a rather surprising finding when we looked at our surveillance data and I think that this is important because we now have this expanding window of opportunity in which to vaccinate persons at

increased risk of hepatitis.

Let's talk now about vaccination. We're also able to use our surveillance data to gather information on missed opportunities to administer hepatitis B vaccine. And in the next two slides, I'm going to be talking about missed opportunities, and I would like to thank our EIS officer, Amy Kahn, who put together these data.

Of all patients -- of all persons with acute hepatitis B, 36 percent have been previously treated for another STD and 39 percent have been previously incarcerated. In total, 56 percent were either treated for a STD or incarcerated. So we could have potentially prevented over half of all cases of acute hepatitis B had hepatitis B vaccine been routinely administered in these settings.

This slide shows missed opportunities to administer vaccine by risk group. Again, heterosexuals on the left, MSM in the middle, and injecting drug users. Although the proportion of patients in each who reported a missed opportunity were different for the risk groups -- about 66 percent of heterosexuals, a much

lower percent, 37 percent for MSM, and over 80 percent for injecting drug users -- there were a substantial number of missed opportunities to vaccinate all of these persons.

I'm going to end by presenting some recently published data about hepatitis B virus infection and hepatitis B vaccination among MSM from the Young Men's Survey. And the Young Men's Survey is a cross-sectional survey that was conducted in seven large metropolitan areas between the years 1994 and 1998 among young MSM, and those are MSM 15 to 22 years old. It was conducted primarily to obtain risk factor and seroprevalence information about HIV, but other data were also collected. And the results of the hepatitis B portion of this study are rather alarming.

Overall, 11 percent of these young MSM had serologic evidence of hepatitis B infection. Now, this compares to the overall prevalence in the United States of 4.9 percent. The prevalence of infection among these young MSM increased from two percent when they were 15 years old to 17 percent by the time they were 22 years old. It's only a matter of seven years. Only nine

percent had been immunized against hepatitis B, only 27 percent knew about hepatitis B vaccine, and what I find particularly alarming was only nine percent believed they were at risk for acquiring HBV infection. When asked about health-seeking behaviors, 90 percent of these MSM reported a regular source of health care, 65 percent had been previously tested for HIV, the majority of whom had been tested more than once, and 19 percent had been previously diagnosed with a STD. Again, a lot of compelling data showing that we have multiple missed opportunities to administer hepatitis B vaccine.

Now, based on these data, I think we need to rethink our strategy for immunizing high-risk adults, and rather than targeting these specific high-risk adults, perhaps we need to think about routinely offering hepatitis B vaccine in settings where high-risk adults are frequently seen. And at this point, Cindy Weinbaum is going to talk about some of these strategies.

**DR. WEINBAUM:** Thanks. I think that Dr. Goldstein pretty well illustrated why we should be addressing

viral hepatitis in various kinds of prevention settings. She's shown that many high-risk adults access services, that viral hepatitis -- the viral hepatitis are major public health problems. You already know that effective prevention tools exist in the form of immunization for hepatitis A and B. The roots of transmission overlapping with STD and HIV - STD's and HIV gives us opportunities for integrating services in those venues and the lack of integrated activities allows transmission of viral hepatitis to occur.

What prevention settings am I talking about? Here's a list. This is a list of venues in which hepatitis B vaccine programs have been tried and have been successful: STD clinics; HIV/AIDS testing and counselling sites; family planning centers; drug treatment programs; harm-reduction programs including syringe exchange programs; job corps sites; and correctional facilities, jails and prisons.

This slide shows an overview of some of the literature, published literature, showing that, in fact, there's pretty high acceptance of vaccine when it's offered in

these different venues: in STD clinics, anywhere from 45 percent, which was the 1993 data, to 85 percent, which is unpublished, actually data from this year; HIV testing and counselling sites; the IDU treatment that I'm talking about actually includes both methadone programs and syringe exchange programs where there was acceptance rates in the 50's; prison and detention including jails and juvenile detention facilities where acceptance has also been high. I broke these out by acceptance of the first, second, and third doses of the vaccine because even one dose of the vaccine is going to be efficacious in providing immunity for 50 percent of people who are vaccinated. So while the goal is to get three doses of vaccine into folks, in fact, in our first dose we can get this kind of acceptance, we feel that we might as well offer our first dose.

Now I'm just going to focus on two settings. That would be jail and prison settings and STD clinics. Hepatitis B vaccination of incarcerated persons has been recommended since 1982. It prevents infection both outside of correctional facilities where people

are engaging in high-risk behaviors and also inside of correctional facilities where people might continue to be engaging in high-risk behaviors. And actually, in MMWR that's coming next week, we'll show this.

Hepatitis B vaccination in prisons has been shown to be feasible and cost-effective. However, there are a number of challenges, of course, to its implementation.

I'm going to show a couple of examples of program that work. In Massachusetts, they've been vaccinating all juvenile detainees since 1996. Vaccine is offered and it's not mandatory, but they only have a one percent refusal rate for hepatitis B vaccination. 43 percent of kids coming through the system have been able to complete all three doses of vaccine.

Now, this is kind of a busy slide from Hampden County, Massachusetts, which is Springfield and its surrounds, where a seroprevalence study was done for hepatitis B markers. It shows -- I'm sorry, my pointer is not working. It shows prevalence along the left axis and age group. You can see there's a very high bar in the less-than-20 field. This top segment represents

people whose -- who were hepatitis B surface antibody only. So, in other words, the top half of that first bar represents people who had been vaccinated. The cross-hatched bar represents a combination of different hepatitis B serologic markers. So although among people ages 20 to 49, in fact, there were a total of only two more people who were surface antibody only. So, in other words, it really looks like the fact that Massachusetts if vaccinating their juvenile detainees is showing up as good immunity to viral hepatitis B in their adult inmates.

Another question is, you know, is it feasible, can we actually do this? How about a big system like Texas? Well, in Texas, the legislature mandated vaccination of all incoming inmates into their prison system, and in fact, the latest data that they shared with me was that in January, they vaccinated 20,000 people that month. So it is something that can be incorporated even into a very busy intake system like that of Texas.

Now switching gears to talk for a minute about STD clinics, as Dr. Goldstein just explained, hepatitis B is definitely a sexually-transmitted disease and

vaccination has been shown to be feasible also in STD clinics. I'm going to give the example of San Diego which did a sero survey of clients and found that 85 percent of their clients are susceptible to hepatitis B, eight percent of their clients are men who have sex with men, five percent are injecting drug users, and 87 percent don't admit to either of those two things. These are all people who are coming to STD clinics for treatment, 13,000 in 30 months.

Out of the total of 13,000 people coming through their STD clinics, 74 percent accepted a first dose of hepatitis B vaccine when it was offered to them, and 31 percent overall got three doses of vaccine at that clinic.

Then they did a study to see whether they could increase the rate of acceptance by giving some counselling to people while they were waiting to be seen at the STD clinic and, in fact, among all clients, they did increase their rate from 77 percent to 84 percent. They saw that in their injecting-drug-using clients that rate went from 66 percent to 82 percent. In their clients who were men who had sex with men, they didn't

see any change. They thought that that represented a well-educated population at baseline.

So, overall, there is a high rate of vaccine acceptance when it's offered in unconventional settings, acceptance increases with education, there's a high rate of series completion, it seems to be relatively easy to integrate a vaccine program against hepatitis B into existing services, and there are still some challenges to implementation.

What are those challenges? Well, funding, of course. For people under the age under the age of 19, of course, there's the Vaccines for Children Program and juvenile detention facilities are increasingly signing up to the VFC provider sites so that they can access vaccine for their kids. For adults vaccination, funding is still a question.

Another issue is that of pre-vaccination screening which may be cost-saving depending on local costs associated with vaccination and also depends on the prevalence of immunity, both history of previous vaccination and history of past infection. And thirdly, the fact of three-dose completion being the

goal, whether we can do it inside the system or outside the system, they're starting the transfer of records presents another challenge. The bottom line really is that the goal is preventing not getting all three of those doses. So, again, if one dose acceptance is good, that should perhaps be our goal.

I'm going to turn the mic over Dr. Margolis to talk about turning recommendations into policy.

**DR. MARGOLIS:** Well, as a summer student who is a MPH student told me many years ago that he was a -- came from a business school, he said turning recommendations into policy equals adding money.

All right. So where have we been? Just to kind of review with hepatitis B vaccine: obviously, it's been licensed for over 20 years; you have a good vaccine, three doses give you high efficacy shown in controlled clinical trials; shown in population-effectiveness studies; and at this stage, still almost 20 years out, no recommendations for additional boosters and showing that the vaccine is safe. I think we know that vaccinating infants where we have a very defined program works well. We have 90 percent three-dose

coverage rates. We also know that even adolescent immunization, which is something new, a recommendation that really only occurred in late '96, early '96, we now see that there's about a 60 percent coverage. This is based on National Health Interview Survey data in 13- to 15-year-olds, and as more states bring in requirements for school entry, we see that we very effectively can vaccinate adolescents. So I think, as Dr. Goldstein pointed out, incidence is going down in these younger age groups, but we're still left with the adult issue.

I think we're convinced that vaccination of high-risk groups is feasible. I think there have been enough demonstration projects now and that once you really have a program, you, in fact, can vaccinate high-risk groups. And I think this goes back to that very first slide that Dr. Weinbaum put up, which is that we have a very good infrastructure in this country, mainly built around prevention of STD's and HIV, that sees a very high proportion of high-risk adults and they're there and, in fact, you can vaccinate in that setting.

We've also shown that vaccination of persons at

occupational risk is quite feasible. Hepatitis B is no longer a risk in this group because of immunization, and the other two were shown, I think, in terms of the data presented. And then the last thing is that there have been a number of studies that have now shown that immunization of again high-risk adults is cost-effective. There are data for incarcerated adults, persons visiting STD clinics, as well as persons at occupational risk.

The problem is there is no national program. I put this up here, though, because this is a website from the Immunization Action Coalition that lists actually about 40 programs that are basically all run by states and local jurisdictions and that have been highly successful. And Deb Wexler is collecting more of these, but they are the success stories. And the bottom line is that this has been all local endeavor. And when you put local endeavor in there, in fact, it works, the funding is spotty. And actually, we at CDC don't know how much funding and how much coverage is going on nationally. Currently, both CSTE and American Social Health Association, the STD group, are

now conducting surveys to actually find out what's going on around the country in this area. You know, our anecdotal evidence says there's a lot happening, but it change from year to year depending on funding streams.

One of the other things we've done -- and we think that at this point we have the right recommendations going back to this issue of why isn't it happening, but one of the things that's happened, I think, in the last five, six years is that we have now started to retool these recommendations for specific adult risk groups. And the first one that came out was "Immunization of Health Care Workers," for which, again, the hepatitis B recommendations are in there and revised recommendations. The "Guidelines for Treatment of Sexually-Transmitted Diseases" in 1997 and the new guidelines that are coming out, but in that one in '97 for the first time had, you know, prevention of vaccine-preventable diseases, and hepatitis B as the mainstay, is being part of the treatment guidelines. So it's out there in terms of what people can use. Most recently, there have been recommendations that

came out for prevention of diseases in the chronic hemodialysis setting and here's an area where the vaccine is paid for, but actually, only 50 percent of hemodialysis patients were being vaccinated. That's kind of inched up now to somewhere in the low 70's, but we're still not at 100 percent coverage.

To come, as I said, are the new guidelines for treatment of STD's, and in the fall will be a set of recommendations for the prevention of viral hepatitis in correctional settings which will also include prevention of hepatitis B as well as A and as well as C. But again, retooling are recommendations for use in various high-risk populations.

So where are we going? And this was actually part of a presentation that I gave at the National Immunization Conference which was, where have we been and where are we going with adult immunization issues. And to be quite honest, it comes down to this. We know it works, we have good recommendations, but is there the political will to put the resources in it. Some of that political will has been stated. The Institute of Medicine, in their analysis of preventing STD's in this

country in 1997, said that hepatitis B should be in every STD clinic in the country. Most recently, the Institute of Medicine report on immunization funding talked about adult high-risk immunization and included hepatitis B as something that we ought to be doing. In a soon-to-be-released publication from the National Institute of Justice and the National Correctional Health Care Commission and in a report to Congress, it talks about the need for hepatitis B immunization in soon-to-be-released inmates, which, again, as Cindy pointed out, transmission goes on both inside the walls as well as outside the walls in the high-risk populations.

But as I started out, we really don't have a program and it's right now kind of this what local jurisdictions can put together and what we can do from the CDC standpoint in terms of technical assistance. There is the opportunity to use 317 funds at various discretions. And in fact, most recently now, the National Immunization Program has been asking states, what would it take or what could you use in terms of resources for hepatitis B immunization. Well,

recognizing that the likelihood of there being resources is not very high.

I put down here some of the barriers, and just to list the usual ones we think of in adult immunization, Medicare currently pays for end-stage renal disease patients, but it's interesting that in contract to flu and pneumococcal vaccine where 100 percent is reimbursed, it's only actually 80 percent for hepatitis B vaccine.

Employers, we know that has worked. And again, I think that is our model for success, that via the OSHA rule, employers are required to pay for vaccine. As I said before, state and local jurisdictions are putting up fairly substantial amounts of money. If you look at that Texas program, you're looking at about 13 to 16 million dollars a year for hepatitis B vaccine for their inmates. And Michigan has been doing this even longer with routine vaccination of inmates. I don't know what their price tag is. There are about five states that routinely vaccinate prison inmates at this time. Other public sector is really nonexistent. Medicaid does not cover hepatitis B vaccine. And then lastly,

I put the question mark up there in terms of the private sector, where we hear that many health plans might cover but, as was the experience with infant immunization, it's not first-dollar coverage and, in fact, it also requires the -- having to divulge risk factor status, which becomes a real problem in terms of practical implementation of these types of activities. It's very much like what is seen with HIV.

So I just kind of leave you with this, that I think it's a frustration we've all had, that can adult immunization have some degree of funding parody with infant and adolescent programs.

I think at this point --

**DR. MODLIN:** Do you want some feedback?

**DR. MARGOLIS:** -- some comments and then Bill Schaffner and Jane Siegel wanted to transition into the next part.

**DR. MODLIN:** Okay. Rich?

**DR. CLOVER:** You specified in the discussions throughout all the presentations certain missed opportunities where people presented to various high-risk clinics, yet you showed the greatest percent

of increase in the changing epidemiology being the heterosexual group. What percentage of that heterosexual group that's acquiring hepatitis B is presenting to these other high-risk opportunities?

**DR. MARGOLIS:** I mean, that's actually one-in-the-same data set. These were the data actually from the Sentinel County's study of viral hepatitis. So if you look at those people with -- whose risk factor is heterosexual acquisition, one-third of them have been previously seen in a STD clinic.

**DR. MODLIN:** Stan Gall?

**DR. GALL:** Hal, what is the current status of the neonatal vaccine business? Because with the thimerosal, the pediatricians sort of dropped the ball. Have they picked it up again or has it still dropped?

**DR. MODLIN:** The question is, newborn immunization --

**DR. MARGOLIS:** Starting at birth.

**DR. MODLIN:** Starting at birth with the suspension temporarily with thimerosal in vaccines and the reinstitution now that thimerosal has been taken out

of the vaccine.

**DR. MARGOLIS:** I don't have the data. There have been several -- the most recent publication in Pediatrics. There was a survey done by CDC. Basically, it goes like this, that there was about a 70 percent reduction in birth dose. Prior -- Let me back up a minute.

Prior to the recommendations, the joint recommendations in July of '99, about 50 percent of infants in this country were being vaccinated starting at birth. Those were national data from the National Immunization Survey. In various studies that have looked at birthing hospitals or some national surveys, there was about a 70 percent reduction in that that occurred very rapidly after those recommendations were made in 1999. The recovery of that -- in other words, coming back to that level -- has been very slow and I think now it's about 30 percent. I may be a few percentage points off on either side, but that's about what it is. The other very troubling aspect of this was that for infants born to surface-antigen-positive mothers for which the recommendation said don't change

anything, there was actually a change that occurred after those 1999 -- you know, mid summer of '99 recommendations with about a 15 percent of drop. In other words, hospitals that had standing orders took those orders away and that never came back up to the -- to the pre-recommendation point. So the bottom line is that newborn immunization is lower than it was in '99 and it's unclear whether it's still, quote, "recovering."

**DR. MODLIN:** Hal, if you were to do a back-of-the-envelope calculation in terms of just the total proportion of adults that would be considered to be at risk or at high risk, what -- and secondly, how many of those adults would already be seropositive, what would that number be?

**DR. MARGOLIS:** I don't know the number, but I can give you -- I can kind of piece some numbers together since we're doing this back-of-the-envelope. There are about two million people who are incarcerated in the United States long-term every year. That's our -- That's the number. And about 80 percent of them are susceptible, but if you look -- as Cindy pointed out,

if you watch them when they go back out and then they come back in, 20 percent of them get infected every year. So there's two million right there. In terms of injection drug users, we don't know what that number is, and the same with persons with heterosexual risk. But I've been saying that CDC, for instance, sees about two million people in STD clinics every year for which there's public sector funding. That's our CDC-funded STD clinic population. And there are about another two million -- there's some overlap, nobody quite knows how much overlap -- who are seen in HIV counselling and testing sites. So right there, there's about six million people plus a very large number of injection drug users in various treatment or syringe and needle exchange programs. Actually, I don't know that number. So there's at least probably in the eight to ten million range.

**DR. MODLIN:** Jaime?

**DR. DESEDA:** I agree that it would be great to be able to get this population -- high-risk population, but I'm a little bit concerned in the mid-80's this was the similar strategy. And one of the reasons, as I

understand, that universal vaccination was taken was that it didn't work in terms of being able to -- Of course, if somebody is incarcerated, it's relatively easy to target, but there's going to be a lot of people that are going to be out of the system.

**DR. MARGOLIS:** Well, I think -- Let me try and go back and address the mid-80's. The mid-80's were -- it didn't work. We at CDC funded several demonstration projects in STD settings. There were actually none in corrections at that time and there were a couple that were done amongst injection drug users. But I think the thing that has been changed -- and I go back and as Cindy put on her very first slide -- is that there is a whole infrastructure, a whole public health infrastructure now, that accesses high-risk adults in this country that didn't exist to the same degree probably in 1980, and that's really driven by HIV/AIDS and a lot of resources going in there. And whereas, no, you're not going to get 100 percent coverage or maybe even maybe overall 70 percent coverage like we do for adolescent immunization, you're going to get pretty high coverage rates in -- you know, what we're

seeing now when people are really doing it is very different than the early '80's.

So I guess we are concerned actually that while we are moving cohorts of immunized infants and adolescents forward, there is still a tremendous amount of hepatitis B that is circulating the adult population and eventually, yes, these immunized individuals are going to bump up against that, so to speak. Hopefully, they're going to be protected, but we're never going to drop -- or we're never going to really eliminate transmission unless we can get rid of this adult side or wait 30 years. I mean, that's kind of what we're into.

**DR. MODLIN:** Sam Katz?

**DR. KATZ:** Dr. Katz. This question is really for Walter Orenstein.

I wondered, under the year 2000 Institute of Medicine report calling for augmentation and implementation of 317 funds, what has happened as far as 317 funds becoming available for adult immunization with hepatitis B?

**DR. ORENSTEIN:** There has not -- There was 42 and a half

million dollars put in for infrastructure funding over and above that that was appropriated in the FY 2001 budget, which states have the opportunity to put into hepatitis B although many of them put it into their childhood programs to make up for budget losses that had occurred before. There were no appropriations in the 317 vaccine budget for hepatitis B vaccine for adults even though it was one of the recommendations of the IOM.

**DR. MODLIN:** And one more -- Eric, did you have a comment?

**DR. FRANCE:** I'm wondering, Dr. Margolis, if you considered making a similar recommendation to what we have with PneumoVax in seniors, where if the patient says by history they have not had it at the STD clinic, then we give it to them. I can think of seeing young adults in a clinic where we don't have their records. There's no actual statement anywhere saying if they say they don't have it, give them the hepatitis B shot.

**DR. MARGOLIS:** I mean, operationally, that's what STD clinics are doing. And somewhere in the near future, on the young end of the STD clinic, very similar to that

those data that were shown in terms of corrections, you're going to start having young adults coming into STD clinics who were vaccinated, but that -- operationally, that's basically what they do. They ask, have you been vaccinated? And there are probably 10 percent who have been vaccinated and the rest of them get -- you know, get vaccine.

**DR. MODLIN:** Let's move onto consideration of the statement itself. Jane, or Bill, or both, were you going to lead off with some introductory comments?

**DR. SCHAFFNER:** This is Bill Schaffner. We were asked by Hal Margolis and John to look over the statement and make larger and smaller comments. The interest is in moving the statement forward. There are many individual and small comments which I am sure members of the Committee can make, and I believe Hal will be most receptive to receiving those. We both found that the revision was a strong one and should be supported. Having said that, we each have some comments of which Dr. Margolis is already aware that we would like to share with you, just observations. The first one of mine has to do with that proportion

of individuals, approximately a third, for whom we do not have good risk factor information. That is, despite best attempts, indeed in the CDC four-county study, where I am sure the investigation of cases is about as good as it can be, we are left with about a third of patients who have either acknowledged or identified risk factors. Now, theoretically, we can be perfect in our administration of vaccines and we will not find those people in advance, and we all know that in practice we are not perfect. That's a very important segment of the population. And in the epidemiology portion of this document, I at least believe that it deserves a separate statement, a separate description, and a strong emphasis. And the reason for that is that that one-third underlies -- is the foundation for the universal immunization concept. The subtitle of the document is that we are on the route to interrupting transmission and, indeed, to eliminating transmission. We can't eliminate transmission if we can't immunize everyone -- unless we can immunize everyone. So I believe that segment of the population deserves greater emphasis and is part

of the communication that we have that we're really trying not only to provide personal protection but trying to eliminate transmission. That's my larger comment for the document.

Now I'm going to look at little bit to the future and actually key on the lovely presentations we've heard this morning.

We are doing an increasingly fine job in protecting infants, children, and adolescents against hepatitis B. We have a universal concept up and until the 19th birthday, and then the moment we become 19 we enter a new era where the concept underlying our recommendations is no longer the elimination of transmission, it's more the control of hepatitis B through individual and personal protection. As Dr. Goldstein has shown us, of new cases, 38 percent now are a consequence of heterosexual transmission. And only a proportion of those people show up in prisons and in STD clinics. Furthermore, I notice that the public facilities, the governmental facilities, the prisons and STD clinics are emphasized. We haven't defined the role for the many individuals who go to

private practitioners in helping us try to eliminate this disease, analogous to the way we try to eliminate disease in pediatric populations. Dr. Margolis is, of course, absolutely correct. We need a funding base so that we can build a structure and reach out to partners. I would maintain that before we can achieve that, we need a plan and we need recommendations. So what I'm proposing for the future is perhaps a working group to look at the whole area of hepatitis B epidemiology and possible interventions in adults. My own personal preference, as some of you know, is to extend -- yes, to extend -- the universal immunization concept beyond the 19th birthday through those periods of young adulthood where we know so many cases of hepatitis B still are occurring, but that's a look to the future. Thank you.

**DR. MODLIN:** Thanks, Bill. Jane? Dr. Siegel?

**DR. SIEGEL:** Jane Siegel. I have just a couple of comments.

Of course, we're really pleased to see this document. I would like to see the message conveyed in the document that these -- the recommendations for health care

workers apply across the continuum of care and not just for the acute care hospital, the outpatient settings, the surgicenter. Hemodialysis has already been addressed, but I think this goes along with a lot of the themes in HICPAC that were addressing the entire continuum of care.

And along with Dr. Gall's comment about the birth dose, the background discussion leads us up to a very -- the concept of the strong support for the birth dose, but the recommendations didn't quite carry that through. So we would like to see that.

And then the other point is we would like to see the recommendations be rated based on the evidence, and we appreciate the fact that this document probably has the most A-1 recommendations of any document we have, but there are some that maybe don't have a strong evidence and a strong demonstration. I think that helps the provider determine, with limited funding, what we really need to do and what we don't have the evidence to support. So we would like to see some attention given to that.

**DR. MODLIN:** Thanks, Jane. At this point, would it

be useful just to open things up other members of the Committee or do you have additional points regarding the document that you wanted to point out?

**DR. MARGOLIS:** On the recommendations, there were a few changes as we -- once it gets out there and we look at it again but, yeah, maybe it's better let's just go with general things. And then if they haven't been addressed -- For instance, the one about the birth dose, we would suggest that actually in that very first recommendation that we say "it is recommended that the first dose of vaccine be given during the newborn period" instead of "strongly encourage." And that's actually consonant with the Academy of Pediatrics' current statement. So, again, that was one that we had just missed.

**DR. MODLIN:** Why don't you just go ahead and go over the others that you're going to go over, and then we'll

**DR. MARGOLIS:** The one I had here is -- All right. Well, that was that small point. Is there any discussion about that? We might take these one at a time.

**DR. MODLIN:** Comments? Dr. France?

**DR. FRANCE:** I did notice that the very last sentence of that first paragraph said that the third dose should be given at six months and no later than 18 months. I thought maybe that was a bit strong, to say that it should be done at six months. And my concern there is that we often have children who come in for a six-month visit but they're really five and a half months, and people may be giving the vaccine. So I know that the Harmonized Schedule has this window of six to 18 months and some folks actually schedule that shot at a nine-, a 12-, or an 18-month visit in express effort to avoid potentially giving the shot before the six months of age. And having it say "should be given at six months" might actually lead to more children receiving their third shot before they turn six months of age.

**DR. SMITH:** It also seems a little bit different from what we're saying in the general recs, which we'll discuss tomorrow, but that sentence says "for infants at low risk of infection with hepatitis B virus, the hepatitis B vaccine series may be completed at anytime after six months of age."

**DR. MARGOLIS:** All right. We'll adjust that. Because actually, in the -- in this last section down here, "In populations with previous or current high rates of infection," there they should be completed by six months of age and no later than 12. I mean, this is really the group for which HBV transmission occurs. So we'll adjust that to give the flexibility in the first group but make it that they really should be completed at six months, giving that third dose at six months in the high-risk populations.

**DR. MODLIN:** Due to early post-natal transmission.

**DR. MARGOLIS:** Right.

**DR. MODLIN:** Jon?

**DR. ABRAMSON:** I do think there's a little bit of problem there, and that is when we go back to the general recommendations, we're asking for four months between the second and third dose. When you say "by six months of age," you are, in that case, clearly implying that you should do it before. There I do have some problems with the wording.

**DR. MARGOLIS:** And it should be at six months of age, yes.

**DR. MODLIN:** Deb Wexler?

**DR. WEXLER:** Deborah Wexler, Immunization Action Coalition.

I would just like to -- in the statement about the first dose, it says it is strongly encouraged that the first dose be given during the newborn period. I'm wondering if you could include language about birth, at birth or during the newborn period, because if you just say newborn period, that's really vague and it can be, I understand, a month of age. But I think you should also keep the possibility in there that you can give it at birth, and I think it should be stated.

**DR. MARGOLIS:** We will -- I think we can adjust that also to -- I think the other major thing that was not in the version that you have had to do with sex partners and persons with chronic HBV infection. I left a line in there and we actually didn't put any recommendations behind it. And this is actually now consonant with what's in the STD treatment guidelines. It's an issue that comes up all the time. You have a screening situation where you find someone with chronic HBV infection and then what do you do with the sex partner.

Our recommendations have always been just give vaccine, don't give vaccine HBIG, and that's been an area where we get a lot of calls and there's been a lot of confusion in that. And that's actually the way it is in the STD guidelines. We just felt that it should be consistent with that. So that was -- should be there. And then we also put the post-vaccination testing recommendations, which is also in that table on post-vaccination testing, but we brought it all together in that one sentence. It's -- Again, that's the way we've been doing it with the STD treatment guidelines. So that's different. You don't have that in your current draft.

**DR. MODLIN:** Okay. Dr. Gall?

**DR. GALL:** Hal, I've looked at this and I can't find anything about pregnant ladies in here. I see adolescents. You say all adolescents should be vaccinated, adults in certain high-risk things. A person who becomes pregnant has one STD on board right there. So what is the policy in pregnancy? It's my impression that this vaccine is safe to administer in pregnancy.

**DR. MARGOLIS:** Yes, it's safe to administer during pregnancy. Our recommendation has been that if a pregnant women has risk factors that they should be vaccinated. And again, there are some clinics that do that. Routine vaccination of pregnant women, which goes -- which Bill Schaffner is suggesting in terms of age groups or a wide category has not been a recommendation, one based on risk overall in terms of the four million pregnant women a year and cost-effectiveness. I mean, that's really -- those are really the two competing issues in adult immunization for hepatitis B. So high-risk pregnant women, for which there are many, should be vaccinated. I guess we have not explicitly, other than in the background part of the statement, said that it's good, and it's okay, and it's safe to do that.

**DR. GALL:** I would think there should be some statement about pregnant women in this.

**DR. MODLIN:** Okay. Georges?

**DR. PETER:** Hal, you mentioned a change in the American Academy of Pediatrics recommendation related to the immunization of the premature infants born of

hepatitis B surface-antigen mother, and I'm sure Jon can give us the specifics, but it would be worth mentioning to the Committee.

The second comment is that I think that since the ACIP now recommends that the time for administration of hepatitis B is at or shortly after birth, we should make sure that the Harmonized Schedule that we develop this fall and discuss tomorrow indeed puts hepatitis B directly under zero months of age, which was the way it was prior to the thimerosal episode.

**DR. MODLIN:** Good point, Georges.

**DR. MARGOLIS:** The preterm issue -- I've been working with Tom Saree [phonetic] and I guess we don't yet have your statement together but we're close, but there are new data, to follow up on Georges', that would suggest that the poor response in preterm infants is not as poor as we thought. So the Academy is coming forward with a statement and we will -- it will mesh, as we've done before, with these issues.

**DR. PETER:** Could --

**DR. MARGOLIS:** I actually don't have their -- I was on the e-mail this morning with Tom and he still didn't

have the statement. So I wanted to work with his statement first, and we will send it out.

**DR. PETER:** I think it would be important to share the data --

**DR. MARGOLIS:** Yes.

**DR. PETER:** -- remembering that the Red Book Committee draft of statement, we still have to get approval and it may not see the light of day for a few months.

**DR. MARGOLIS:** We will put the data in the background in terms of that. And again, Tom is putting that together.

**DR. MODLIN:** Good point. Karen Midthun?

**DR. MIDTHUN:** Karen Midthun, FDA.

I'm sorry I don't have a package insert with me, but my recollection is that this is Pregnancy Category C, which means that there are no animal data that look at reproductive toxicity, and I don't believe that the package insert includes anything about clinical data.

So I guess my question would be, what exactly are the data that support the safety of vaccine in pregnancy? Certainly, the package insert, when it says Pregnancy

Category C will also say that pregnant women can be vaccinated if clearly indicated, which gets to the point I think that you are making, Hal. But with regard to just a blanket statement that there are safety data, I guess my question would be, you know, what are these? And I don't know if the manufacturers might want to comment.

**DR. MARGOLIS:** Getting into background, there are -- we do have a statement. There have been a number of published studies where pregnant women have been inadvertently vaccinated during large trials but have then been followed, at least in terms of the newborn. Again, there -- we're looking at probably a total of about 200 instances. So, again, it's not the strong confidence, but there's been no evidence and then we use the issue of the risk versus the benefit in terms of HBV.

**DR. MODLIN:** So the real place to address that is probably in the safety section as opposed to -- Well, that would be --

**DR. MIDTHUN:** Well, one would -- I would just say that making a blanket statement that it's safe, I think that

would really have to be qualified.

**DR. MODLIN:** Fair enough. Other comments? Dr. France?

**DR. FRANCE:** I was thinking it would be nice if you could add some of that new epidemiology that we saw earlier today and part of the success story of hepatitis B in this recommendation in the beginning because we really don't get much sense from the document now about all the success we've had in the last 10 years.

I also wanted to point out that on page 35 at the bottom, line 28, it suggests that we need to repeat the series of the hepatitis B vaccination if someone is off schedule. And I'm concerned that if a child, for instance, gets their third dose by four or five months, it hasn't really been my practice to restart the whole series of the three but provide instead a fourth dose after that age of six months. I may be incorrect there, but the statement here seems to say that we need to receive a three-dose vaccine series again.

**DR. MARGOLIS:** Well, I'm going to let someone from the general recs and the -- because we thought we had that consonant with what this amounts to or a lot of the

school entry and other policies. So it was our understanding, unless this has now changed, that if someone was not properly vaccinated on schedule that they would -- that the series was to be readministered. Am I wrong?

**DR. MODLIN:** There's two issues here. There is number of doses and there is catch-up. I think that in order to be consistent with everything that we do with respect to childhood immunizations that, regardless of the interval from the last dose, there's no reason to add additional doses. So long as the total number of doses equals three, that would consider the child to be adequately immunized. Isn't that the question that you're getting at, Eric? We can deal with that --

**DR. MARGOLIS:** We'll deal with that --

**DR. MODLIN:** We can deal with that easily outside of this.

Are there any other comments specifically about policy? We can talk about details, but --

**DR. MARGOLIS:** There's one other addition here, and that has to do with victims of sexual assault, which is, again, coming from the STD guidelines, which I

didn't have in there at all. And to make that -- and it's come up as an issue in terms of, again, what should one do? Again, not based on any clinical trials data or even any case control data but at least based on data of post-exposure efficacy of vaccine alone and also the expected frequency with which the perpetrator might be surface-antigen-positive -- We had had this discussion in this meeting before -- we felt that vaccine alone, active post-exposure immunization versus passive-active, which has been an issue that has come up, is the recommendation of choice. Again, putting it here instead of the background. It's in the background and I have discussions there but bringing it up to the recommendation side since it comes up a lot.

**DR. MODLIN:** Terrific. Dr. Severyn?

**DR. SEVERYN:** Dr. Kristine Severyn, Vaccine Policy Institute, Dayton, Ohio.

I believe a lot of this discussion is a bit disingenuous because more than 95 of people in this country will never catch hepatitis B and never been exposed their entire lives. And if one maintains what's called a --

or at least what I call a wholesome, moral lifestyle, they most likely will go to the grave without ever having been exposed to this virus.

Secondly, I find it highly offensive Dr. Gall's statement here, that all pregnant women already have one STD on board. As a mother of three children, I look at my children as fruits of mine and my husband's marriage and gifts of God. My children are not STD's. I find that highly offensive and I'm sorry, Dr. Gall, but I'm glad you didn't deliver my babies.

**DR. MODLIN:** Any further comments?

**DR. MARGOLIS:** John --

**DR. MODLIN:** Yes.

**DR. MARGOLIS:** -- I have another one. And this has actually happened since this all came out, is that people may be aware, this has to do with Table 1, which as well, we tried to put all the vaccines there. You basically have it to this point. Since this -- Since we went to bed, TwinRix, which is the combination hepatitis A and hepatitis B vaccine has been licensed and has been approved in the United States for adults. So that is now added in there showing that, and then

we will have to write a section and I do have at least a table that would show the groups for which there are overlapping -- the overlapping risk groups for which we feel the recommendations will be made. Now, I think it's a question in terms of format and whether we bring that to the recommendation side or just put that back in the discussion in terms of the combination vaccines, but I will work on that since this all happened recently. And I know that TwinRix data had been presented here to the Committee several years ago and then the recent licensure of it. But these are the groups for which there are both recommendations for hepatitis B and hepatitis A immunization.

**DR. MODLIN:** I guess this certainly raises the issue of whether or not there needs to be specific recommendations for the other new combination vaccine or not, and I think that's something we'll have to consider. But that's also the topic for, I think, another time and another place.

Anything else, Hal?

**DR. MARGOLIS:** That's all I have.

**DR. MODLIN:** Great, okay. First off, I want to thank

Hal for an immense amount of attention that he and the others on his staff have paid to this document in the last few months and, obviously, we can see the fruits of those efforts.

I'm going to ask that members of the Committee, liaisons, and everyone else read over the document carefully, get your comments directly to Hal within the next month, and we will set a goal of completing -- Lucy?

**DR. TOMPKINS:** Finish your statement.

**DR. MODLIN:** Okay. We'll set a goal of reviewing the hepatitis B statement again at the October meeting and, hopefully, taking a vote on the statement at that time. I think at the same time, we need to be paying attention to the issues that Bill Schaffner, Stan Gall, and others have raised and that we probably will and probably should set up a group to begin to address some of these broader and important public policy issues, but I personally hope that they won't hold up publication of this statement.

Lucy, did you --

**DR. TOMPKINS:** That was going to be my comment, that I hoped we would pursue a judicious consideration of

Bill's point about universal immunization.

**DR. MODLIN:** We certainly intend to do so.

Okay, let's move on to Yellow Fever. There are some predominantly safety issues that have come up around live-attenuated Yellow Fever vaccines that we have touched upon here at several recent meetings, at least a couple of recent meetings. There are some new data. Dr. Marty Cetron is going to lead the discussion.

**DR. CETRON:** While we're setting up and switching the laptop, I just want to thank the Committee for the opportunity to present an update. I think the last time we discussed this was in February 2000, and we'll use that as a starting point. There's been a significant amount of hard work on the part of many people in many places around the globe in addressing safety issues around Yellow Fever vaccine, and I think it's worth bringing those to the attention of the Committee members to see what progress has been made in looking into some of these issues.

In addition, there's also some sensitivities around the issue of Yellow Fever vaccine adverse events and it has -- some of the information that we've been

privileged to share with the Committee is sensitive and suppliers of those bits of information prefer that not only the individuals but the countries from which these cases are -- these cases are occurring remain anonymous at this point. So we'll refer to some of them as Country X. For those of you who may be aware of which country Country X is, we'll ask you to preserve their confidentiality during the discussion, if you would. One of the -- The last time that we met, we talked mostly about some work that had been done by folks in the National Immunization Program, the Division of Quarantine, and FDA and CDC, in looking at the VAERS database over a period of about nine years in assessing adverse events related to Yellow Fever vaccine. And this was triggered by a report in 1998 over a period of about a month of two cases of elderly persons who received vaccine and shortly thereafter developed febrile illnesses and went on to multi-system organ failure, one of whom died and the other who recovered. And the question was raised at the time whether the elderly were at an increased risk for some of the adverse events related to Yellow Fever vaccine

compared to a young adult cohort.

And I showed you some data which will be sort of starting point for this, suggesting that those increasing in age were more likely -- at least from the reporting biases that may occur to VAERS, be likely to suffer some of these adverse events, multi-system adverse events that resulted in hospitalization or death.

But I think prior to going into some of that, it's probably important to give a little bit of background history on the origins of Yellow Fever vaccine. This is a vaccine that has a remarkable track record of both safety and efficacy and has been used since the late 1930's, over 70 years of experience with this vaccine around -- all around the globe and it's been remarkably effective and an important public health tool, particularly in controlling Yellow Fever outbreaks in South America and Africa. In the U.S. and other developed countries without endemic transmission, the vaccine is predominantly used to immunize travelers who are going to endemic areas or areas in which transmission is ongoing.

The origins of the vaccine date back into 1927 actually,

independently when two patients who survived their Yellow Fever infection, their serum was used to inoculate monkeys in one case and mouse brains in another case, and go on and develop the live-attenuated Yellow Fever vaccine. The French neurotropic virus derives from that French origin in Senegal, and that vaccine was no longer produced after about 1982 due to concerns -- safety concerns about neurovirulence. All the vaccine that's currently in production today and there are about seven different locations that are manufacturing vaccine -- are all derived from the Asibi strain, a Ghanian patient whose viral isolate was put into monkeys and then the monkeys were transported to Nigeria to a research lab in Legos at the time, and passage serially in which some of the virulence factors were attenuated and yet some of the immunogenicity and protection was preserved. The early work with this virus -- And it's important to note that this is not a clonal derivative of a live virus but, in fact, it's a whole population of virulents with a variety of characteristics, although remarkably homologous in

terms of their genetic variability. And in the early use of the vaccine, particularly in Brazil, between 1939 and 1941, there was a higher rate of neurotropism and encephalitis, especially among young children under six months of age. And this observation actually led to the development of a seed lot system in which the number of passages was standardized. And this seed lot system has diminished, strikingly, the risk of encephalitis and neurotropism from the virus, and this had become the United Nations standard beginning in 1945.

So all of the vaccine now employs this secondary seed lot process, and we refer to these as a family of 17D vaccine type Yellow Fever virus. Its history dates back, as I've shown here, and it predominantly gives rise to two offspring strains of vaccine: one, 17DD, which is used in Brazil; and the other 17D-204. The events that we're going to talk about today really all are around both 17DD and 17D-204.

And in the late 1970's, 17D-204 was passage-derived one other time and developed a reference strain which is at WHO, which is the 17D-213.

The countries shown in white under each of these 17D viruses are the places where the vaccine is manufactured, and I believe most of these are still ongoing sources of manufacturing. The Senegal site now manufactures the 17D-213 WHO reference strain and has not continued to produce 17DD. So 17DD is predominantly produced in Brazil, which is one of the largest manufacturers of Yellow Fever vaccine globally.

It's also probably important to point out at this stage that 17DD and 17D-204 are remarkably similar in their sequence homology and their amino acid homology, greater than 99.5 percent homologous. So the reasons for discussing adverse events in regard to both DD vaccine produced in Brazil and 204 produced in most of the rest of the world is because these share so many common characteristics.

Now, this is where we left off I think at the last time I had the privilege of presenting data to ACIP, which was the observed through our passive reporting system of adverse events due to 17D vaccine as it were stratified by age. And one can see that as you

increase in age, even beginning at some point in the mid-50's and into the '60's, there was a stepwise increase in the reporting risk of adverse events that were classified as systemic, multi-systemic involvement, onset after 48 hours, duration longer than 72 hours, and resulted -- among these 35 significant adverse events resulted in 14 hospitalizations and three deaths.

One of the important recommendations that came away from that meeting was to try to validate this observation with any other sources, and we had the opportunity through working with some collaborators in the United Kingdom to take advantage of a similar adverse event reporting system through a group of primary care practitioners in the U.K. This is just the comparison of the control vaccine that was used at that time with hepatitis A which really didn't show the similar stepwise increase in age-related reporting risks, and there were -- no deaths occurred in over three million doses that were administered over this five-year time period.

And then we had the opportunity to review a database,

a five-year look at Arilvax, which is produced in the United Kingdom. And in this case, the number of doses over that five-year period was fewer. It was one million total doses. There were 36 systemic adverse events, and the same criteria, in the fact, the same investigators who were blinded in -- age-blinded to do the VAERS review participated in this review of the Arilvax database. And while there was more other nonserious adverse event reports, like local reactions and other minor fevers that quickly resolved, there was the same stepwise increase in risk. One of the notable exceptions is that in the U.K. there are many fewer, in fact, hardly any vaccine recipients that were over 15 years of age. So we're sorting of missing that last step in the ladder there.

What I'm going to summarize for you over the next 20 minutes or so are a description of a newly-described syndrome, a sepsis-like syndrome, associated with 17D Yellow Fever vaccine over a period of the last five years. There are seven cases that I'm going to tell you about. Five of these are from non-endemic countries that received 17D-204 vaccine. Four of them

are in the United States and their age is 63 to 79 and one is in Country X in a 53-year-old male. The other two cases that I'll describe for you today are from Brazil, and as I mentioned, a lot of work and collaboration has been done between the U.S. and Brazil in clarifying, identifying, and working up these cases. This was from -- in association with 17DD vaccine, and these were in a five-year-old and 22-year-old otherwise young adults who were receiving vaccine as a part of a nationwide campaign.

Many of you may be aware that Yellow Fever is on the resurgence, both in the Americas and in Africa, and particularly threats to reurbanize in Brazil. So Brazil, over the last four or five years, has been embarking on a massive vaccination campaign, both in the endemic area where it's part of the EPI program, as well in the epizootic transition zone areas, and in some cases moving even further toward the coast and then in the non-endemic areas. So between 1998, I believe, and 2000 or so, they administered over 38 million doses of Yellow Fever vaccine.

The onset of this syndrome is going to be within two

to five days after vaccination. All seven of the cases share common features of multi-organ system failure, six of them died, and five of the seven cases, 17DD or 17D-204 vaccine-type virus, was isolated by viral culture, and the virus was sequenced in four of these five isolates, two from Brazil and two from the U.S. And in no instance was wild-type Yellow Fever isolated from any of the patients.

In order to sort of fully appreciate the syndrome as it relates to the vaccine, I would like to just share with you a brief clinical description of what wild-type Yellow Fever looks like. WHO estimates there are about 200,000 cases of Yellow Fever occurring annually in South America and in Africa. The incubation period from a bite -- insect infected mosquito bite to the first fever, onset of symptoms, is between three and six days. The clinical spectrum varies widely, including many asymptomatically-infected patients to the ultimate sort of extreme of fatal hemorrhagic disease. And the first three days are characterized by a viremia with sudden onset of fever and chills, very nonspecific viral-like syndrome, occasionally

followed by a brief period of remission. And then the intoxication phase, which is three to five days later, marked by the onset of jaundice, renal dysfunction, hemorrhage, DIC, and in those cases that go on to the jaundiced form, the case fatality rate is approximately 20 percent. It usually occurs within seven to 10 days of onset and death occurs by shocks, delirium, coma, and in many cases, hemorrhage.

Now, the differential diagnosis is quite broad, including in the tropics. It includes things like severe viral hepatitis, typhoid fever, severe malaria, leptospirosis, dengue, and many other viral hemorrhagic fevers. So the clinical syndrome in itself is not specifically pathodigmonic.

In order to really nail down the diagnosis, one needs to pursue histopathology. The target organ, in particular, in this disease is the liver, although other organs are involved -- visceral organs are involved as well -- and the classic histopathology in the liver on autopsy is a midzonal necrosis of the hepatocytes, some microvesicular fatty changes, the appearance of councilman bodies with eosinophilic

degeneration, and very characteristically, an absence of inflammatory cells, that the injury is by direct viral assault on the hepatocytes.

Here's a picture from a recent case that serves as a poignant reminder that Yellow Fever is still around in the Americas and in the U.S. This is a patient from California who was exposed to Yellow Fever in Venezuela, unvaccinated, travelled unvaccinated, returned, and had acute wild-type Yellow Fever and died. And here are some sections from a liver postmortem, one showing the H and E on the left and the immunohistochemical stains using monoclonal antibodies showing the red region throughout the liver that lights up the presence of Yellow Fever antigen.

Now let me give you a brief description of the characteristics of the four U.S. cases that were uncovered.

The first case was actually detected retrospectively by going back and doing that VAERS assessment. This is a 63-year-old male, vaccinated in 1996, and within five days of vaccination developed fever that progressed rapidly to hypotension, renal failure,

pulmonary failure, C and S findings, including some concerns about encephalitis, Rhabdomyolysis, thrombocytopenia with a very low platelet count that dropped to 25,000, increase in liver enzymes, and a peak bilirubin of 7.8. This patient ultimately died after 30 days and a liver biopsy on day 28 was done, and I'll show you some of the results from that in a few minutes. The second case was a 67-year-old female, also five days after onset, with a very similar clinical syndrome and progressed rapidly to die within eight days.

And then the two index cases from April and May of 1998 are shown as case three and four on this slide: one with a very rapid onset, about two days after vaccination, similar clinical profile, died 21 days later, and then this was one of the cases that I mentioned in which 17D vaccine strain virus 204 was isolated from serum on day seven; and the fourth case fortunately survived, onset about four days, similar clinical syndrome as well, with elevation of liver enzymes and bilirubin, and survived after a 22-day hospitalization, and in this patient 17D-204 was isolated from serum on multiple days as well as from

spinal fluid.

One always has asked the question, well, what's the incidence -- what's the risk or occurrence of this type of event? It's very difficult to actually get this information from a passive reporting system like VAERS and all the inherent biases about passive reporting, but it's sort of the best estimates that we have at this point. Over the study period of nine years, there were 15 million doses sold for civilian use and the occurrence was about -- of the event was about one in 100,000 cases and the case fatality rate, three in that one and a half million gives you about one per 500,000 doses. That's similar to the occurrence of paralytic polio following OPV -- first dose of OPV and similar range. But we actually don't really know what the true incidence of the event is.

And then very recently this year, the end of January, early February, there was another case that was reported from another non-endemic country, and then this patient was travelling to Saudi Arabia, actually. The fourth case that I mentioned before was also travelling to a destination without a Yellow Fever risk

as well. The onset was within two days, a similar clinical course, death at 11 days, and the autopsy and material liver, skeletal muscle, and heart all had pathology and virus isolated, 17D-204 virus isolated. Electronmicroscopy suggested flavivirus particles in the liver and the IHC and the sequencing results from this case are still pending.

As well is the important thing about all these cases is that, despite an aggressive search, no other pathogens were identified and no other medical etiology could account for the syndrome.

And then in 1999 and 2000, there were these two cases that were well worked up and very well described by our Brazilian colleagues following convening a -- PAHO had convened an expert panel to review the evidence for causality in these cases in Brazil in May of 2000, and several of us in the room had the opportunity to participate in that panel. The consensus was strong, 100 percent among the group that looked at the evidence that these two cases were clearly associated with the 17DD vaccine. There was a five-year-old female, previously healthy, vaccinated in '99 with onset three

days and death eight days after vaccination, a clinical course characterized by jaundice, hemorrhage, and multi-organ failure. The virus was isolated from multiple visceral tissues and the histopathology from the visceral tissues was classic for Yellow Fever, including large amounts of antigen present in the tissues in the same areas where the injury and the pathology were seen, and a subsequent case in February of 2000 in a 22-year-old woman, nearly identical clinical syndrome.

The expert committee that met down there also worked with the Brazilian government to establish some protocols for the laboratory work-up of cases like this, as well as some surveillance protocols to enhance surveillance in the setting of vaccine campaigns to look for cases of febrile jaundice actively in catchment areas and in hospitals.

So, in clinical summary, these cases all share the sort of common features. There are some variations, subtle variations between them, but they all share these features in common: sort of rapid onset after vaccination; fever; myalgias and arthralgias;

elevated liver enzymes and elevated bilirubin; low platelet counts, profoundly low platelet counts; lymphocytopenia; low blood pressure that requires vasopressor support; renal failure that requires dialysis; and respiratory failure requiring ventilatory support.

In terms of the other possible explanations, one looked at concurrent vaccinations received, there were no known prior doses of Yellow Fever vaccine given in any of the cases that I've described. In some cases, the medical record is actually silent on this issue rather than specifically addressing it. Four of the recipients received other vaccines but no one other consistent vaccine. Many of them in the non-endemic countries received other travel-related vaccines and, in Brazil, received other vaccines commensurate with routine EPI immunization.

There are four liver samples that were available for review, two of them from Brazil, one of them from the U.S., and one from Country X. Three of these show classic midzonal hepatic necrosis and two of them, the Brazil cases, in particular, show large amounts of

viral antigen in the area of tissue damage and injury. The IHC is pending from the -- from Country X, and the EM showed consistent flavivirus virions.

In the U.S. case, the only case for which there's any tissue at all -- and none of the cases were subjected to autopsy -- it was the 1996 case which was identified retrospectively and initially misattributed to hepatitis A vaccine. The patient had presented with jaundice on the same day of receiving hepatitis A vaccine, which, in fact, was several days -- five days after a Yellow Fever vaccine, but there was a piece of liver that was available in the CDC pathology archives and we went back -- Dr. Sherif Zaki went back to pull this and then relook at and stain it with monoclonal antibodies to Yellow Fever and found it to be positive. It did not show the classic midzonal necrosis and it was a late liver biopsy tissue, at day 28 after onset of symptoms, but I'm going to show you some of the pictures.

This is the skinny needle biopsy from the U.S. case in 1996 and there is the microvesicular fatty chamber, parenchymal degeneration, and minimal inflammation,

but these are not pathopneumonic per se. There is -- When Dr. Zaki went back and restained this with monoclonal antibody, a small amount of Yellow Fever antigen was seen in Kupffer cells and that's indicated in red and pointed out by the arrow. This is a small amount compared to the amount of antigen that was seen, for example, in the Brazilian histopathology.

These are the more recent images that came from Country X, and the lower power sort of identified some of the key features for myself and those of us who have forgotten the structure of liver pathology, but the portal track is shown on the left with the central vein in the center, and the area of hemorrhage and hepatic necrosis in this general midzonal area shown here.

Higher power magnification of this same tissue shows some of the hepatic necrosis with the absence of inflammatory cells and some of the acidophilic necrosis which is sort of on the way to producing the councilman bodies that I referred to earlier. It's a fairly classic pathology, but it's also nonspecific and it is seen in many other types of hepatic viral injury which elucidates the importance -- or

highlights the importance of doing the monoclonal immunohistochemical staining.

The molecular sequencing results are available from four cases, two of the Brazilian cases and two in the U.S. In the Brazilian cases, 17DD Yellow Fever viral isolates were obtained from serum and multiple tissues as I indicated, and there was really no consistent mutation in envelope protein or immunodominant region to explain this event on a reversion to wild-type, for example. And the patient isolates as well as the vaccine vial and secondary seed lots were fully sequenced on the part of the Brazilians, a really sort of monumental effort in working this up, and it was basically determined that what was isolated from the patient was similar all across all of those different isolates.

In the U.S. case, two different patient isolates were available for sequencing and they showed 17D-204 viral isolates, one with serum alone and I recall the other was serum plus CSF. In one of these patients, there were some mutations in the envelope region and the membrane protein regions that were not directly

present in the vaccine vial but, in a sense, amplified in terms of the proportion of these types of variations that were found in the patient isolate. And in the other case, there were no significant changes at all. One wonders what the significance of those changes are. Virulence -- Follow-up virulence testing has not yet been done and it's difficult to interpret. These are not changes that are compatible with reversion to wild-type, but they are -- do represent a change in the proportion potentially of quasi-species that are in this pool of Yellow Fever virions in 17D vaccine. The sequencing work from Country X is still pending.

So let me just wrap up. I'm kind of weighing on both sides the evidence for a causal relationship, the evidence for and against. I think the supporting evidence is: some of the striking temporal associations; the 17D vaccine strain being isolated from blood as well as multiple target organs; the compatible histopathology in the target organs in conjunction with a large amount of antigen, in particular in the Brazilian cases that were seen in the target tissue; the hepatic necrosis in Brazil and

Country X; and myocarditis and myocytis in Brazil and Country X as well; the absence of other pathologies or etiologies; a similar sepsis-like syndrome, similar in some ways to wild-type Yellow Fever, although not completely; the fact that there are multiple cases, now seven, plus others under investigation; multiple countries are involved, three countries and manufacturers; both vaccine strain subtypes 17D-204 and 17DD; and in fact, there's actually precedent and biologic plausibility for live-attenuated viruses to cause disease similar to the wild-type disease like oral polio and perhaps the case with measles.

There's also some evidence against a direct causal relationship: not all of these patients have a classic Yellow Fever finding, some things are typically absent that are seen in wild-type disease; in the U.S. cases, there are some atypical features, in particular one case that had rhabdomyolysis which is not well described with wild-type Yellow Fever; there's not a consistent reversion to wild-type in all these cases where you look at the sequences; in Brazil, they've done some elegant follow-up virulence work by

taking these vaccine isolates, patient isolates, and putting them back intrahepatically and intracerebrally into primates and into a hamster model, and there is no pathology seen when they went back and did that; and of course, the fact that the syndrome has not previously been reported prior to 1996 makes one -- despite the fact that we've been using -- I don't know, someone said to me recently millions, close to a billion doses of Yellow Fever vaccine have been distributed over the last 70 years or so. There are some unanswered questions, particularly what is the pathogenesis of this sepsis syndrome, is this really a new event or is this a newly-recognized event? My bias is that this is a newly-recognized event and one that would be, in fact, quite challenging to recognize. If it's as rare as we hope it is, the small amount of vaccine that's used in non-endemic countries targeted specifically to travelers would make this event occur once every couple of years and difficult to detect. Where the vast majority of Yellow Fever vaccine is used worldwide is in endemic countries and frequently to control outbreaks. In the setting of an

outbreak, it's not clear to me that one would distinguish, i.e., vaccine-induced cause of febrile jaundice from an actual wild-type case of Yellow Fever. So I suspect the occurrence of -- the co-occurrence of vaccine use in areas of outbreak control is one way that could have masked the observation of this syndrome for many years.

The question is whether this is a clinical spectrum or an all-or-none phenomenon. I don't think we really know but, again, my own bias is that this probably falls along a clinical spectrum. There have been cases that have recovered. Some of the more recent cases coming from Brazil during active surveillance suggest that there are folks who have recovered, and I suspect that there is a continuum.

It's not clear yet what the risk factors are and how many of these risk factors are host-related. Age may be playing some role -- but as we've seen from Brazil, it's not an exclusive relationship to age -- and whether there's also underlying host factors like flavivirus susceptibility genes or flavivirus resistance genes, which have been recently described in mice, could be

playing a role. And again, further work is really needed to firm up the vaccine strain issue and the production process for sure and whether there's some risk associated with that.

We don't have good quantitative incidence data yet and we also lack quantitative risk benefit analyses, although my bias would be that to go into a Yellow Fever endemic area and a Yellow Fever outbreak area for certain unvaccinated represents a much higher risk to an individual than using a vaccine with the safety record that this one has had.

Clearly, additional research is needed to clarify these things further, including animal virulence studies, full laboratory work-up of cases that are coming to attention more recently, perhaps additional retrospective reviews of suspect cases, and to define host risk factors, in particular.

In conclusion, the -- I think we can say that 17D is a possible cause of this sepsis syndrome. It's not clearly due to the emergence of a wild-type clone. It's not exclusively due to any one known clear mutation in vaccine type virus. It may be related to an

idiosyncratic host response. Most of these cases are occurring after primary immunization as far as we can tell and the incidence is really unknown. I think the bottom-line message and recommendation is that Yellow Fever vaccine should be reserved for U.S. travelers who are going -- actually going to risk areas, endemic and epidemic areas only. As the only internationally regulated vaccine with actual country entry requirements, there are sometimes other reasons why people are receiving Yellow Fever vaccine even when there's no medical risk. And I would certainly caution against that approach. Two of the cases that I presented here had no -- were going to countries without any risk at all of Yellow Fever.

The proposed response that we've outlined is a revision to the 1990 ACIP statement on Yellow Fever which would inform -- make more folks aware of this observation, in an effort to inform practitioners by letters to vaccination centers, letters to practitioners, a possibility of a package insert change, in addition to publications. Both the work from Brazil and the work in the U.S. has been submitted for fast track

publication in Lancet and the VAERS work is scheduled to come out in the next issue of Emerging Infectious Disease. These will help increase awareness. But in addition, I think we need to enhance passive reporting with some of the Infectious Disease Society and International Travel Medicine Network of Providers and link these to the VAERS system and also make widely available a protocol for how one goes about working up these types of cases, which really requires a fair amount of laboratory sophistication and needs to be done in reference centers.

And finally, one proposal is to establish an active surveillance system of Yellow Fever vaccine and this could be done through the certified Yellow Fever vaccination centers and other networks. We've recently, over the last year, completed a project where we've attempted to map and update the directory of certified approved Yellow Fever vaccination centers in the United States. There's about 3,600 of them. They're distributed fairly sporadically, if you will, across the United States and are certainly concentrated in coastal regions where there's larger

populations and perhaps larger populations of travelers. But this represents an opportunity for a network partnership in doing more active surveillance perhaps by a postcard mail-back or something where we can more adequately look at both the denominator and the numerator.

That's sort of concludes my remarks to provide some update to the work that's been done.

**DR. MODLIN:** Terrific. Thanks, Marty. Let's open it up for questions for Dr. Cetron.

Jaime, go ahead.

**DR. DESEDA:** (Inaudible)

**DR. CETRON:** The question was, what do you normally expect following immunization in terms of viremia or distribution of vaccine virus in target tissue? And I think there's some early work that suggests there is a viremia after vaccination, but viral replication is very much contained and it's minimal. And also the serologic response to vaccination is much milder than what you would see in wild-type. It's generally -- The purpose of the attenuation is to not have this widespread viral replication and hepatocytes and

tissue damage in heart muscle and spleen and other organs. There are others in the room, including Dr. Monath, who have done some of these studies who are perhaps in a better position to comment. But I think it's distinctly unusual to see this amount of viral antigen in target tissue with histopathologic damage. This would not be what would be expected after vaccination. And as far as CSF, for example, there's some work that Bob Chen and Ted Syn [phonetic] and others did in Trinidad and Tobago looking at -- after childhood immunization with Yellow Fever, enrolling cases of encephalitis and meningitis where a spinal tap was indicated otherwise. And in none of those cases were they able to find Yellow Fever vaccine strain in spinal fluid. So I think this is quite distinct and unusual.

**DR. MODLIN:** It's an important question. Dr. Monath, did you want to --

**DR. MONATH:** [Inaudible)

**DR. MODLIN:** Okay, fair enough. Paul?

**DR. OFFIT:** Yeah. I'm just -- If we're choosing to recommend that if someone from this country is going

to be travelling to an endemic or an epidemic area with Yellow Fever that's greater than 65 years of age receive the vaccine, I'm trying to get a better sense of what the risk and benefit analysis is for that person. I mean, what you list here is it's 2.5 -- estimated reported incidence of 2.5 per million doses, but that's not -- that's presumably not per million doses given to the greater-than-65-year-old.

**DR. CETRON:** Well, in fact, if you -- depending on how you bracket the denominator, for example, the deaths are skewed toward the elderly in the U.S. experience and they're occurring, you know, at a reported rate of one in 50,000 as opposed to one in 500,000 by looking at the whole population.

I think your question is a really good one, and the really difficult part of that is getting a true handle on how many people going to these areas are actually at risk. In the last few weeks, we've been trying to compile data that gave us a sense for vaccine coverage and how many people are protected and how to interpret the numerator of cases. Clearly, there's been a resurgence of Yellow Fever in South America and in

Africa that's well documented and described by WHO. There's more activity now than there's been in any five- or ten-year period prior in a long time. And this shows you a map of the areas that are both at risk and where there have been recent outbreaks in the last five years. It represents a large population but not every place within these countries shows an equal risk, but what we did recently is look at tourism data, statistics looking at U.S. travelers and tourists going to these countries at risk and entering the country at all, not necessarily trying to distinguish where they went in the country. And one can see that recently there's been a very dramatic -- a 300 percent increase in travel to South America to endemic -- Yellow Fever endemic areas, for example. About a ten percent increase is documented by WHO data for Africa and I think the data aren't quite as good on U.S. arrivals.

So there's very rapid increase potentially in the denominator of people being exposed. Here are some of the vaccine doses sold for civilian use provided by the manufacturer. The rate of increase in vaccine is not nearly as steep as the rate of increase in travel to

these countries. And what we've done most recently is try to guesstimate, and the best we can really do is guesstimate coverage, because these data aren't available. And we've modeled this and made various assumptions here that may not be accurate, but if you assume that everybody going to a country -- at the country level where there's reported transmission -- is in that target population of those who should be immunized and make some assumptions about one percent wastage -- Actually, it doesn't matter whether you use no wastage -- and a previous immunity of folks who were vaccinated within the prior ten years, you have a rough numerator and a rough denominator to look at coverage. This is, I have to emphasize, quite crude and based on modeling only. We've not yet had the opportunity to look at surveys that would estimate this type of coverage. But it's disappointing. The trend that's here, regardless of the model parameters you pick, are that coverage is going down and it's not very high, somewhere between ten and 20 percent. Now, even if only a third or a quarter of the people going to those countries are actually going into risk areas in those

countries, you still don't get coverage up into the 90 percent range which some of us had hoped that it might be.

So that's one piece of data about that risk piece in terms of protection. Now, the other thing is that, you know, we haven't had an imported case of Yellow Fever in the U.S. I think since the 1920's and in the last five years we've had two in the U.S. and there have been two in Europe, three of those with exposures in South America and one with an exposure in Cota Voire [phonetic].

So that's the best data that I know of that are available regarding the risk side in terms of travelers and the potential benefit of immunizations, but it's very difficult. It's a difficult nut to crack.

**DR. OFFIT:** So just one quick follow-up.

What you state here is -- And I think it's a good way to put it, actually -- is a physician should therefore be cautious to administer Yellow Fever vaccine only to those persons truly at risk for exposure, that's great, but I think you could arguably take it another step which is that if someone is choosing to be a tourist

in a country where the disease is endemic and is an older person, one option is that they not be encouraged to travel, you know, that if we don't think we have a safe - a vaccine which can safely protect them, that's an option. I'm just throwing it out there because I think this is real and I think it's worrisome, and I think we do have to communicate it and the question is how best to do that.

**DR. MODLIN:** Rich?

**DR. CLOVER:** I want to compliment on your presentation and the detailed investigations that were done in various countries. Paul actually asked my first question. The second one was just a curiosity question.

Do we know if the doses that were given to the cases were they single-dose vials, multi-dose vials? And do we know anything about the management of multi-dose vials, if it was?

**DR. CETRON:** Yeah. All of the cases, the five cases that I described from the developed countries, if you will, not endemic countries, were single-dose vials. There were look-backs at the lots. There wasn't any

common lot number. There were others who received vaccine from the same lot but not necessarily from the same vial because they were single-dose vials. In Brazil, it's a totally different story. They're using large amounts that are being prepared for mass campaigns.

**DR. MODLIN:** Myron?

**DR. LEVIN:** Myron Levin.

Did you say that we knew that the people who died were normally previously? The older people, particularly, they had no underlying illness?

**DR. CETRON:** There are a variety of underlying illnesses that were in control that weren't requiring immunosuppressives, the usual panorama of underlying illnesses one might expect in an elderly population, previous history of --

**DR. LEVIN:** Nothing like common variable immunodeficiencies?

**DR. CETRON:** No. And many of them were worked up for specifically for immunodeficiencies that were absent, and the two cases from Brazil also occurred in people that were entirely healthy young folks prior --

**DR. LEVIN:** And that was my next question, the young people. Do we know that they were HIV-negative from Brazil?

**DR. CETRON:** I believe, yes, we know that they're HIV-negative in both instances.

**DR. MODLIN:** Dr. Jackson?

**DR. JACKSON:** The comment by Paul about possibly making it optional for a person who is, let's just say, 65 or older going into an endemic area. It's been my own personal experience to be detained in Zaire because I did not have a current Yellow Fever shot. So it goes both ways. Some countries will require that you have it when you come in --

**DR. OFFIT:** No, I was actually saying if a person -- if it's an option trip, they should be encouraged not to go --

**DR. JACKSON:** Oh, an optional trip, okay. An optional trip.

**DR. OFFIT:** I mean, I tell you, if my father were telling me he was going to go to an Yellow Fever endemic area, I think I would encourage him not to go as compared to get the vaccine and go. I'm saying it's -- I think

this is a worrisome side effect, a very worrisome side effect.

**UNIDENTIFIED SPEAKER:** Death.

**DR. OFFIT:** Death, death is a bad side effect.

**DR. JACKSON:** Being detained Zaire wasn't any better.

(LAUGHTER)

**DR. MODLIN:** Dr. Helms?

**DR. HELMS:** Right. Just pursuing Dr. Levin's questions.

Another thing about the elderly is medications that they might be taking and some that might be hepatotoxic, thinking particularly about acetaminophen or any other medication like that.

**DR. CETRON:** Yeah. There were a variety of medications, especially during the course of managing and supporting these folks, including empiric antibiotics and so on. There were no known hepatic toxins. And your point is well-taken. Clearly, toxic exposures can cause some similar histopathology, but there weren't any seen. And again, especially from Brazil where the benefit of working these cases up sort of aggressively, knowing that some of the

earlier reports had occurred, allowed for the collection of more organ tissue and do the histopathology. We're hampered by the fact that in the U.S. the only real organ tissue that's available is a fortuitous liver sliver from 1996.

**DR. MODLIN:** Natalie?

**DR. SMITH:** Could you just clarify the booster dose recommendations? I know some countries the regulations require every ten years even though we think one dose may be good for life. So, certainly, if you had a 70-year-old who got vaccinated when they were 50 and there was some risk with the vaccine, you wouldn't want to give it again if there was no need.

**DR. CETRON:** Yeah. I think the -- there's been some nice work done in military recruits showing immunity is durable probably for 30 or 35 years and possibly for life, and there at one time was some discussion about bringing that data back to WHO to change the decennial vaccination requirement, which is a legal requirement within the International Health Regulations. It's a politically-driven requirement. And the concern was that the experience in the U.S. in an observed vaccine

controlled setting like military recruits may not apply globally. So the recommendation for re-immunization at ten years kind of helped. The other piece I think that's relevant to this issue is that while we don't really understand the pathogenesis, the sense is that this is occurring as a result of primary immunization, and I suspect that perhaps that down the road we will find that boosted vaccinees are at much lower if not no risk because of prior immunity. And I think some of the age difference that we see in Brazil and in an endemic area that's used a lot of vaccine in childhood immunizations, for example, where they're not -- I would suspect not nearly as many elderly people being primarily exposed both to flavivirus and to Yellow Fever vaccine might account for some of the epidemiologic differences that we see.

**DR. MODLIN:** Okay. We're going to have to wrap this up fairly soon, but let's try to take those people that have been waiting.

Rick Zimmerman?

**DR. ZIMMERMAN:** I share Paul Offit's concern. And I think the question that I would if faced with a patient

would be, what's the risk-benefit ratio. And obviously, that depends on what is the risk as they travel. And if there's a way to help begin to put that in perspective -- and I realize that's difficult -- I'm somewhat asking for the impossible, but if there's some way to begin to classify that, then you could make a judgment if this is worth doing or not worth doing. But if you don't have the risk side for the travel, then you won't have the risk side of the vaccine and --

**DR. CETRON:** Yeah. And like many vector-borne diseases, you know, even in an endemic country, outbreaks are focal. They're not spread uniformly across a place. It makes it a real challenge. Unless you have your finger on the pulse of global surveillance on a regular basis, you know, assessing levels of risk and then based on a perspective itinerary or what people end up really doing when they get there and decide, oh, yeah, maybe I will take that trip into the Amazon or not. So it's very hard. We're looking at some of these issues in the development of CDC recommendations for travelers at sub-country-level risk profile, for both malaria and Yellow Fever and

other diseases, but it's an enormous challenge.

**DR. MODLIN:** Bob Chen?

**DR. CHEN:** I'm trying to figure out whether this is just an old syndrome in which we just have poor surveillance or this is a new syndrome. I guess one bit of information that may be helpful is to look to see how many doses the DOD has given in the past years and whether you've had the chance to look back, and I don't know, Marty, you've had a chance to work with the DOD to do that.

**DR. CETRON:** We've made some queries to various folks in DOD and their -- the reply that I've had is that they've not seen this type of thing and would have recognized it in otherwise young, healthy military recruits, for example.

**DR. MODLIN:** The age spectrum is somewhat different. Yes, sir?

**MR. PRESLEY:** Jim Presley from Aventis Pasteur. I think there's some really important that should be made available to everybody in an updated Yellow Fever statement. However, I think it should be presented in a little different way. I think the Brazilian cases

should be separated from the cases in the United States for two reasons: first, the strain is different and the strain -- if you sequence the virus, you can see a difference. They're similar to 17D. The two strains that -- the DD strain and 204 are different. Second, you can demonstrate a difference by monoclonal antibodies. And third, there's some difference you can demonstrate in neurovirulence testing. So on that basis, they're not the same vaccine and they should be separated.

Second, the cases in Brazil are quite different. They're young people. There's no other obvious cause of death. They had an acute illness quite compatible with Yellow Fever. They all had autopsies done which showed the typical histopathology of Yellow Fever and they had Yellow Fever virus isolated from a multitude of tissues isolated and they were present in high titer. That's not the case in the United States. The cases in the United States are elderly population. In some cases, there's an alternate cause of death -- sepsis, for instance. Another thing is that these cases -- in two of the cases, there's no autopsy

findings. And in the one case where the Yellow Fever virus was demonstrated, in the liver it didn't have the typical histopathology of Yellow Fever.

So, at any rate, I think there's enough question that there really is a syndrome of that nature in the United States. At least I think that it bears further investigation, and I hope that we could convene some kind of panel involving the CDC and the FDA to try to resolve this question. Because we've already submitted an amendment to our package insert describing these cases and we have to do that under the guidance of the FDA. So if we could get some consistent -- consensus between the CDC and the FDA, I think we could send out one message to the people. Thank you.

**DR. MODLIN:** One last comment. Yes, sir?

**MR. MARKHAM:** I'm Tony Markham. I'm from the Division of Vector-Borne Infectious Diseases and I'm actually a co-discussant on this presentation. I just wanted to point out that Dr. Cetron and Cy and others have done a terrific job in looking at these cases, especially the American cases, with the information

that they had available. And the reason that I'm here is that I'm not hearing enough skepticism about some of the cases in terms of being weighed. Dr. Offit's father doesn't get to go to Africa now because of that. I think that -- to pick up a little of this last message is that these cases have to be looked at, they have to be taken seriously. Some of these cases are not classic presentations. Some of these cases have atypical presentations, and Marty had presented that rather well. The real emphasis here is that we have to take them seriously, especially in an active surveillance situation where we could look at these.

And with regards to what Vector-Borne is going to be doing towards this, we will provide the technical support to evaluate these cases so that we do get either the same level of investigation that they had in Brazil so that we can state it as to -- with surety. It's hard to look at those Brazilian cases and say anything else but what PAHO has said, and I think that we need that same level of information with regards to the American cases especially.

**DR. MODLIN:** Thank you. The purpose today was to present this as an important body of information that is consciousness-raising and obviously we need to be paying attention to, as everybody has mentioned. I think what we would like to do would be to form a small working group to work with Dr. Cetron and the others, including people from the FDA and elsewhere to -- Rich?

**DR. CLOVER:** Yeah. John, the Adult Working Group had looked at this the first time --

**DR. MODLIN:** Okay.

**DR. CLOVER:** -- and if you want to send it back to us again, we'll be glad to work with --

**DR. MODLIN:** Do you have a subgroup of people that have been working with it?

**DR. CLOVER:** We only reviewed the data that one time. We haven't seen it since then. But I can identify a subgroup.

**DR. MODLIN:** Okay. Let me ask if there's anyone else on the Committee that is really very interested in working on a working group that might work with the subgroup to the Adult Working Group.

(SHOW OF HANDS)

**DR. MODLIN:** Dr. Deseda -- Others? -- Dr. Offit. Anyone else? Okay. We'll put this together after the meeting and hopefully report back in the next couple of meetings.

Marty, thank you very much. I'm sorry. Karen?

**DR. MIDTHUN:** Karen Midthun, FDA.

I just would like to say that we are working with a manufacturer, as was pointed out, to update the package insert to reflect these new findings and, obviously, we would like to really reflect something that's as balanced and informative as it can be. And I think, certainly, the suggestion that's been made to do more active surveillance and other things we might do to gain more information would be, you know, excellent ideas.

**DR. MODLIN:** Obviously, the purpose of the working group will be to revise the statement.

**DR. CLOVER:** I would appreciate if the FDA would -- if they are working with it if they could participate.

**DR. MIDTHUN:** Oh, absolutely. I already spoke with Dr. Lewis Markoff. He's our Yellow Fever expert, and he would be the one who we would like to have participate in this.

**DR. SNIDER:** It may be a good time -- I know we're running short of time, but -- This is Dixie Snider. I'm not sure we've made it public. For every working group we have in which it's relevant to have a FDA representative, we want to have a FDA representative. We have an agreement with FDA that we will do so. So if you all, as members and program staff, would remind us of that fact and that agreement, it would be helpful.

**DR. MODLIN:** Terrific. Let's take a break. We'll return at 4:00, please, to start the last session.

(BREAK FROM 3:45 P.M. TO 4:11 P.M.)

**DR. MODLIN:** We're next going to address a series of issues on vaccine safety and vaccine safety communication. Bob Chen is going to lead the effort. Bob?

**DR. CHEN:** Thank you. Most of you were probably here during our December 2000 ACIP meeting where I gave an update on what kind of things we were doing, and during that, we mentioned two of our new initiatives. One was this Brighton Collaboration to standardize case definitions for adverse events following immunization; and the other one was the new contract

with the Institute of Medicine in conjunction with NIH to assess the appropriate public health level of concern on new allegations. And so our first two presentations by Dr. Katrin Kohl and Kathleen Stratton will speak about that. And then we'll have two presentations on the thimerosal and vaccination issue. First, Dr. Bernier from NIP will give an overview of the Public Health Service and other activities that we're aware of from this arena and then Dr. Bill Thompson, who is an epidemiologist that has joined our group, will talk about the study design for the follow-up validation study that we have planned.

So with that introduction, Katrin?

**DR. KOHL:** Good afternoon. Thank you for giving me an opportunity to present to you one of our new vaccine safety initiatives, the Brighton Collaboration, which aims to develop standardized case definitions for adverse events following immunization. The idea was initially formed by Bob Chen and others about two years ago at a meeting in Brighton, hence the name. We officially launched last fall when Dr. January Bonhoeffer, research associate at the University in

Bosert, Switzerland, and I, a medical epidemiologist in vaccine safety and development at CDC, were hired as the two coordinators. We are currently supported by CDC, WHO, and the European Research Program For Improved Vaccine Safety Surveillance, or EUSAFEVAC.

So why do we need standardized case definitions for adverse events following immunization?

Well, as most of you know, we are currently in the situation in the U.S. and other countries around the world where vaccine-preventable diseases have become much less frequent than the adverse events associated with preventing such diseases through immunization. And in such a mature immunization environment, it has become increasingly important to be able to assess immunization safety date to ensure ongoing trust in immunization programs.

The lack of standardized case definitions, as is currently the case, have led to a lack of comparability of immunization safety data which is one of the reasons for lack of scientific progress in immunization safety and represents a missed opportunity to maximize scientific output from both data from pre- and

post-licensure vaccine trials as well as from post-marketing surveillance data.

This slide illustrates the diversity in safety methods in the more recent clinical detail trials with the example of fever. As you see across the seven different study sites, investigators used different cut-off points for what they called high fever, ranging from 39.5 degrees Celsius to 40.5 degrees Celsius reported at intervals from one week to 48 hours with different methods of temperature-taking and reporting. I think it is easy to see that given the different parameters of fever data collection and reporting that it is, at best, difficult to be able to interpret reported rates of fever from these trials, particularly with the aim of comparing rates across different trials.

With this in mind, the Brighton Collaboration was formed to enable comparability of immunization safety data through the development of case definitions for adverse events following immunization and a broad implementation throughout the world.

We are currently composed of the Steering Committee,

which consists of the five initiators: Bob Chen at CDC; Elisabeth Loupi from Aventis Pasteur in France; Tom Jefferson from the Cochrane Collaboration and Health Review in England; Ulrich Heininger from the University in Basel, Switzerland; and Harald Heijbel from the Swedish Institute of Infectious Disease Control in Sweden; and the two coordinators, January Bonhoeffer and myself.

The case definitions are to be developed through expert working groups with one working group working on each AEFI, and we aim for representation from a broad range of expertise within our collaboration through collaborating with participants from regulatory, public health, scientific, professional organizations, and vaccine manufacturers.

Our target groups include investigators, health officials, health care providers, and regulators who carry out immunization studies, who make clinical decisions on immunizations, and then to get, interpret, provide, and report information on immunization safety.

This includes an inventory of existing case

definitions from the published and unpublished literature, including study protocols and surveillance systems. The gathered information is then being reviewed by the working groups and initial case definitions are being developed through a consensus process. Initial case definitions will be reviewed and validated through comments by broader reference group representatives of organizations occupied with vaccine safety and the individuals who have expressed an interest in commenting and few testing wherever possible and deemed necessary. The final definitions will then be globally disseminated through the Worldwide Web and other means of dissemination.

This shows the country distribution of our collaborators including reference group members and working group members. As you can see, there's an over-representation of collaborators from the U.S., however, some of those do have expertise in other parts of the world, and we are still aiming to grow and include collaborators from additional countries.

The selection of the first six adverse events to be

defined include fever, local reactions, intussusception, abnormal crying, convulsion, and hypotonic-hyporesponsive episode. The working group for local reactions has come up with a list of sixteen different injection site reactions that will all be defined.

Working groups currently include approximately 50 working group members with five to 16 members for each working groups. All working group have begun the compilation of existing definitions from the published and unpublished literature. The working groups for fever, intussusception, and injection site reaction with abscess at injection site have begun drafting their case definitions and are well on the way on deciding on the different parameters going into a definition. We have also begun to think through the development of a protocol for validation studies.

This slide shows the summaries of some of the literature found in published and unpublished manuscripts for various temperature cut-offs used, and as you can see, currently temperature cut-offs are all over the place and we use this in order to guide our decision what we

will recommend to be used as unified cut-off for future studies and surveillance systems. Additional parameters being discussed right now in the fever group, for example, include stratification by type of vaccine in order to decide on the duration of follow-up needed post-immunization.

This slide shows various cut-offs for reporting for swelling and erythema that we found in studies and surveillance systems, and as you can see again, cut-off points right now have a broad range of different sizes.

We have tentatively selected the next set of seven AEFI's to be defined which include allergic reaction, rash, asthenia, paresthesia, sudden infant death syndrome, myalgia, and idiopathic thrombocytopenia. However, this is still open for change and suggestions.

Our decision was essentially guided by the frequency and severity of occurrence of these adverse events or by public interest and funding concerns.

This table shows the top 10 non-serious AEFI's reported to VAERS over the last 10 years stratified by age group, and in yellow, those adverse events that we are currently defining and in orange, the ones that we will

define in our next set. And as you can see, we cover a good range of the most frequently reported adverse events.

This slide shows the top 10 serious adverse events by age group reported to VAERS and "serious" defined through the FDA criteria of adverse events leading to death, hospitalization, permanent disability, and again, in yellow, those that we are currently defining, and in orange, those that we so far have decided to define in the next set.

In general, we formed the first six working groups which have since begun their work. We have decided on the next set of adverse events to be defined this month. We launched our website at brightoncollaboration.org. Check it out, if you have time. There's no "www" at the beginning. It's all one word. We hope to have draft definitions by September of this year and to begin work with the next seven working groups in December. If you're interested, please let me know. I'm happy to take volunteers at anytime. And we hope to have the final draft of our first six AEFI's by March of next year.

Thank you.

**DR. MODLIN:** A couple of quick questions, comments? Dr. Neuzil?

**DR. NEUZIL:** This is a wonderful project. I'm just curious if the definitions will be age-based and what the age groups will be.

**DR. KOHL:** The definitions are to include all age groups and some may be stratified by age, depending on the adverse event.

**DR. MODLIN:** Thanks. Bob, what's next? The IOM report? Dr. Stratton?

While we're waiting, I'd like to point out that someone has lost a small piece of jewelry that appears to be sort of a greenish translucent something or other, which I have up here.

**DR. STRATTON:** I'm sorry for the delay. Thank you for inviting me. I'm here to tell you about the first report of the Immunization Safety Review Committee. And to the about 20 of you who have heard this five times before in the last month, I apologize. If you want to go do some other work, I would understand. I've been on the circuit of the Advisory Committee, so I've --

we've been talking about this a lot.

I know that at the last ACIP meeting that Dr. Marie McCormick, who's the Chair of the Committee, did come and talk to you. I'll remind you of a few things about the Committee in case some people weren't here.

The project is sponsored by CDC and NIH. It is a three-year project and we'll be serially addressing various vaccine safety concerns. I keep forgetting that I can look at the screen.

For each vaccine safety concern, the Committee has been charged with assessing both the scientific plausibility that the vaccine is causally related to the adverse event in question and the significance of the issue in a broader societal context and to recommend actions for the public health response to the issue.

Just to remind you, there are 15 members of the Committee and most of you probably got a copy of the report, which actually arrived yesterday, and the Committee roster is in the front. The Committee is free of real or perceived conflicts of interest and has appropriate expertise. It's chaired by Marie McCormick, who is Chair of Child and Maternal Health

at the Harvard School of Public Health.

The Committee will have three meetings a year. We'll issue a brief consensus report 60 to 90 days after each meeting. There will be summaries for the public and this particular committee has been charged with doing a lot of outreach to providers, researchers, policymakers, and the public. The first meeting was on MMR and autism. The meeting was held March 2001 in Washington. We will be addressing the thimerosal issue in July in Boston and the question of multiple antigens and immune dysfunction in November probably in Seattle. The topics are chosen by the interagency group of the Department of Health and Human Services. Just to remind you, this is a slightly different project than the vaccine safety work the IOM has done before, which was purely work on causality -- assessments of causality that was geared for the compensation program. This has a broader charge and a broader audience, and the issues are being dealt with in sequence.

The plausibility assessment that the Committee has made, which is what is called the causality argument

in our previous volumes and in this volume, are based on review of epidemiologic studies, what is known about human pathogenesis of the adverse event in question, and relevant animal models. The causality determinations are the same categories. The Committee decided to use the same categories that were used in the 1991, '93, and '94 reports on vaccine safety.

As I mentioned, the Committee was also asked to do a significance assessment of the issue, and the Committee defined that after hearing from the CDC and the NIH and other parties at our organizational meeting to include factors such as: the burden of the vaccine-preventable disease in question, and burden meaning the seriousness of the disease; the risk of the disease should immunization rates fall; the treatability of the disease; the burden of the vaccine adverse event in question; the level of public concern; and other issues that the Committee feels are relevant, for example, the feasibility of doing research that might actually resolve unanswered questions.

The Committee was then asked to make comments about the

public health response to this particular safety concern after making its causality determinations. Public health response includes three main components. One is a recommendation about policy review, the other are recommendations -- targeted recommendations on research and surveillance, and a third on communications. Let me say that with policy review -- and I'm sure Dr. McCormick assured you of this time -- but the Committee is very, very clear that there are aspects of policy review that are outside of the domain of this particular committee because they're domain of committees like you. The Committee would never make a recommendation of what the immunization schedule should be or whether a vaccine's license should be pulled or any of those sorts of things for which there are already astute policy-making bodies. The Committee could decide that the evidence were sufficient to recommend that a policy-making body take up the issue, and that is as far as these -- this committee would go with regard to policy review. How does the Committee gather its information and how did they do it for the MMR and autism? The Committee

reviews the published literature. The Committee receives a lot of information and reviews everything that is submitted to it by interested parties. Those are everything from many of you around the room, the government agencies, advocacy groups, professional organizations. Anything that is reviewed by the Committee is put in the public access file and can be read by anyone who wishes to. The Committee had an open scientific meeting in March, a one-day meeting, and we will have a one-day session associated with each of the topics that we take up. And the information from that scientific meeting can be accessed on the project's website, which I'll show you at the end. There's actually an audiocast, a delayed audiocast, of every single presentation and the discussions, as well as the PowerPoint presentations for those that we received, which was most of them. So you can actually if you can't attend the meeting, within about two weeks after the meeting, you could hear the deliberations of the open session and see the handouts. The Committee commissioned a background paper -- several of you know about that -- with respect

to the MMR and autism. It was controversial, to say the least; however, it proved very effective because it was posted on the website for comment. Many very, very helpful comments were received and the Committee reviewed them all. The paper was misinterpreted by many as a preview of the Committee's view and that, indeed, is not what it is at all. And we will probably continue doing something like this. Perhaps we'll be a little better at making the caveats that this doesn't represent the view of the Committee, although it did say it on the top of every page. People seemed to misinterpret that.

The Committee reviewed VAERS reports as they can. The Committee does hear about unpublished data. It hears at the public meeting. The report has a brief discussion of how it might weigh unpublished data. The more detail that is provided about those unpublished data, so the Committee can assess the methodology and the strengths and the weaknesses of the design and the analyses and the conclusions drawn from it, the more the Committee can weigh that material. However, unpublished data would probably never

actually sway a causality determination because it hasn't been through the peer review process yet, but it is reviewed and it can be important. The use of it depends on the details provided.

We have public access responsibilities that I mentioned. That's the phone number, if you wish to call, to get access to the work. There's also a listing of everything the Committee reviewed on the website for the project now so that you can know every single paper that was reviewed, even if it didn't make it into the final report, as part of the formal evidentiary base.

The reports go -- All reports of the IOM go through an extensive peer review process. This particular report had 17 reviewers. Their names are listed in the front. We thank those who reviewed the report. However, as much as we thank them and we benefitted from their comments, we do have to say that the responsibility for the report, of course, lies with the Committee and not with the reviewers. The reviewers do not see the report before it is released after they make their suggestions. So they do not see, until the

rest of you do, whether or not their suggestions were taken. It was an extremely extensive review panel for a report of about 60 pages.

I'll jump to the chase. The Committee was looking at the relationship between MMR and autistic spectrum disorders. The Committee concluded -- I'll go through the data in a minute -- that the evidence favors rejection of a causal relationship at a population level between MMR vaccine and autistic spectrum disorders. The Committee bases this conclusion on the following evidence.

The first and most important is that there is a very consistent body of epidemiologic evidence that shows no association at a population level between MMR and autistic spectrum disorders. These studies are summarized on a table on pages 34 and 35 of the report. I'm only going to review them very briefly, because I think many of you in the room know them probably better than I do.

A summary of the epidemiologic data. The case series, there's the famous Wakefield case series that was in the Lancet in 1998. There were 12 children with

enterocolitis and autistic regression or some other diagnosis similar to that. There were some -- It was a little difficult in some parts to tell what the diagnosis of the children were. There was a study from Peltola in 1998. There were 31 vaccinees with gastrointestinal symptoms after receiving MMR between the years of 1982 and 1996. This was their passive surveillance system. The Patja 2000, 169 vaccinees with 173 serious adverse events between 1982 and 1996. There were no autism cases reported in these last two major case series from the passive surveillance systems.

Ecologic studies, there were three of those that were published. The Dales Study of 2001, which was children born between 1980 and 1994 in California with a diagnosis of autistic disorder. While the rates went up in these -- in this particular data set for services for autistic disorder, their immunization rates did not. Case study of 2001, there were 350 children 12 years and younger diagnosed with autism between 1988 and 1999 who were identified through the U.K. -- let's see if I can remember -- General

Practitioner's Research Database, I think is what that stands for. And again, there was no ecologic -- there was no trend in the increasing rates of autism with the immunization. And the Gilberg and Heijbel 1998 was a reanalysis of data from a 1991 population study of autism and they looked at the rates pre-introduction of MMR and post-MMR, and again, there was no evidence that the introduction of MMR caused -- was associated with an increase in autism.

There were -- There was one very major cross-sectional study that was probably the strongest data reviewed by the Committee. It's the somewhat famous Taylor 1999 study from the North Thames Region of the United Kingdom. There were three analyses of the children who were identified, a time series but noticed no step-up in the autism diagnoses after MMR was introduced, no change in the age of diagnosis for autism with the age of vaccination, and there was no clustering of diagnosis, parental concern, or autistic regression.

There were three pieces -- three unpublished data that were also reviewed by the Committee at various levels

depending on what was submitted to them. Dr. Elizabeth Miller sent in a letter saying that they were working on an update of the Taylor Study. The data were not able to be presented because of the problems with publication. However, it did state that the Committee would support -- that the results were -- the preliminary analyses were supporting their previous work.

Dr. Fombonne, who was a speaker at the workshop, presented extensively a lot of his data looking at time periods of no vaccine, monovalent measles vaccine, and MMR vaccine. And in fact, they saw a step-down in the incidence of autism with a shift to the MMR vaccine rather than an increase, which would have been what the hypothesis would be if MMR was related to autism. They also did some separate study of the frequency of bowel symptoms in autism spectrum disorder and regression, and these data were extensively presented and discussed.

Dr. Wakefield talked about two pieces of data that had potentially had some relevance, which he reported some rechallenged cases of regression after MMR

vaccine and also claimed that they had confirmed the presence of measles virus and were working on typing that as wild-type or natural wild-type vaccine strain. However, none of those data were presented in enough detail for the Committee to make any analyses of the strength of those particular data, and these are all discussed in the report.

Going back to the causality argument, those were the three pieces of -- the main epidemiologic data. In addition, the Committee felt that the original case series with children with autistic spectrum disorders and bowel symptoms as well as other available case reports were uninformative with respect to causality. As many people know, the IOM long ago felt strongly that case reports could be used to -- in great support of causality and we heard some wonderful case reports just in the session before here. None of the case reports reviewed by the Committee on this particular issue were of that kind of depth and analysis and presented the kind of data you would need to strengthen a causality argument.

The biologic models linking the MMR vaccine and

autistic spectrum disorders were fragmentary, and what that means is there's a long series of events that would have to happen for the -- the Committee believed, for the MMR vaccine to cause autistic spectrum disorder, and there is not a complete chain of evidence that would support that particular hypothesis. It was fragmentary. We actually felt that was a terrific word, but people don't seem to understand it. Maybe they will or we'll change the word.

Finally, the Committee believed that there's no relevant animal model linking MMR vaccine and autistic spectrum disorder. Animal models on autism exist but they are applicable to postnatal insults such as the MMR vaccine if it were related.

The Committee noted, however, that its conclusion rejecting causality does not exclude the possibility that the MMR vaccine could contribute to autistic spectrum disorder in a small number of children, and it says this because the epidemiologic evidence, although consistent and all indicating that there is no association, lacks the precision to assess rare occurrences of the response to the MMR vaccine that

would lead to autistic spectrum disorders and because the proposed biologic models linking MMR vaccine, although far from established, are not disproved. With respect to the recommendations, the Committee recommended that continued attention be given to this issue despite its finding that the evidence favored rejection of causality because of the identified limitations of the evidence. The epidemiologic studies, as we said, as a body favored rejection but no one study was particularly exemplary or strong in and of its own and each study had flaws as all epidemiologic studies do. So the Committee felt that there were still some limitations of the evidence, although as a body it favored as rejection. The burden of autism is severe -- I don't need to tell the people in this room that -- and therefore, it is a very big problem that needs to be understood fully. And the burden of the diseases prevented by the vaccine are very, very high, particularly measles and congenital rubella. So that if this issue were not resolved to the comfort of the parents who are questioning the safety of the vaccine and immunization

rates fell, the public health burden of natural measles, mumps, and rubella would be terrible. There is a very real and immense concern of parents -- You all that; the Committee certainly knows that -- and the issue is very prominent in public debate. Despite the fact that continued attention -- the Committee recommended a continued attention be paid, they were very circumscribed in what sort of attention they felt that needed to be. For example, the Committee did not recommend that there be a policy review of the MMR vaccine, the licensure or the current schedule or recommendations for administration of the vaccine at this time. The Committee did make several specific targeted research recommendations, some of which are already being addressed by various people, including some in this room. The Committee felt that some of the epidemiology data was really hampered by the problems of case definitions or assessment protocols for autistic spectrum disorders, and certainly recommends the use of standardization. And we understand that that is going on through efforts between NIH and other parties. And so that will help resolve some of the

remaining issues about whether or not there is an increase in autism or not.

The Committee recommended an exploration of whether exposure to MMR vaccine is a risk factor for autistic spectrum disorders in a small number of children. However, it was pretty clear that this particular exploration might be best delayed until there's either a better -- until there are some biomarkers, biomarkers of either regressive autism -- and some people don't even believe that that syndrome exists -- so that they could detect -- you could see that what you're detecting is regressive autism or children at risk for autistic regression or biomarkers for one of the steps along the proposed biologic models. Right now we don't know enough about who would be at risk for regressive autism at all or children who would be at risk for some of the steps that would have to take place if the pathogenesis was as has been proposed by some people. However, if some is understood, this might be a research project that could be undertaken.

The Committee did recommend that there be an investigation of whether or not the measles vaccine

strain virus is present in the intestines of some children with autistic spectrum disorders. This is basically a replication and a validation of some of the Wakefield work, and we understand that this is being considered through some of the Centers for Excellence in Autism and some of the work already.

The Committee encourages that people who report to VAERS provide as much detail and documentation as possible when any diagnosis of autistic spectrum disorders is thought to be related. Those of you who review VAERS reports when you get the company material, sometimes they're helpful and sometimes they're not. And there was very little documentation on many of the VAERS reports that the Committee recommended. So if people believe that their child regressed after getting the MMR vaccine, it would be helpful to know about the neurologic status of the child before the vaccine and just much more detail about the child's health immediately before and after the MMR vaccine.

The Committee also recommended studying the possible effects of different immunization exposures, for example, children whose families have chosen to have

them not receive the MMR vaccine. The Committee makes it very, very clear in the report that this is not meant to be interpreted as encouraging alternatives to the recommended immunizations, but they felt that it would be very naive to ignore the fact that there are children out there who are receiving immunizations in a different way because of this concern and that there might be some targeted clinical studies that could be done in these children or these families at some point. There probably would never be a large enough end of these children and especially given how some of them may be very different for other reasons for an epidemiologic study, but there could be some clinical studies.

And finally, the Committee recommended -- which is really an endorsement of the existing research portfolio of CDC, NIH, and other funders on the risk factors and biologic markers of autistic spectrum disorder, in general, independent of any specific concerns about vaccination.

With respect to communications, the Committee didn't have much time to go into this in much detail, but it

had heard some concerns from some of the advocates that getting information that they perceived to be uninflammatory and unbiased information on the putative link between MMR vaccine and autism was very, very difficult. So the Committee just recommended at this point that particularly CDC and FDA review their communications, particularly those on the net, which is such a popular form of communication these days to make sure that it's as easy to access and as uninflammatory and unbias as possible.

The Committee identified a large number of issues during its deliberations that were tangential to the specific question of whether or not the MMR vaccine is related to autism and couldn't address them in their very first meeting. We have eight more meetings over the next three years. So over that time, the Committee hopes to address various issues, and these are discussed in the report. For example, the Committee saw a need for a discussion between the professional the vaccine professions and the public health professionals and members of the public about certain terms such as how difficult is it -- why is it impossible

to prove a negative relationship and what else can you say about that? And I know some people in this room have some strong feelings about that particular issue. What is a level of risk that is acceptable for a given benefit for a vaccine and how do you even talk about that with various people, with various stakeholders, as well as the meaning to various people of terms such as "association" versus "causality" and the type of evidence required to support it?

Finally, the Committee would hope at some point to discuss ways to research vaccine exposures which might not be a direct cause but would be a trigger for conditions of multi-factorial etiologies, as well as the appropriateness of alternative immunization schedules or practices which might be requested in a clinical setting. As you, who are practitioners, will affirm, you get asked about whether or not you can give vaccines in a slightly different way due to their concerns and there hasn't been, the Committee felt and heard from people, good discussions about how to handle that and what are the parameters of those discussions and those possible alternatives. And finally, there

are, of course, the general issues of vaccine, risk benefit communication, which a lot of people in the room here have made a lot of important steps toward sort of understanding better and having dialogue about, but there is still a big need to communicate the risk and benefits of vaccines in a way that's more understandable to all parties.

The project has a website where the report is, the announcements about the next meetings, all the material from our public meetings and that's up there, an e-mail box, a phone number. There's a listserve. Many of you are on it. Our next meeting will be July 16th in Boston on thimerosal, and actually, several of you in the room are actually presenting at that meeting. I'll come back about two or three months after that and report on that.

**DR. MODLIN:** Thanks, Dr. Stratton. Comments, questions? Dr. Jackson?

**DR. JACKSON:** Jackson, AMA.

Dr. Stratton, how has the report been received by those from all sides in your estimation?

**DR. STRATTON:** In my estimation. About what I would

have expected having done the safety work for a little while. I think that -- I think the medical -- I think the pediatric and the public health community agree with much of what we had to say. There are there some things that I think that they are less than happy about -- some people. I think the research recommendations were reviewed as being very sensible. I think obviously the call for no policy review was considered sensible. I think that for some of the people in the medical and public health communities who were very worried about the makeup of this committee, I think most people now understand that this committee can, in fact, do very informed and helpful work, even though they don't have vaccine safety expertise, per se. Some of the vaccine safety advocates have, for the most part, approved of the report. I think what emphasis they put on the conclusions depends on where you sit. There have been other -- Other groups have not been quite so happy, mostly because of the emphasis of the conclusion that -- is the major conclusion, that the evidence favors rejection of the causal relationship or is the major conclusion but we couldn't rule out the

possibility.

**DR. JACKSON:** Thank you.

**DR. MODLIN:** Further questions, comments?

(NO RESPONSE)

**DR. MODLIN:** Dr. Stratton, thank you very much for bringing us up-to-date on the IOM report and that the next task of the Safety Committee will be thimerosal and that's a nice segue into our final item on the agenda, which will be an update on research that's currently being conducted with respect to adverse effects of thimerosal in vaccine.

This will be led by Dr. Roger Bernier.

**DR. BERNIER:** Yes. Thank you, John. The main purpose of this presentation will be to give an update on progress in conducting the transition from a vaccine supply in the routine pediatric schedule which contain thimerosal to a situation today where that is not -- no longer true. The Committee will be asked a question at the end of my presentation. It's mostly informational, but we will be asking a question as to whether the Committee approves the current policy that we currently have or whether there's any desire to make

a change.

Let me give a little background of the policies that have come out in relation to thimerosal. In July of '99 when this first came to widespread public attention, there were three vaccines that contained thimerosal -- hepatitis B, DTaP, and hib -- that were part of the routine schedule. In the first Joint Statement that was issued in July, I've taken some of the language from that statement: "Clinicians and parents are encouraged to immunize all infants even if the choice of individual vaccine products is limited for any reason." So there was not any preferences made at that time, and there was also language about hepatitis B in that first Joint Statement. Because of the circumstances in which that Joint Statement was created, the ACIP actually did not give their opinion until a few months later, in November of 1999, when they said hepatitis B, DTaP, and hib vaccines that contained thimerosal as a preservative can continue to be used in the routine infant schedule beginning at two months along with monovalent or combination vaccines that do not contain thimerosal as

a preservative. And then, as you may recall, following reports from the Vaccine Safety Datalink of a possible association for some health effects associated with thimerosal, a second Joint Statement was issued. And this one stated that the AAFP, AAP, ACIP, and the Public Health Service recommend continuation of the current policy of moving rapidly to vaccines which are free of thimerosal as a preservative. Until an adequate supply of each vaccine is available, use of vaccines which contain thimerosal as a preservative is acceptable.

Now, what's happened since July of '99 as far as vaccine changes? Hepatitis B has become thimerosal-free, and here I want to clarify in my presentation that each time I say thimerosal-free, what I mean is that that is either 100 percent free of thimerosal or vaccines contain very small trace amounts.

Hepatitis B, there were two products in July of '99 and now both of these are thimerosal-free, Merck, rather shortly afterwards, in September '99 and then Glaxo Smithkline in March of 2000.

For hib, at the time, there were four manufacturers,

but all of the hib supply is now thimerosal-free. Wyeth switched to single vials only in July of 2000 and that made the entire hib supply free because the other three companies were already thimerosal-free in July of '99.

And as far as DTaP is concerned, there were four manufacturers. Now the DTaP supply is thimerosal-free. Aventis Pasteur in March 2001 obtained a license for their product. Glaxo Smithkline was already thimerosal-free I believe since 1997. And the other two companies, while I don't personally know all the reasons for these departures from the market, it may well have had something to do with thimerosal, but two of the companies are no longer distributing DTaP in the market. So we now have two, where before we had four.

So I think the basic message today is really one of very good news, that all the DTaP, two companies, all the hib, four companies, and all the hepatitis B, as well as the other vaccines in the recommended immunization schedule, including polio, pneumococcal vaccine, MMR, varicella, and hepatitis A, are thimerosal-free.

Other vaccines do still contain thimerosal, including influenza vaccine, Td, and DT, although these are not part of the routine immunization schedule, per se.

Also, we can say today that not only do we have a license for these products but that all the vaccines for the routine pediatric schedule that are being produced or distributed by the manufacturers are thimerosal-free, and in the public sector, there are no purchases -- or anywhere, no purchases of these vaccines.

We expect that the supply of any remaining T-contained DTaP which -- because the last manufacturer to get a license was in March of 2001, there was a supply continued to be put in the pipeline as recently as March, we expect that the supply of any remaining T-DTaP vaccine has been or should be used quickly because the DTaP supply has been very limited in the recent past and the so-called burn rate of that vaccine should be very rapid and there is probably not much of that vaccine still remaining.

As far as hib and hepatitis B, we can note that the expiration dates that were on the vaccines that were last released into the public sector have not yet been

reached. However, the last purchases of these vaccines in the public sector were made in 2000 and the remaining supply should be quite limited, if any still remains. We don't have a good exact estimate of that, but most observers, informed observers, believe that, as we say here, the supply should be quite limited, if any at all still remains.

In the past, the ACIP, as I noted in the earlier slides, has given the option -- has been given the option of expressing a preference for thimerosal-free vaccines while the transition from thimerosal-containing to thimerosal-free vaccines has been underway. And previously, the ACIP has chosen not to express a preference.

So where are we today? In summary, there are now at least two manufacturers for hepatitis B, for hib, and DTaP. And the option of expressing a preference could now be considered, and the actual and potential supply from these producers has improved. Now, since all the hepatitis B, hib, and DTaP vaccines that are being manufactured and distributed by manufacturers in the United States are now thimerosal-free, if the

Committee chose to express a preference, it would have no impact on any future purchases. All of the vaccine is currently thimerosal-free and that's all that we can buy. However, expressing a preference at this point would mean that the use of any existing stocks of vaccines containing thimerosal, the use could be reduced if replacement vaccine is purchased for those remaining stocks, however large or small they may be. So we would appreciate the Committee's consideration of this question at this time: Does the ACIP, given the progress that we've made -- does the ACIP support the current policy at this time or does the ACIP wish to make a change regarding the use of thimerosal-containing vaccines in order to decrease the use of the estimated small number of remaining doses of hep B, hib, and DTaP with thimerosal, which may still be in doctors' offices and public clinics?

**DR. MODLIN:** Thanks, Roger. I hope that most everybody in the room recognizes, as I do, the immense amount of time and intellectual energy that Roger has put into this issue the last two years and certainly appreciate the thought and -- the balanced thought and

approach that Roger has brought to this issue.

We're being asked now to consider the possibility of what would be a change in policy by the ACIP or at least a nudge in a different direction as to whether or not we now want to express a preference for vaccines that are free of thimerosal now that the supply is -- at least in the public sector is largely -- the pipeline no longer contains thimerosal-containing vaccines. I assume that, in addition to the policy implications that you raise here, Roger, that there might also be implications for vaccines that are used throughout the rest of the world that do contain thimerosal still and that we really haven't raised what issues or factors that the fact that the ACIP now does make a change might mean for -- in terms of influences that we've discussed in the past about policies for WHO, the EPI, and elsewhere. Would that not be the case as well?

**DR. BERNIER:** Yes. Just let me add that we're not prepared this afternoon to identify options that the Committee might want to consider and what the pros and cons would be. If the Committee were to give us the signal that it wanted to do that, we would be prepared

to come back tomorrow with a list of options with some pros and cons. So today, we just wanted to put in front of the Committee what the current situation is and get the Committee to give its opinion on whether it wants to consider this further or is it happy with the current situation and would like to leave it the way it is.

**DR. MODLIN:** Let me -- Well, Bob Chen, do you want to comment?

**DR. CHEN:** Just to say that I just came from the WHO immunization safety meeting where this issue did come up and the -- I think the first thing is that the Europeans reported that basically they're moving very much in the same direction that we are. Number two, there is a concern for WHO, EPI. However, I think it is really more of a matter of education in the sense the schedule that is used in the EPI simply does not contain the amount of thimerosal exposure that led to the concern in the U.S. And so, again, similar to the OPV/IPV and other past issues, it's a matter of framing it in the right format.

**DR. MODLIN:** Dixie?

**DR. SNIDER:** Dixie Snider.

Roger, what is the thinking about other vaccines that are not included now, particularly what about inactivated influenza vaccine if it were to be considered? Would there be an implication of the Committee's action that would impact on any recommendation that might be considered for giving influenza to children late?

**DR. BERNIER:** Um . . .

**DR. SNIDER:** Or is it just restricted to the --

**DR. BERNIER:** Well, we're only talking about these particular vaccines, but if I understand your question, does any change that the Committee might make have implications for the other ones as well, and I take that to be a very difficult question because one of the difficulties we've had in this whole process has been understanding for ourselves and communicating to the public how it could be that we have adopted a policy to remove something, while at the same time we do not consider this a demonstrated threat to health. So I think one of the -- And again, without getting into the pros and cons of what the change might be -- I didn't want to get us into that this afternoon

but, clearly, I think one of the potential consequences of making change would be what does that portend for people's perceptions of the other vaccines. And we have been told many times to be careful about attaching the concept of hazard to thimerosal because if that doesn't represent what we think, we have to careful not to attach that concept to it.

So whether that would happen if we did what you say, that might be a risk and that's something the Committee would have to consider.

**DR. MODLIN:** Hal?

**DR. MARGOLIS:** Hal Margolis.

A question -- and this is a question for the manufacturers -- in terms of adult hepatitis B, because there are federal contracts, is that now all thimerosal-free?

**DR. VERNON:** Not completely.

**DR. MODLIN:** I think Dr. Vernon's answer was not completely.

**DR. MARGOLIS:** So I think that raises an issue here because that's a vaccine that is both for infants and adults.

**DR. MODLIN:** Good point. I hope not to completely revisit all of the thimerosal issue in the last 15 minutes here. Let's try to keep the comments focused specifically on Roger's question, if we can.

Rick, did you --

**DR. ZIMMERMAN:** Rick Zimmerman, AAFP.

I'm concerned that if the Committee moves that direction, that is going to have implications for influenza, TD, and perhaps other things. And obviously, since the routine basic schedule vaccines are already reduced to thimerosal-free, I think we raise potential problems by going beyond where we are.

**DR. MODLIN:** Lucy?

**DR. TOMPKINS:** I was going to move that we support the current policy.

**DR. MODLIN:** Okay. Is there any -- Let me just cut quick to the chase and ask if there's anyone, voting members of the Committee, who feel otherwise?

(NO RESPONSE)

**DR. MODLIN:** It looks like there's none, Roger, so I think that's your answer.

**DR. BERNIER:** Thank you.

**DR. MODLIN:** Yes?

**DR. ZINK:** Hi. Tom Zink with Glaxo Smithkline. I was just conferring with Dr. Vernon to be sure that when he answered that we also had sort of a coordinated answer about the manufacturer status on indirect -- in our world at least to hepatitis B vaccine that Hal was requesting some input on.

Ours is free of preservative completely at this time.

**DR. MODLIN:** Thank you.

**DR. THOMPSON:** Good afternoon. I'm just going to be presenting an update on the proposal we've been developing looking at thimerosal-containing vaccines and our developmental deficits.

This is a proposal that was written by Paul Stehr-Green with a significant amount of work carried out by several other people including Gina Mootrey, Frank DeStefano, Phil Rhodes, Tom Verstraaten, and Bob Chen.

I'll keep the background to a minimum. So the Food and Drug Administration Modernization Act of 1997 required a review of mercury-containing biologics, including a review of thimerosal vaccines. The review looked at existing guidelines for methylmercury, thimerosal's

ethylmercury, and methylmercury studies were really all that are available. They looked at guidelines for FDA, EPA, ATSDR, and WHO. The FDA recently published a study showing the guidelines of the four agencies and the EPA's guidelines are the most stringent, and in terms of mercury exposure for children less than six months of age following the routine vaccine schedule, you would exceed the EPA's standards for methylmercury exposure.

There was a Joint Statement that Roger discussed. I won't go into that right now given that this is the end of the day. There was a Simpsonwood meeting held in June of 2000 where they reviewed analyses using two VSD HMO's. That was Northern California Kaiser and Group Health Cooperative. In that study, they found that cumulative ethylmercury exposure during the first year of life was associated with language delay, speech delay, ADHD, tic, stammering, and unspecified developmental delays, and that's been presented previously to ACIP.

The caveats to that study is there were weak statistical associations, subsequent analyses carried out using

Harvard Pilgrim, another HMO, were not consistent with these results. The study used nonspecific outcomes, ICD codes. And for these particular outcomes, the ICD coding of these events are difficult and an additional concern was possible, health-care-seeking bias in the study. So it warranted further studies.

The follow-up study that was proposed would be initiated to control for potential biases in the previous study, measure outcomes on all participants, better to find the diagnostic outcomes, and collect data on other possible confounders. The external review of the initial proposal was carried out in March of this year included toxicologists, pediatricians, neuropsychologists, statisticians, epidemiologists, various individuals from federal agencies, and other interested parties, including SafeMinds. So now I'll discuss the details of the proposal.

In March, we proposed a two-phase study, a retrospective cohort study. In phase I, we would focus on sensitivity versus specificity. So we would look at a broad range of neuropsychological tests, include outcomes from the VSD screening analysis, and

also include domains affected by methylmercury exposure reported in previous studies. Phase II would be a follow-up of phase I that would focus on specificity as opposed to sensitivity, it would focus on deficits and patterns from the results of phase I, would require a larger sample size and not necessarily the same children would be looked at from phase I. So the comments from the consultants were this. For the study design, in terms of the separation of phase I and phase II, the estimated time of carrying out was three to five years. They suggested that wasn't efficient or timely. So they recommended a hybrid study that would increase the timeliness of the results and should also reduce the cost of the study. In terms of the study population, there was a discussion of inclusion or exclusion of low birth weight infants and there were a lot of different opinions about what to do there.

In terms of the VSD study sites, there was a discussion of whether NCK should be included a study site. That's where the strongest results were found in the VSD screening analysis and the question is, if we included

them, would we simply be replicating that result or biasing results by including that particular site.

In terms of the exposure variable, as I said, there's few ethylmercury studies available to guide definitions of the exposure groups, so there's not -- there was discussion about timing of the exposure, weight-adjusted exposure, rate of excretion of ethylmercury -- There's very little known about that -- and possible threshold effects.

The consultants recommended that pharmacokinetic studies need to be carried out and they supported extensive collection of information on alternative exposures and potential confounders.

Finally, in terms of the outcome measures, they made a number of suggestions. They suggested our initial proposal had -- was too broad, covered too many domains. They suggested reducing the number of domains in the study. They suggested focusing on domains based on methylmercury studies and results, select highly sensitive but brief tests, and add measures on speech and visual-spatial ability. So there were two numbers that the proposal was a little weak on in terms of the

outcomes.

So the questions put forward to the panel at the end of this two-day meeting were: Is a study using a retrospective cohort design worth doing? The overwhelming response was, yes, this should be carried.

If yes, is the proposed two-part study a sound approach? There were various opinions on that. And we also asked, if we found positive results in phase I, which are these continuous measures, neuropsychological measures, would that require us to do phase II?

Another question was, if we found negative results in the first phase of this study, would that require us to do phase II or could we stop? The general opinion was you -- just because you did or didn't find positive results in phase I, that wouldn't necessarily give you any information on whether you would find results in phase II.

In terms of should NCK be included as a site, they recommended not alone, but there weren't -- there weren't any strong opinions not to include NCK.

Additional questions were, can the association between

thimerosal and autism be studied within this design? The overwhelming response was no. They recommended carrying out a case control study and that will be carried out by NIP. In addition, we asked, is a study using a prospective cohort design imperative? And the response was no. There were some disagreements on this issue in terms of the correct interpretation of the results from a retrospective study, but as we all know, there would be ethical considerations and that weighed heavily on people's response to that question.

So we had a follow-up meeting in May. We reconvened the psychologists, neuropsychologists, and experts on the various outcomes. We reviewed the revised test battery, added additional measures to the battery based on input from the group, and this month we finished the revised protocol.

So I'll give you the brief details of the study design. So, again, it's going to be a retrospective cohort study. We're going to select subjects based on cumulative thimerosal exposure from vaccines at three months of age. That's driven by the fact that the highest exposure per kilogram occurs at two months of

age if you follow ACIP recommendations, as well as the fact that exposure at all -- at other months if highly correlated with cumulative exposure at three months of age. We'll test all participants with standard neuropsychological test battery at seven and nine years of age and then we use confirmatory evaluations of children who test positive on certain screening tests. So the phase II will be carried out immediately, actually the same day as phase I in terms of this hybrid study.

In terms of the exposure groups, we'll have three exposure groups: a low exposure group -- that will be characterized as less than 25 micrograms of ethylmercury; a medium exposure group, which will be 25 to 62.5 micrograms; and a high exposure group, which will be 62.5 micrograms or greater. We've built in an option for just having two exposure groups depending on input we receive subsequently and we are going to attempt to split each exposure group into groups that receive hepatitis B vaccine at birth and those who didn't. We'll examine that issue. And then we'll also examine alternative exposure groups in terms of

cumulative exposure at six months, one year, and two years, and we'll also do weight-adjusted analyses, and that's again reinforcing the idea we'll select the sample based on three-month cumulative exposure, but we'll look at all exposures.

There are exclusion criteria for the proposal. There's selected severe perinatal disorders that will be excluded, selected congenital disorders, receipt of hepatitis B immunoglobulins, and we have decided to use birth weights -- to exclude children that are low birth weight, less than 2,500 grams and exclude kids with gestational ages less than 38 weeks.

The outcome measures from phase I in terms of the phase I piece will be -- will include measures from previous methylmercury studies such as verbal ability, visual-spatial ability, executive functioning and attention, short-term memory, fine manual motor tasks and achievement, and then we'll have measures from the positive VSD results which will language delay, speech delay, and ADHD.

In terms of phase II, the focus of phase II will be on prevalence estimates. So phase I will look at

continuous measures. Phase II will be looking at specific results from the VSD analyses. So we'll be attempting to characterize prevalence estimates for language deficits, speech deficits, and ADHD. And the way that will be done is individuals that fall 1.5 standard deviations below the national norms on the selected phase I measures will be tested with the phase II measures. So for those three particular outcomes, language deficit, speech deficit, or ADHD, if they fall below this 1.5 standard deviation relative national norms, they will be given further testing to characterize language deficit, speech deficit, and ADHD.

There will also be measurement of other exposures and potential confounders, including proxy measures for other forms of organic mercury, lead, PCB's, alcohol, and other drugs. And we will also obtain potential confounding information from abstracted medical records, response to questionnaires, and IQ tests will be given to the parental caregivers of these individuals.

The sample size -- for sample size and study setting,

phase II is really what drives the sample size estimates. You need a much smaller sample size for phase I. So phase II assumes background prevalence of 2-5 in the low exposure group for these prevalence disorders, with a power of 80 and a two-fold difference in rates of the neurodevelopmental delays. This would require approximately 3,400 individuals, 1,100 individuals per exposure group. The assumption is we would use four VSD HMO's, so approximately 800 or 850 individuals per HMO.

So the next steps are to submit the protocol to NIP for review. We're going to be discussing funding and budgeting considerations for the study. We're going to present this at the IOM meeting in July and get recommendations regarding the study and we're in the process of attempting to identify an independent contractor to do the planning phase for the study, for study procedure, sampling frame, standardized testing, pilot study, and the actual study.

So I'll stop there.

**DR. MODLIN:** I'm curious about the reason for excluding low birth weight babies --

**UNIDENTIFIED SPEAKER:** Yes.

**DR. MODLIN:** -- which we might expect to be -- actually, if anyone is going to be at risk and you're going to signal, this would be the group of greatest interest.

**DR. THOMPSON:** Yeah. There was a lot of discussion about this. The first thing to note is that in the screening analysis, there was no effect within the low birth weight kids with thimerosal exposure. And then the second piece is there was a discussion of sample size and sampling and how to get at that issue. So I don't know if any other individuals want -- Bob, if you want to speak up on this, but I think this was a hotly-debated issue.

**DR. CHEN:** Yeah. The most major consideration for excluding this group is that all of the studies of this group showed that their severity confounded, that basically children with very low birth weight are more likely to have poor neurodevelopmental outcomes down the road and, secondly, they're less likely to get immunized. So it's a true confounder and it's a problem of what they call confounding by

contraindication, and all past safety studies have shown that basically you're unable to resolve it in this type of epidemiologic study, that you have to go to a randomized trial. So the feeling was that -- this was also the feeling of most of the consultants -- was that there was not any way that we could resolve this issue in this study design.

**DR. MODLIN:** Bob, maybe I could argue with you a little bit here, in that the true confounding effects of low birth weight on adverse outcomes really don't begin to take hold until you get down below 30 to 32 weeks or even lower. Most babies from 30 weeks on up, which are going to be the great majority of infants, actually do quite fine. Nonetheless, I would expect this to be a group that would be truly vulnerable to adverse effects of toxin exposure early in life. And I just wonder if you might want to think about addressing that issue one more time because of that.

**UNIDENTIFIED SPEAKER:** Yeah.

**DR. MODLIN:** And it's going to be a sizable group. And I would think that -- Well --

**DR. CHEN:** And it was exactly from what he just

described that we decided to abandon it, and that is when you look at the curve of the weights, most of them are, in fact, around 2,500 grams, and there's actually only very few that go down to much lower weights. So the feeling was that, biologically, this was a bit of an artificial cut-off in that it really -- what you really wanted was, in fact, a very low birth weight group. And those, unfortunately, are, in fact, severely confounded in terms of them being very -- So, anyway, we will continue to discuss it with IOM, but those were the considerations.

**DR. MODLIN:** Okay. Walt?

**DR. ORENSTEIN:** I think it's important to make clear that a decision has not been made to go forward with this study at this point. There are substantial budget considerations and the question, given the removal of thimerosal from the supply, is where should the highest priority studies go? The major issues deal with vaccine injury compensation therapy and developing world implications, and is this the study that is going to best answer those questions or should we focus our efforts on some of the case control

approaches to deal with the more significant outcomes, but this is a very costly study. We certainly will be looking to the IOM in terms of prioritization and where this fits in the priorities for research.

**DR. MODLIN:** Other questions or comments from the Committee members?

**DR. JACKSON:** Yes.

**DR. MODLIN:** Yes, Dr. Jackson?

**DR. JACKSON:** I tend to agree with -- Jackson, AMA. I tend to agree with you, John, that one of the major questions was of the effect of thimerosal on the low birth weight baby. And while if you take a cut-off at 2,500 grams, you'll find a lot of African-American babies who are very well developed who fall below that weight and they may be excluded with the exclusion criteria.

**DR. THOMPSON:** If we used a cut-off of 2,000, would that be adequate?

**DR. MODLIN:** 2,000 grams?

**DR. THOMPSON:** Yeah.

**DR. MODLIN:** I wouldn't get down to the specifics right now --

**DR. THOMPSON:** I'm just --

**DR. MODLIN:** I think something -- I would have suggested something much lower than 38 weeks and 2,500 grams or whatever the birth weight was.

Stan?

**DR. PLOTKIN:** Plotkin.

I'm confused about the phase I/phase II. Perhaps you could clarify this for me.

Normally, I think of phase I as a hypothesis-finding phase. So you look for some difference. Now, as we all know, if you look for 100 variables, five of them are likely to be abnormal.

**DR. THOMPSON:** Yeah.

**DR. PLOTKIN:** Okay. So you identify one of those that you think is really important and has an apparent strong effect and then you go to phase II and try to confirm that. Now, what I am confused about is -- that's what I thought you were saying at first, but then I seem to hear you saying that phase II is simply going to take the same population and try to confirm whether or not that statistical difference really exists among all of those different variables. Am I --

**DR. THOMPSON:** Well, let me --

**DR. PLOTKIN:** -- incorrect?

**DR. THOMPSON:** -- clarify it for you. Phase I is a more traditional toxicology type study, and in toxicology studies, they'll use these continuous measures and they will stop there and that will be the result. The exposure caused x point difference in a particular outcome. So phase II is more concerned with following up on the VSD results. So we use screening measures in addition to the traditional toxicology study that's built into phase I. We have screening measures in phase I that are used to follow up on the same individuals and accurately classify them as either speech-delayed, language-delayed, or ADHD. So phase II is really to get at the specific outcomes that were found to be associated in the screening analysis.

**DR. PLOTKIN:** But how do you deal with the multiple-measure issue?

**DR. THOMPSON:** The multiple-measure issue is a known problem that we know we'll have to deal with in the study.

**DR. PLOTKIN:** Okay. Well, the other question I would ask is, is this going to be blinded as far as the parents are concerned? That is, presumably, some of them will be aware of this issue, if not already, lawsuits that are beginning will create publicity.

**DR. THOMPSON:** Uh-huh (affirmative).

**DR. PLOTKIN:** So are you concerned at all about the influence of the parents?

**DR. THOMPSON:** Yeah. There's been discussion about the appropriate way to recruit people and possibly not there's been a lot of discussion in terms of the blinding of the parents and the way to design this study in a way that will reduce that potential confounder.

**DR. MODLIN:** Dr. Halsey?

**DR. HALSEY:** Neal Halsey, Johns Hopkins University. A couple of points.

You didn't specifically describe the masking or blinding of the investigators and the reviewers. I assume they'll be mixed and be getting simultaneously low, medium, and high exposure and the examiners will be totally masked to what that exposure was.

**DR. THOMPSON:** Yes.

**DR. HALSEY:** The second point has to do with the power of the study. You have a 80 percent power to detect a two-fold increase in terms of the -- it's the odds ratio. As I recall, the screening analyses showed relative risks between 1.4 and 1.8. I realize the high cost that Walt is alluding to here, but the risk is the potential of not -- of having a result that basically validates the initial screening analysis, let's say, with odds ratios of 1.6, but yet, it doesn't quite reach the statistical significance. I think you should explore whether you can, in fact, increase the power of the study to the rate that you would be able to detect those differences because they still are important differences, even if it doesn't reach a two -- an odds ratio of two, as I think most people who deal with chronic disease epidemiology and things that have multi-factorial causes, such as these outcomes do. So, if anything, I would encourage you to increase the power. I definitely think the study should be done because of the added strength of a retrospective cohort analysis as compared to case control studies. It's very rare in chronic disease epidemiology that a single

case control study convinces anybody one direction or the other.

So I think it should be done, but you really ought to look at how much power you will have to detect smaller differences, which is what I think is the most likely outcome here.

**DR. MODLIN:** Thanks, Neal. Yes?

**MS. REDWOOD:** Lynn Redwood, SafeMinds.

First, I want to applaud CDC for agreeing to look further into the issue of thimerosal-containing vaccines and neurodevelopmental delays. I think they've done a wonderful job in terms of identifying the neurobehavioral battery of tests that will be performed on these children, but I have some basic concerns about the risk category exposure groups, looking at only the first three months of life. When you look at those exposures, there's only 12.5 micrograms separating the medium and low exposure groups. And I think classifying children in those three groups the first three months of age doesn't really follow along with mercury pharmacokinetics, because the long half-life of mercury in the blood,

you're not going to reach peak blood concentrations until six months of age. So I really would encourage you to look further into not classify those children based on their first three months of exposure. If you do that, I don't know how you're going to deal with the situation where, say, a child had gotten a hepatitis B at birth, missed their two-month vaccines, got their two-month vaccines at three months one day, and then were on an accelerated schedule but got maximum exposure by six months of age, but yet, the way you've classified them, they're still in the low exposure group. And I think that's a major flaw in the design of the study, and I really hope that you consider looking at that issue again. I know this was voiced at the actual meetings with the consultants. I just don't think the way you've devised your exposure groups really is in keeping with mercury pharmacokinetics.

**DR. THOMPSON:** Yeah. Just a response to that. The correlation between three-month cumulative exposure and six-month cumulative exposure is approximately .7 to .8. So there's a very high positive correlation between three-month cumulative exposure and six-month

cumulative exposure. So that's our thinking behind it, and the other piece is the highest exposure per kilogram occurs at two months of age for most individuals.

**MS. REDWOOD:** Right. But then it says six months because of the stair-stepping of excretion concerns that need to be addressed. Thank you.

**DR. MODLIN:** Any other additional comments regarding the study?

(NO RESPONSE)

**DR. MODLIN:** If not, we do have a period of public comment. We have two individuals who have signed up and I believe that each have spoken. Dr. Zink from Glaxo Smithkline, do you have anything --

**DR. ZINK:** We're fine.

**DR. MODLIN:** You're fine. And Ms. Redwood, who has just spoken, I assume that you have nothing else to say?

**MS. REDWOOD:** No.

**DR. MODLIN:** Thank you. Thanks very much. We'll adjourn the meeting for this evening. A reminder that the Rotavirus Working Group is meeting at 6:30, Myron, in the Magnolia Room. We'll start at

6:30 with dinner.

Secondly, we will start tomorrow at 8:00. Ben Schwartz has a draft to hand out which will help a whole lot in getting things started. We'll start at 8:00 tomorrow to revisit the influenza supply issue. Have a nice evening.

(Whereupon, the meeting was adjourned for the day at approximately 5:36 p.m.)

# C E R T I F I C A T E

STATE OF GEORGIA

COUNTY OF FULTON

I, PAMELA T. LENNARD, BEING A CERTIFIED COURT REPORTER AND NOTARY PUBLIC IN AND FOR THE STATE OF GEORGIA AT LARGE, HEREBY CERTIFY THAT THE FOREGOING IS A TRUE AND COMPLETE TRANSCRIPTION OF SAID PROCEEDINGS; AND THAT I AM NEITHER A RELATIVE, EMPLOYEE, ATTORNEY, OR COUNSEL OF ANY OF THE PARTIES, NOR A RELATIVE OR EMPLOYEE OF SUCH ATTORNEY OR COUNSEL; NOR FINANCIALLY INTERESTED IN THE ACTION.

WITNESS MY HAND AND OFFICIAL SEAL, THIS, THE 14TH DAY OF JULY, 2001, IN ALPHARETTA, FULTON COUNTY, GEORGIA.

PAMELA T. LENNARD, CCR, CVR

NANCY LEE & ASSOCIATES

CERTIFICATE NUMBER B-1797
(CCR SEAL - NOTARY SEAL)

NANCY LEE & ASSOCIATES

**THE U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**CENTERS FOR DISEASE CONTROL AND PREVENTION**

convenes the

**ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES**

**VOLUME II - DAY TWO**

The verbatim transcript of the ACIP Conference commencing at 8:03 a.m. on Thursday, June 21st, 2001, at the Marriott Century Center Hotel, Atlanta, Georgia.

# C O N T E N T S



(Continued)

# P A R T I C I P A N T S

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Lebanon, New Hampshire

Executive Secretary:

Dixie E. Snider, Jr., M.D.
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Wyeth Vaccines and Nutrition
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# P R O C E E D I N G S

8:03 a.m.

**DR. MODLIN:** Good morning. I'm wondering if I could ask people to take their seats so we can get started on time.

We have a full agenda today, and the agenda actually extends later into the afternoon than we usually do on the second day. I recognize that a number of people have flights that they'll need to catch. So it's my intention to move things along as briskly as we can and to, at the very least, stay on time, if not make up some time.

Just one quick announcement. There will be a photographer in the audience taking pictures today. So if there's anyone who would prefer not to have their picture taken, they need to be aware of that and let the photographer know or in some other way get out of the way.

(LAUGHTER)

**DR. MODLIN:** We're going to continue with our discussion on the influenza supplementary statement.

We made great progress yesterday, and Ben Schwartz was able to hand out a draft statement at the end of the day that I hope the Committee members have had a chance to review in the meantime.

Ben, what's the best way to do this? Should we just go over the statement and, just very quickly, ask people to respond to it?

**DR. SCHWARTZ:** If you don't mind, I can very briefly summarize some of the changes that were made, the rationale for those changes. And as so often happens when one gets caught up in kind of the sense of the Committee, I tried to make changes that reflected some of the conversation yesterday and I'm thinking about it more. And on talking with Walt, I decided that some of those changes may not be warranted in particular in distinguishing between delay and decreased availability.

So if I can have maybe three minutes to summarize those changes to highlight those issues and then turn it over to the Committee for discussion.

I did try to reflect a lot of the concerns that folks had yesterday in -- with respect to the recommendations

in the draft. Most notably, the format has been changed, putting the goals up front, the description of production estimates, and the recommendations first, and then following that with the supporting data. The text under the recommendations has been simplified so that the recommendations themselves stand out more. I included a recommendation for mass immunizers, included health departments under that recommendation, and commented on the timing of those campaigns. Local health departments were included along with state departments reflecting some of the concerns that the Committee expressed. The wording of the recommendation for high-risk patients regarding communication has been modified so that all the high-risk patients wouldn't be calling their physician's office, deluging the physician with phone calls about do you have vaccine available. And also, I indicated that this year's situation may become the norm and that ACIP will consider later what recommendations should be routine as opposed to what recommendations are unique for this season. So I did try and take into account all of those concerns and

suggestions from the ACIP.

One of the major issues to discuss is whether we call it a delay or decreased early season availability, and in thinking about decreased early season availability, there were several advantages that were proposed with that particular terminology. First, that it would reflect concern about the causes of the delay; secondly, it may decrease the amount of alarm that people feel; and then, finally, it may more accurately reflect the long-term situation where delay becomes the norm based on manufacturing and distribution decisions made by the companies.

However, I think the advantages of using the terminology "delay" far outweigh those of "decreased early availability," and the advantages there include that it accurately reflects the perceptions of physicians and of others in the system compared with what is perceived as the norm, what was the norm before last season when we had the very definite delay. Secondly, it better captures the attention of stakeholders and so they are more likely to pay attention and respond to these recommendations.

Third, and perhaps most importantly, it preserves CDC's credibility in the face of investigations and conspiracy theories, as Dr. Tan described yesterday, coming out of the AMA meeting. And then finally, it more accurately reflects the situation this year without making any assumptions about future production and distribution decisions so that while the manufacturers tell us that the decisions they're making this year may be carried on for future years, we haven't yet seen the consequences of those decisions. We don't know whether there may be unintended consequences, whether vaccine will go unused, and then they'll move to earlier distribution in the future to try and sell more product. So in the face of that uncertainty, I would prefer that the terminology be "delay."

A couple of other issues. Putting the magnitude of the problem in perspective was one of the comments that people had. I think I tried to do that in the first paragraph of the new draft. The ability to address this year and future objectives in a single document was one concern, whether it was too confusing. And to

address that concern, I've explicitly put in a goal for a prioritized or phase system for this year while still emphasizing our overall Healthy People 2010 goals. And then there was the issue of the close contact for pediatric patients, and I did put in a parenthetical comment, but as Walt has pointed out to me and others have pointed out, that was confusing and perhaps it may be better dealt with in a footnote, and we can work with Walt and with Jon Abramson and AAP folks to better clarify that issue.

So that's it.

**DR. MODLIN:** Terrific. Discussion on the changes? Is there anyone who is -- Georges?

**DR. PETER:** Unfortunately, Ben, despite your efforts to give me the statement, I misplaced it. So I didn't have a chance to read it. But one of the points you make about delay versus the -- What was the other term you used?

**DR. SCHWARTZ:** Decreased availability.

**DR. PETER:** -- decreased availability is that you compare it to October 1999. And perhaps another phrase -- sentence could be added to the effect of what

the situation is probably better for October 2001, where that was October 2000, and that would help to put the situation in perspective.

**DR. SCHWARTZ:** Yeah --

**DR. MODLIN:** That's in there.

**DR. PETER:** Maybe that's in there, but I --

**DR. SCHWARTZ:** Yeah, the wording is in here. Distribution through October will be substantially greater than during 2000 when production delays occurred. So it talks about production delays for 2000. It doesn't mention the production issue for this year, I think, more accurately, reflecting the situation.

**DR. MODLIN:** Other comments?

**DR. SMITH:** I think it's a much better --

**DR. MODLIN:** Natalie?

**DR. SMITH:** I think it's a much better, clearer statement. So I'm happy with this.

**DR. MODLIN:** Dr. Smith is happy with it. Dr. Siegel?

**DR. SIEGEL:** Yes. Jane Siegel. I'm the first recommendation, the health care worker is somewhat buried. So I guess I would like to see a more

a more specific statement about health care workers. Because the way it's written now, I don't think the idea of protecting the patients is the strongest motivation for health care workers. I think they're more motivated to protect their elderly relatives, or whatever, and the way this is written, it kind of attaches that and I think we need to think about what motivates health care workers and make it very clear that we think they need to be immunized early.

**DR. SCHWARTZ:** The first recommendation states that the provider should actively target vaccine available in September and October to persons at increased risk of flu complications and to medical personnel who care for them. In the table also, there listed is a high-risk and priority group for early vaccination.

**DR. SIEGEL:** Right.

**DR. SCHWARTZ:** Are you suggesting that we add something to that? I'm --

**DR. SIEGEL:** Or just maybe having a separate sentence. The way it's worded, it kind of sneaks it in somewhat. I think it doesn't have -- at least as I read it, it doesn't come out and hit me. And I agree that that's

what the sentence says, but I think it needs to be a little bit more definitive.

**DR. MODLIN:** Jane, do you think this is an issue for the supplementary statement -- This is a statement that is supplementary to the flu statement that was published earlier -- or do you think this is an issue that we should be examining carefully in the full flu statement?

**DR. SIEGEL:** I think it's an issue for this supplementary statement because I think those are some of the people that you want immunized early and there's always a lot of resistance.

**DR. MODLIN:** Chuck?

**DR. HELMS:** On that same theme, the phrase "who care for them afterwards," I happen to agree with that concept, that people who are in direct contact with patients should be the ones receiving the vaccine, but if there's a Department of Pathology who, if it gets sick, is going to put a hospital at risk and so forth and so on, I'm wondering whether we really need "who care for them" in there. It's medical personnel, period.

**UNIDENTIFIED SPEAKER:** Or to health care workers.

**DR. HELMS:** Or to health care workers. Whatever --

**UNIDENTIFIED SPEAKER:** Whatever --

**DR. MODLIN:** Peggy?

**DR. RENNELS:** I think you need to put "involved in their care," because otherwise, you're going to have room clerks and people who don't have any contact.

**DR. HELMS:** Well, I can understand for transmission issues that you want to make sure that the that we don't transfer it within the hospital, but at the time of an epidemic, you also don't want any of your hospital staff really down to the point where the hospital becomes inoperable. And I guess my argument would be that some hospitals -- I think if you go from hospital to hospital you'll find certain groups slipping in that might not be immunized at another institution. I think this maybe too --

**DR. MODLIN:** Hospital employees take on the same significance as public safety --

**DR. HELMS:** Well, I don't agree that secretaries and so forth, but I do agree that -- I think that Departments of Pathology ought to be, those that are taking care

of specimens that are coming in and so forth and so on. So I just wonder whether simply saying medical or hospital -- health care personnel.

**DR. SCHWARTZ:** The reasons I put "who care for them" is I think the issue of home health aides, the issue of people who come into the households of elderly folks and care for them -- I wanted to include the implication that anyone who cares for an elderly person in a medical context could be eligible for vaccination under this recommendation.

**UNIDENTIFIED SPEAKER:** That's health care workers.

**DR. HELMS:** I think health care workers.

**DR. SCHWARTZ:** Okay.

**DR. MODLIN:** Further comments? Yes, Dr. Neuzil?

**DR. NEUZIL:** Kathy Neuzil.

I have one other comment under four, "Recommendations for Manufacturers." I think it's important that you make the third statement, which says that manufacturers, distributors, and vendors should inform providers of the amount of vaccine. I don't know if we can even make that recommendation stronger, and I suppose the issue is we deal with manufacturers

as a group three, and yet we know that individually, they will have different time tables and different delays. I think for the individual provider, it's quite important to know how the manufacturer that they contracted with -- how they are doing and exactly when they can provide vaccines so that they can plan.

**DR. MODLIN:** Yes, Kevin Reilly?

**MR. REILLY:** Kevin Reilly from Wyeth. Let me make it clear that we that very extensively already and that is part of our routine procedure, that because this is a seasonable product, the customers that have orders with us, we give advance notice of when they should expect shipments. If there's any changes in that, we give them advance notice of changes. We have a very extensive communication process for people who place orders with us.

**DR. MODLIN:** Jon Abramson?

**DR. ABRAMSON:** Yeah. Let me give you a sense of what happened last year, and we don't tell people that they -- I need to give everybody a sense of what happened last year. That is that it was coming in such bits and pieces that we were prioritizing intensive care units,

intermediate care units. That's how you were giving out vaccine last year, in little bits and pieces. We need to give them a sense of whether that is -- If we write this thing out and we don't give them a sense of how it's going to come in, they'll start doing that as they get a little bit of vaccine. They're going to start prioritizing down the list again. My sense is they don't have to do that this year, but I don't know if that's true or not.

**DR. MODLIN:** Yes?

**MS. McKIVEN:** Linda McKiven, CDC Office of Health Care Partnerships.

We've worked on the HICFA/CDC standing orders project with NIP for the past year and feel it's pretty important to recognize the vulnerability of the long-term care population and would suggest that there might be several places in the recommendations where the priority of distribution to nursing homes could be placed, including under providers for manufacturers and for health departments.

**DR. MODLIN:** Ben, do you -- did you catch --

**DR. SCHWARTZ:** Yeah. Linda gave me some suggestions

on -- I think it's reasonable to include. I had some concerns that the forum and the emphasis be appropriate for this document. There are, I think, some special concerns about the elderly population, about waning immunity and vaccination in October rather than earlier that make it a little bit tricky to include. If the Committee feels that there should be a recommendation that talks specifically about long-term care facilities, we can certainly include it and then work on the wording with the recognition that these are groups that should be given priority for earlier vaccine and that standing orders are one approach to improve immunization rates within this population. I can work with Linda and others if the Committee wants that recommendation included.

**DR. MODLIN:** So, in essence, sorting them out as a separate risk group apart from individuals over 65? We're talking about the frail elderly and giving them a separate risk group designation? Is that what I'm hearing?

**DR. SCHWARTZ:** Well, I guess just giving them some additional emphasis as a site to make sure early vaccine

gets distributed to.

**DR. MODLIN:** Kristin?

**DR. NICHOL:** Would it help in this regard to -- when referring to providers saying -- or making it clear that the term "provider" probably includes not only individual practitioners but also health care organizations and long-term care or something like that, to broaden the scope, and then each time we talk about providers and even under the -- I don't have the statement here. When we're talking about distribution of vaccine to providers, including individual providers, organizations, and long-term care or something like that might highlight the long-term care without a specific separate recommendation.

**DR. SCHWARTZ:** And certainly, in recommendations to manufacturers, if a manufacturer is planning on giving a small portion of vaccine early to all providers and then the rest of it later in the season, I think for long-term care facilities, that would be a -- not a good idea in that they should provide the full order to the long-term care facility as expeditiously as possible.

And that could certainly be added as a recommendation to manufacturers and distributors.

**DR. MODLIN:** Okay. Other comments? Bonnie?

**DR. WORD:** Maybe I was just a little confused, because when I look back at his table, nursing homes and chronic care facilities were listed as being in a priority group. So that's why I was a little confused with that entire discussion, because he does identify that group.

**DR. MODLIN:** Okay.

**DR. SCHWARTZ:** I'll go whichever way this committee thinks is optimal.

**DR. MODLIN:** I have feeling, Ben, that the Committee is going to be content to let you deal with the final wording here and make these final decisions. Everybody is nodding in agreement.

Are there other comments? I hope and assume that the Committee is comfortable voting on this without seeing the final document and the final wording right in front of us and going over it word by word and we can trust Ben to reflect the will of the Committee with the final wording. Is that fair enough? Okay.

Dixie, are individuals who vote -- who are conflicted with the influenza manufacturers required to recuse themselves for this vote?

**DR. SNIDER:** Yes.

**DR. MODLIN:** Okay. I assumed that they were. So how many members of the Committee are not conflicted with Aventis, or Wyeth, or Mediva?

(SHOW OF HANDS)

**DR. MODLIN:** We certainly do have a quorum. Okay. Let me entertain a motion that the Committee supports the supplementary statement as has been presented to us by Dr. Schwartz.

**DR. JOHNSON:** So moved.

**DR. MODLIN:** It has been moved by Dr. Johnson.

**DR. LEVIN:** Seconded.

**DR. MODLIN:** Seconded by Dr. Levin. Those in favor of adopting the supplementary statement, if they would hold their hands up. Those in favor: Dr. Levin, Dr. Brooks, Dr. Word, Dr. Tompkins, Dr. Helms, Dr. Offit, Dr. Johnson, Dr. Smith, Dr. DeSeda, Dr. Modlin. Those opposed? None. Those abstaining? Those abstaining are Dr. Rennels, Dr. Clover. That's it.

The motion passes. Thank you.

Ben, thank you very much.

**DR. MODLIN:** Let's move on to the updates from -- first of all, from the National Immunization Program. Walt?

**DR. SNIDER:** John, Dixie Snider.

I think it's only appropriate and fair to alert everyone, but especially the Committee, to the fact that this statement has, as I indicated yesterday, received a lot of interest from CDC management and higher level management. And I think the Committee has done a superb job in putting together some great recommendations. I would anticipate that any involvement that management might have would be along the lines of exactly how to do the wordsmithing rather than any substantive issues. And if there were any substantive content questions or concerns we certainly would get back in touch with the Committee. But if there are issues only with, you know, how to wordsmith this, then we'll proceed. But as in all cases, just as a reminder, we've had what appears to be a seamless process but, in fact, it is a two-stage process where the Committee does advise the CDC and the CDC decides

whether to accept those recommendations. And our track record has been such that CDC does virtually always accept your recommendations as you approve them.

**DR. MODLIN:** Thanks, Dixie.

**DR. ORENSTEIN:** I just wanted to talk about a few things. One, I just want to let you know that between May 29th and June 1st we had our 35th National Immunization Conference with over 1,500 people participating. I think there are a number of new things that we'll put in there, including a Cyber Cafe, a webcast, and coming out of that is a CD that is titled "Everything You Want to Know About Immunization." I think we need to be careful in the future about everything, but it's being handed out to you and I've been told that we should have copies available for everybody in the room by the end of the meeting. Is that correct?

**UNIDENTIFIED SPEAKER:** Yes.

**DR. ORENSTEIN:** I wanted to let you know, in terms of the President's budget submission for FY 2002, CDC overall received a three percent decrease in budget

submission compared to last year, or a decrease of $109 million. However, immunization, or NIP, received -- or it's really immunization received a four percent increase in the President's budget submission in FY 2002. This includes $14 million in 317 grant program for primarily the pneumococcal conjugate vaccine purchase; four million for vaccine safety activities; one million for global immunization activity, which is really polio; one million for extramural research; and a $2 million mandated cost of living increase.

We have been concerned about uptake of pneumococcal conjugate vaccine and we are seeing, through May, a major increase in public sector vaccine doses purchased, but by May of 2001 we have almost nine -- a little over eight million doses actually purchased of pneumococcal conjugate vaccine.

To put that in perspective, this shows the pubic sector purchases of Hib-containing vaccines in blue and pneumococcal conjugate purchases in orange, and you can see they're roughly comparable. However, I want to inject a couple of notes of caution.

First, the pneumococcal conjugate vaccine not only has

to deal with routine delivery, but filling the pipeline, and so substantial purchase is probably filling the pipeline. So I wouldn't want anybody to leave this room thinking we're implementing pneumococcal conjugate vaccine at anywhere near the routine immunization levels.

The other issue on pneumococcal conjugate is it's unclear as yet what the resource needs will be, and that is, it's still not clear what the degree of catch-up particularly will be in the state programs. Clearly, the VFC program is adequately covering all of it, but we will have to continue to monitor the 317 and state vaccine needs to see whether there are impediments to full implementation of the ACIP recommendations.

This year marks the end of, a decade ago, the measles resurgence, and I just wanted to point out that measles in this hemisphere is still at record lows. These are data from the PanAmerican Health Organization showing, with very, very high immunization coverage now, about 90 percent, numbers of cases of measles. The only places where there are measles reported in the Americas thus far this year are the U.S., Canada, Mexico, with

three cases which appear to be importations, El Salvador with two cases. The only place where there appears to be indigenous transmission of measles in the Americas at the moment is Hispaniola, interestingly, where the -- I'll talk about it in a moment -- the polio problem is also going on.

In the U.S., in terms of measles, last year was a record low, the first time we ever went below 100 cases of measles. Thirty percent of them are importations. Many of these so-called indigenous ones are import-associated, and the feeling here is that probably all of them are in some way either related to importations or false positive reports, in that there's no evidence for re-establishment of indigenous transmission.

Thus far this year we have 60 cases, which is substantially higher than what we had last year at this time, but -- there were 36 cases last year at this time. But again, a very, very high proportion of them are importations. And to put all of this in perspective, in 1990 we had almost 28,000 cases of measles. So this is -- continues to be a remarkable accomplishment.

The polio eradication program in the world is making tremendous progress. At the end of 2000 approximately 20 cases -- 20 countries were considered endemic for polio on two continents, primarily the Indian subcontinent and Sub-Saharan Africa. This is a reduction of more than 99 percent from when the program began in 1988. And the major problems now are some of the poorest, most difficult countries, but the target now is to try to terminate transmission by the end of 2002 and certify eradication of polio, which requires three years without any cases, by the end of 2005.

The last thing I wanted to talk about, and we had a presentation before on the outbreak of paralytic polio due to vaccine-derived viruses. These are the latest information that I could get. We currently have 20 known cases as of June 18th. In the Dominican Republic, things are looking good. The last known case in the Dominican Republic is on January 25th. The situation does not look as good in Haiti at the moment. The last known case had onset on April the 29th. So I think it's much too early to say whether the problem has been eliminated in Haiti, and there are efforts

going on in both countries to try and terminate transmission during -- using oral polio vaccine. That's all I have.

**DR. MODLIN:** Thanks. Questions for Walt? Sam?

**DR. KATZ:** Walt, in your presentation on funding, you said there was $1 million for global polio.

**DR. ORENSTEIN:** Correct.

**DR. KATZ:** Can you remind me of what we had in previous years? I seem to remember numbers like 23 million.

**DR. ORENSTEIN:** Well, this is a $1 million increase. So it's about 107 total.

**DR. KATZ:** So it's an increase.

**DR. ORENSTEIN:** Yeah. These are all -- These are not the budget. I'm sorry if I left anybody the impression.

**DR. KATZ:** Thank you.

**DR. ORENSTEIN:** These are budget increases that -- in the President's budget above what we had in the FY 2001 budget. So, clearly, immunization received special attention, particularly when you look at the overall CDC budget.

**DR. KATZ:** Thank you.

**DR. MODLIN:** Other questions or comments? Walt, thanks very much.

Next, an update from the FDA, Dr. Midthun.

**DR. MIDTHUN:** Good morning. Is this on?

**DR. MODLIN:** Yes.

**DR. MIDTHUN:** Since the last ACIP meeting, the Vaccines Advisory Committee of the FDA has met twice. In the March meeting, there was discussion of Smith -- GlaxoSmithKline's combination vaccine product, a license application for that. This combination vaccine contains DTaP, hepatitis B, and inactivated poliovirus vaccine. The efficacy for this product was evaluated on the basis of a comparison of the immune response induced by this product as compared to the immune response induced by separate injections of DTaP, hepatitis B, and oral polio vaccine. And the non-inferiority for the combination vaccine was met with regard to all the components except for one of the three pertussis components, the FHA component, and that was slightly outside the prescribed non-inferiority margin.

The Advisory Committee was split with regard to whether

efficacy had been demonstrated for this product. The safety of this product was also discussed. There was not actually a vote on this because there were some outstanding manufacturing issues, but there was extensive discussion. The Committee, as a whole, all agreed that additional safety data should be obtained for this product, especially with concomitant administration of Prevnar. There was no such data in the license application because Prevnar was not licensed at the time this combination vaccine was being developed.

Where there was not complete concurrence with regard to when these data could be obtained, the majority of the Committee felt that some data should be obtained with concomitant administration with Prevnar prior to licensure, although some members thought that could be obtained post-licensure.

There was also discussion at the March meeting of the development of new conjugate pneumococcal vaccines, especially in the context that in the United States, of course, Prevnar is recommended for routine use, which means that it would not be possible to do a

placebo-controlled efficacy study with a new pneumococcal conjugate vaccine. And so the Committee discussed alternative strategies to supporting efficacy for new pneumococcal conjugate vaccines, and there was a -- the great majority of the Committee believes that one could support efficacy for new conjugate vaccines through comparative efficacy studies with Prevnar, the licensed pneumococcal conjugate vaccine. There was also discussion, of course, of how one would support efficacy of newly-added serotypes which were not contained in Prevnar. That, of course, is a complex issue, and I would say that there was agreement that this, too, could be done through an immunological evaluation, although it wasn't quite clear what the comparators should be in these particular instances. This is obviously an area that we'll have to continue to work on.

During the May Advisory Committee, we discussed the use of new cell substrates, in particular use of transformed cell lines as substrates, and this is an issue in that certain newer vaccines, including some

target against HIV, cannot be produced in more conventional cell substrates. And as a result, there was discussion of adenovirus transformed cells. And we sought advice from the Advisory Committee on whether the assessment with regard to tumorigenicity, oncogenicity, and adventitious agents, whether they were in agreement with the approach that we had taken for that. And I would say that they were, although they also had some additional very helpful input on how some of these things might be further evaluated.

I guess one -- for upcoming highlights, as you heard yesterday, during the July Advisory Committee meeting that's scheduled for the 26th and 27th of July, we will be discussing the -- Aviron's license application for their live-attenuated influenza virus vaccine, and I guess that wraps it up for Advisory Committees.

With regard to new product approvals, as you had heard yesterday from Dr. Margolis, in May we approved the TwinRix product. It is Glaxo SmithKline's combination hepatitis A/hepatitis B vaccine. It's indication is for active immunization in individuals 18 years of age and older.

And one other noteworthy approval was the new formulation of Aventis Pasteur's Tripedia. This is a formulation that no longer contains a preservative in it, although it still contains a trace of thimerosal. However, it's a marked reduction compared with the previous formulation. The previous formulation contained 25 micrograms of mercury per dose. This contains less than 0.5 micrograms of mercury per dose. So it's like a 98 percent reduction in that. So that's all I have to report.

**DR. MODLIN:** Thanks, Karen. Are there questions for Dr. Midthun? Dr. Katz?

**DR. KATZ:** Karen, I wonder if you can tell us when these combination vaccines that we have not yet licensed are used in Europe and in Canada? Do we accept or gather the information on immunogenicity and efficacy and safety from their experiences in those countries and can they be used at all to reinforce applications in this country?

**DR. MIDTHUN:** They are used. I mean, the manufacturer frequently, as a matter of fact, will use the same clinical trials that were used in support of licensure

of a given product in Europe for licensure in the U.S. So they're used in that context. And also, of course, when there are post-marketing data, the sponsor will routinely submit those with the application, also.

**DR. MODLIN:** Other questions?

(NO RESPONSE)

**DR. MODLIN:** Thanks, Karen.

The next report will be from Dr. Geoffrey Evans of the Vaccine Injury Compensation Program. Geoff?

**DR. EVANS:** Good morning. Can you hear me okay? I'd like to start with the monthly statistics sheet. And as you trace for fiscal year 2001, you'll see that we've received 143 claims so far this year, which is actually an increase from about an average of about 15 per month to 18, probably due to the fact that there's been more publicity surrounding the Vaccine Injury Compensation Program, more awareness, and this is -- even though it was the previous couple of years, it's probably a lag time in terms of claims being filed. The two claims you see under the pre-88 program, of course, were dismissed because the deadline passed in '91.

Under new vaccines, for new vaccines that have been added to the program, currently at 343 hepatitis B, which are in the very slow process of being -- medical records being gathered and it probably will take the next three to five years to begin to adjudicate them. Small numbers for Hib and varicella. And in terms of rotavirus vaccine, as I pointed out previously, we have ten claims so far which fall under a statute of limitations of three years. There is no injury specifically listed for rotavirus vaccine, but we are in the process of developing a notice and proposed rule-making that will add intussusception under rotavirus vaccine. And once that is published as a final rule several years from now, hopefully, there will be an eight-year retroactive coverage period. So any claimant, any petitioner that had a child that experienced that and had either residual effects or had surgery would be certainly eligible to file and rightly receive compensation.

And although DTaP is not a new vaccine, per se, it's just interesting to note that we've received only 32 to date.

Only thing to note under claims adjudicated is that there is still about 20 pre-88 claims remaining. These are some of the more complex, complicated cases that have taken a little bit longer to get settled. And under awards, a little over a billion dollars paid to date, and the trust fund keeps growing. It's now 1.67 billion. Roughly $200 million comes in annually. I thought it would be interesting just to take a look, noting that there's been this increase of claims per month as an average. Over the course of the program this is a little bit of a moving target because we've had table changes in '95 and '97, but for the most part, during the first half to three-quarters of the program, DTP was the predominant vaccine that was filed in terms of overwhelming numbers, followed by MMR and, of course, the OPV and IPV for the most part reflect experiences during the fifties and sixties when polio was endemic in the country. Rubella vaccine, three percent, mostly postpartum or health care workers and administrations, and small numbers for tetanus-containing. And non-applicable would be filing for non-covered vaccines or they just didn't

specify which one.

So the experience we're seeing in terms of percentages, more recently we're seeing -- there was certainly more attention on hepatitis B and MMR is still about a quarter of the claims. Of course, there's been a significant fall-off in DTP with the change in recommendation, and so on.

So that at least gives you an idea of the kinds of claims that we're receiving currently.

There's been some confusion about pneumococcal conjugate vaccine and its coverage under the program. Actually, this was raised by some program managers across the country, and I wanted to be clear that it is covered, but it's covered with a minor caveat. Just as a quick review, because of legislation passed by Congress in '93, in order to add a vaccine to the program, to the Vaccine Injury Table, it has to be recommended by CDC for routine administration to children -- So any universal recommendation covers that -- and there also has to be an excise tax passed by Congress. And once this is in effect there's eight years of retroactive coverage, as I pointed out, and

a two-year window to file claims before it became effective.

Now, in the case of conjugate pneumococcal vaccine, the excise tax actually predated licensure by a little bit, and it was licensed during the ACIP meeting in February of 2000 and the CDC recommendation followed later that year. But because of the way the law is today, it's included on the table but it's included in a special category, and that's currently a category XIII, box XIII.

And in May, the Secretary published notice in the Federal Register notifying the public that it is indeed covered under the compensation program now because of the two prerequisites in effect. And this box XIII is a general category reserved for new vaccines and the coverage dates back to when the excise tax became effective. And again, we're in the process, as part of this NPRM, to include the fact that we are adding pneumococcal vaccine with no specific injury listed. And of course, the 23-valent pneumococcal vaccine that was given to adults and older children is not included because that's not a general use recommendation.

And this NPRM unfortunately is going to require six months of public comment, a public hearing. And again, I think within a couple of years, we should have that published as a final rule. And the final rule allows pneumococcal conjugate vaccine to now be in the box XIII. Whereas, the new vaccine box XIII will be box XIV. So I trust that this is now a little bit more clear.

(LAUGHTER)

**DR. EVANS:** This is what our website says. It has box XIII with the standard language but then a note of that, and the footnote that is included below this simply, again, notes the publication in the Federal Register and refers people to a different site on the web for additional explanation so they can be even more confused.

Under legislation, again, we have the "Vaccinate America's Children Now Act" which would reduce the excise tax on vaccine, and we've heard that it's gotten some support on both sides. Again, there's interest in it. But this is probably one of the more uncertain legislative years recent. So it's not clear as to

whether there will be a tax bill later on or whether it will be included and so on.

But there's another piece of legislation I think does demand some attention, and that is on March 29th, Representatives Dave Weldon and Jerry Nadler held a press conference, along with Dan Burton, to talk about the Vaccine-Injured Children's Compensation Act, which I think I have also alluded to in the past because they were separate bills by both Representatives Nadler and Weldon. But they're very similar. Their bills are very similar to what this is, which would basically -- and most importantly, to begin with -- adopt a burden of proof standard that is used in veteran's claims process. And this is a standard that is not the Agent Orange standard, which is positive association, that was legislatively replaced, but this is something more of a preliminary process where they just -- you have a very loose standard where it's what would be vaccine-related would be what a fair and impartial person would deem it to be. And of course, it's a non-science-based approach.

It would also extend the statute of limitations from

three to six years for both death claims, injury claims, and it would be based on when the petitioner first knew or reasonably should have known. So this would of course be a much more vague standard in terms of timing. It also has provisions which actually the program and the Administration has backed such as the payment of family counseling and establishment of trusts. And there's been -- also been some discussion before the Commission as far as payment of interim fees and cost of attorneys. This has been referred to the House Commerce Committee and we're not aware of any further action on it at this moment. But it reflects, I believe, a growing interest in at least considering an alternative standard for the program.

I think the legislation clearly came about because of the hearing on the program in September of '99 and a more recently released report that was bipartisan. And among the three recommendations it did note to -- that the program should determine a reasonable alternative standard but didn't specify how this should be done. And both the legislation now that's been introduced, as well as some -- at least one recent

claims court decision, is pushing toward this -- this consideration of how we might go about increasing the numbers of claims that are compensated in the program. And it's rather easy to understand why there would be this interest. Because if you look at the original vaccine injury table, which had seven vaccines listed and most of the claims that were filed under this for the first half, if not longer, were claims that would pursue a table allegation. They would look -- They would identify a condition on the vaccine injury table. If it occurred, there was no alternative cause, then they would receive a legal presumption.

But with removal of certain conditions, with the change in the vaccine recommendations, no longer using DTP and OPV, for example, which were predominant claims filed, you have the situation now where among the 12 vaccines and the conditions listed, most claims that are filed have to pursue a causation-in-fact allegation. And that's much more difficult, more burdensome, and more costly, and a significantly increased number are being dismissed. And there's a public policy goal, obviously, that the program at least, you know, as far

as Congress intended, understandably, as far -- which would suggest that we should be compensating at least certain numbers of claims and not again create the situation where people are going back to the tort system. So, certainly, the program is looking at this very closely and trying to come up with some kind of a standard that would embrace science and provide some more consistency than what's currently being suggested as an approach. And I think I'll stop here.

**DR. MODLIN:** Thank you, Geoff. Questions and comments? Jon Abramson?

**DR. ABRAMSON:** Yeah, two questions. One is, for the hepatitis B, is it mainly neonates or is it older people for whom the claims are being, you know, made?

**DR. EVANS:** Of the 300 and some-odd -- I haven't looked at this recently, but I know that when we received the first big bolus, I was able to determine about 50 claims were for individuals 18 or under, and of that there was about half that would be neonatal doses, probably SIDS or other kinds of events.

**DR. ABRAMSON:** What would be a process for someone -- For instance, we recommend flu vaccine for high-risk children. What would be -- if someone thought they had an adverse event due to the flu vaccine, what would be the process they would go through? Would they just go straight to the courts?

**DR. EVANS:** Yes, they would. There is no -- Until there is a general-use recommendation for flu vaccine -- and it will probably a specific coverage proposal for that type of vaccine -- they would have to go through the tort system.

**DR. MODLIN:** Bob Chen?

**DR. CHEN:** Yeah, just to add to what Geoff has said, I think, as he mentioned, this law and whatever changes that it reflects, really is a summation of public policy in terms of what America, as a society, decides how we should deal with this very difficult topic, and I wanted to kind of focus on a couple of aspects of it.

It seems to me that one of the major pushes for these modifications emanate from a major deficit in how the law ultimately got implemented and -- in contrast to

the original hearings in terms of what the intent of the law is. And the contrast comes in this -- in how other arenas deal with the issues of excise tax and how the funding is used.

So in the aviation arena, for example, the excise tax that we pay every time we fly goes to improve the system -- the airports, et cetera -- to prevent future aviation crashes. It is not used just for reimbursing victims of airplane crashes, which is the current way the vaccine injury system is structured. None of the funding goes towards ultimately trying to prevent future injuries.

And so what had happened was that we created this vaccine injury table in which, in order to make any additional changes, it was based on science, which is quite reasonable. However, there was absolutely no funding, no provisions made for who would fund that scientific research. And that continues to be the problem.

So, for example, as Walt mentioned yesterday, that very nice thimerosal study that we proposed, in fact, has no funding for it. And we would have to go through the

annual budgetary process year after year to try to make the case, competing within NIP for -- you know, against purchasing vaccines and other things, while at the same time we have this $1.5 billion surplus sitting in the injury compensation program, which at the moment has no way of being used for that research, which, in fact, has great implications on that law.

So the current Washington scene has decided, well, the way to deal with it is, in fact, to remove the scientific issue related to it so that all the lawyers and the parents would just simply get paid off easier.

So I just kind of want to argue that, in fact, the scientific community really has an opportunity to make an alternative case and that is we -- the intent of the law really has been subverted in terms over the years. Not perhaps intentionally, but that we really need to make an alternative case for how the law should be modified.

**DR. MODLIN:** Bob, how is that going to happen? In other words, is this -- are you suggesting a grassroots effort that we contact our congressmen or is there going to be a sort of an organized approach that may --

**DR. CHEN:** No, I think the -- And again, the original bill was passed via a coalition of AAP, the dissatisfied parents together, and industry. Now, in part, I think the law, as it was implemented, got diverted because the administration at that time opposed the bill and so, in fact, was not at the table to make that case. And so I would argue that perhaps we -- You know, the interested parties, the major players -- and again, I would urge and say perhaps AAP -- you know, there are limits to what us working within the government can do, but the larger community -- I'm happy to discuss with them and I'm sure the industry and AAP and other folks and I think this, in the long term, really is in the interest of the consumers very much, as well. It really is a win/win situation. So it's a matter of figuring out how best to rebuild that coalition that created the original law and improve it.

**DR. MODLIN:** Thanks, Bob. Myron?

**DR. LEVIN:** Myron Levin.

Two questions. Why is hepatitis B currently so predominant in terms of your active claims? And the second, I noticed, in the past, a large percentage of

claims were dismissed, and still a larger percentage is dismissed than are favorably adjudicated. Do you know what happens to those cases? You know, are they costing money in the tort system, or are they dropped, or what?

**DR. EVANS:** Of course, the only way that we would know that is through anecdotal reports, and we've tracked DTP lawsuits up through '97. There was a significant drop, to less than six or eight per year. So as far as DTP, which is the most litigious vaccine, as you know, up until recently. The answer is they seem to be not going through the tort system and staying away because, of course, the standards are much easier in that you don't have to prove negligence. There's a table.

As far as your first question goes, I think it was the fact that there was a deadline for filing the older claims when it was added, number one. Number two, you had the publicity surrounding the French government's decision and a couple of plaintiffs' attorneys got very motivated and solicited claims through advertisements.

**DR. MODLIN:** Other comments?

(NO RESPONSE)

**DR. MODLIN:** Geoff, thanks very much.

The next item on the agenda is a report from the National Vaccine Program Office, Marty Myers.

I don't know if everybody is aware of the fact that Marty has announced his intention to step down as Director of the office. And Marty, I want you to know that I speak on behalf of the Committee in expressing our appreciation for your very effective leadership to that office over the last few years, and we wish you well.

**DR. MYERS:** Thank you very much.

Well, I'm going to talk a little about the NVPO and the interagency vaccine group, and Georges Peter said I should incorporate the NVAC activities, too, but he may want to comment.

There is a new website that gets you directly to the same place that you get if you use our old web address that reflects our relationship with the Office of Public Health and Science in the Department.

Several people asked me to put together something which

showed the relationships of the interagency group. And so within the Department of Health and Human Services, there are a number of agencies that have activities that relate to vaccines, and they represent the interagency vaccine group. In addition, the Department of Defense and USAID in the original Congressional authorization are also incorporated in the interagency group. And then NVPO's role is to facilitate and coordinate those policy activities across the different agencies.

We mentioned all the advisory committees at one time or another. There's the FDA's advisory committee that relates to vaccines, there's this advisory committee that relates to CDC, there's the Advisory Commission on Childhood Vaccines that Geoff was just talking about, and there's the National Vaccine Advisory Committee that advises the Assistant Secretary for Health on vaccine policy issues.

So I thought I'd just make a list of things that -- to run down and report on. As you know, we coordinate the pandemic influenza planning. There is a draft plan that's in the clearings process and it has a series of

annexes associated with it, dealing with each of the different technical aspects. A number of you and your organizations have several of these annexes under review, the infection control one. Jon Abramson and the Academy of Pediatrics is looking at the triage and care for children section, and so on.

In March, we convened a technical workshop to consider how antiviral drugs might be utilized within -- in a pandemic setting to try and develop some options as to how we might approach antiviral drugs in a pandemic response. Particularly with the lead of the National Immunization Program, there are -- you have seen the pediatric and adolescent, plus adult immunization standards. Those have been revised and reviewed and approved by NVAC and recommended for wide distribution for comments, and those are out under review now.

In addition to the eradication Walt mentioned earlier, there's another activity which we're involved with which is the laboratory containment activity. Walt Dowdle is chairing that activity as a special advisor to the Assistant Secretary and we're coordinating it. An initial pilot study has been completed at CDC, an

inventory of samples that may contain a wild-type poliovirus. The NIH pilot study is underway and expected to be completed within the next month. And Emory University and four states have agreed to being pilot surveys soon with the intent that we hope to have a national inventory completed by the end of the year and then the process of increasing the biocontainment level for wild-type poliovirus.

I mentioned yesterday the vaccine supply working group of NVAC. The Secretary has been briefed on the issues surrounding vaccine supply, and I'll say a few more things about that in a moment.

We also have a working group examining the whole issue of the introduction of new vaccines, the whole process of how -- and timing of recommendations, the issue of costing of vaccines, and the financing of new vaccines. And that group has had an open meeting with a Federal Register listing of activities. We had a number of reports from industry that had been provided to us. I know Georges -- I couldn't remember last night the new title of our group. This is a working group that's had multiple titles. It started out being the mandate

guidelines title and this was my most --

**DR. PETER:** That's not it.

(LAUGHTER)

**DR. MYERS:** The intent of this work group is to establish guidelines for states to utilize when looking at implementing new recommendations for new vaccines. It's, as I said, a guideline, but I can't remember the title now of the --

**DR. PETER:** You finish.

**DR. MYERS:** I'll finish and Georges will help. So if we look at just some of the topics that we've talked about in the last year on vaccine supply -- and there are other issues in addition to these, but these are the ones that we dealt with this past year -- that one of four manufactures of influenza vaccine left the market and much of the vaccine that was available was delayed this past year. We've been talking about the delay for this next season.

There's only a single manufacturer of the adult -- the tetanus-toxoid-containing vaccines, except for the pediatric DTaP. There's a single manufacturer of a meningococcal vaccine, which limits activities around

outbreak control. There's also only a single manufacturer in this country of varicella vaccine. Two of four manufacturers of DTaP have discontinued production in the United States. And for outbreak control in the United States, there are no licensed producers of oral polio vaccine.

The NVAC Subcommittee on Vaccine Safety and Communication held a open public forum about the process of how to identify the future topics. Yesterday we heard the IOM report on the first, the MMR. The second issue that they're going to address is the thimerosal issue this summer, and then the -- in the fall looking at multiple antigen and immune responses. We've asked the Vaccine Safety and Communication Subcommittee to consider the process of identifying and recommending to the interagency vaccine group future topics for the IOM Vaccine Safety Committee. We have a -- We're sponsoring an intussusception and rotavirus vaccines workshop. We hope this will be the definitive workshop on addressing the issue of what the attributable risk of intussusception after rotavirus vaccine was and is, and then NVAC's interest in this

is that we believe that rotavirus vaccine is a critical vaccine for development, both for the United States and worldwide. And so we want to look at barriers and opportunities to facilitate the production of a rotavirus vaccine.

I reported last time about the Aluminum in Vaccines workshop. That's in press this month in Vaccine. The Combination Vaccines Workshop is in Clinical Infectious Diseases in press for July.

And John already mentioned the fact that I have asked the Assistant Secretary to begin the process of identifying my successor, and I'm urging the Department to identify somebody who can be based in Washington, because now that NVPO is formally part of the Office of Public Health and Science, I think it's critical that that position be there. I thank you all very much for your support. I agreed with the Assistant Secretary and with Dixie to stay and make sure there's an orderly transition.

**DR. MODLIN:** Thanks, Marty. Georges, do you have anything to add?

(APPLAUSE)

**DR. PETER:** Well, thank you, Marty. Given your commitment to continuity and smooth transition, maybe if we take our time identifying your successor, we'll have you around for a while and you won't be able to spend as much time with your new grandchild. Anyway, we congratulate that on you, too.

Just a few comments. One is on the Poliovirus Laboratory Containment work group which is chaired by Walt Dowdle. I think some very important recommendations that are relevant to this group were made. Dr. Dowdle, as you know, for many years was at CDC and I believe was the Associate Director of CDC and is now working for the Task Force for Childhood Survival. And he presented the plan in some detail, but I think the very important point for poliovirus laboratory containment is to seek the participation and cooperation of laboratories throughout the country, not just those in the government. And I think this will be a major effort if we are indeed to continue laboratory stock of poliovirus that would be unwittingly in laboratories and eventually disseminated. I think this is going to take a public

education campaign and an awareness by all of us of the importance of it.

The second is the work group that Marty struggled with the name of, but that is a work group entitled Work Group on Public Health Options for Implementing Vaccine Recommendations. And that arose from the request of ASTHO for us to help them in establishing priorities in the development of school immunization requirements, as well as those for day care, perhaps, and even colleges. And we are not in any way going to identify vaccines that should or should not be required, but rather to provide the various means by which states may implement vaccine recommendations ranging from mandates to even incentive. And I think an excellent paper that I think sets the framework for some of the options is in Pediatrics last month by Ed Marcuse [phonetic] and his -- and a colleague. And we will hold a series of three workshops throughout the country to learn the perspectives of different state health departments, as well as private groups, industry, and other relevant partners, and we hope to have a report in draft form, at least by the end of the

year.

The final point is that the work group on strengthening vaccine supply really is still embryonic and I think we really need to discuss means by which we address this broader problem because the problems we discussed yesterday with influenza and DT are really more symptomatic of a broader issue than simply immediate problems that can be solved immediately. So we hope -- and again -- I think, Marty, we'll have you back again in October, won't we?

**DR. MYERS:** Yes.

**DR. MODLIN:** Certainly, if the hiring freeze isn't lifted. Thanks, Georges.

Any other questions or comments for either Dr. Myers or Dr. Peter?

(NO RESPONSE)

**DR. MODLIN:** Okay. The next report will be from the National Center for Infectious Diseases, Dr. Allison Mawle.

**DR. MAWLE:** I just wanted to update people on the -- something you may have seen in the press at the end of May, on May 30th, that the Bill and Melinda Gates

Foundation awarded $70 million to support the development and production of conjugate vaccine against meningococcal A. This is going to be a ten-year project. And those of you who are not aware of this particular project, it's been developed by a working group that was spearheaded by WHO and PATH and with the input of five individuals. Nancy Rosenstein from CDC has been the major part of that working group. So that's something that we're very pleased about at NIAID. As you are aware, in sub-Saharan Africa there's something like over 200 million people who are at risk for this disease. And the figures this year, which are doubtless -- serious under-reporting, there's at least 40,000 people already infected, with over 4,000 deaths.

I think people on this Committee are very much aware that this has been a very difficult issue in the field of vaccines, that know how to produce a vaccine against a conjugate vaccine against meningococcal A has been around for at least ten years. What's been lacking has been the guarantee of a market. And this work group was essentially put together, once the Bill and Melinda

Gates Foundation sort of came into being, in order to provide essentially a public push for a vaccine that's very much needed in Africa.

And their goals over the next decade are to develop this mening A conjugate vaccine; to evaluate it in Africa; to create a pathway for the licensure of the vaccine, which will be used largely in Africa, and that in itself may be an interesting process; to assure sufficient volume for the needs; to monitor the programs for -- to assure effectiveness and safety of the intervention; to finance the procurement of the vaccine -- and again, that's another huge issue, but the expectation is that this will be tied into the GAVI process; and of course to introduce the vaccine through mass and routine immunizations.

And the hope is that within the ten years, once this program is jump-started, that there will be an infant vaccine against -- conjugate vaccine against mening A that can be used to essentially reduce and hopefully pretty much eliminate this scourge in Africa.

The other thing I wanted to mention, which has come up from Marty, is the polio containment. As you're

probably aware -- he said CDC, but polio live containment at CDC pretty much means NCID. So that's why Walt Dowdle used CDC as the pilot project. It actually went extremely well. We learned some valuable lessons, as you always do when you do these things, about how to get the information down to those who need to actually do the inventory, how to simplify it. I mean, this seems to be the basic issue, make it as simple as you possibly can. And we're currently in the process of developing a web-based interactive interface. When we actually go out and survey the whole universe of labs out there, it will be done through the web. So, obviously, what we eventually need is to be able to have something very straightforward that people can get in there and answer.

I think Georges Peter made the point about education. That's already happening. Walt and his team have been talking obviously to the professional organizations. They were at APHL, the last meeting, a couple of weeks ago. They've been talking with ASM and they will be going out and visiting all these major institutions.

So we think this is a doable proposition.

**DR. MODLIN:** Thanks. Questions for Dr. Mawle?

(NO RESPONSE)

**DR. MODLIN:** Okay.

On my agenda I don't see a report from the NIH. Dr. Landry, did you have anything to say?

**DR. LANDRY:** No.

**DR. MODLIN:** Okay. Thank you.

If not, we'll go on to the next item on the agenda, which is, hopefully, completion of a process of development of the general recommendations on immunization that Dr. Atkinson will remind us has been underway now for at least a couple of years.

We had an opportunity to review the document at the February meeting and had an extensive discussion on immunization of foreign adoptees at that time. The statement was sent to members of the Committee with the advanced mailing. So I hope that you've all had an opportunity to go over it, and it certainly is my hope that we can finish our work at this session.

Bill, is it your plan to go over highlights or changes in --

**DR. ATKINSON:** Yes.

**DR. MODLIN:** -- the statement? Fair enough.

**DR. ATKINSON:** I thought we would run through -- This is, by the way, the -- by my count, the eleventh discussion of part or all of the general recommendations and, best I can tell, it actually has outlived a number of ACIP members and liaisons. So I'm hoping this will actually be the last time you'll hear about this, at least for a few years.

I have -- you were all given draft three of the document. At the February meeting I did receive a number of excellent -- there were some very good readers and editors out there, and several people pointed out that I have a bad habit of splitting infinitives, but we won't go into that at this stage. But I did get a lot of good comments, and what I will try to do here -- I'm going to go through the things that have changed, the things that I was asked to insert into the document at the last meeting, and hopefully come to some closure on it.

And I'll go through the list. The changes were listed on the cover page. I assume you all have a copy of the

document, and I'll just go through them -- some of them fairly quickly since they're basically additions of things that were in there before. They're short and don't really have a lot of need to discuss them.

Several people wanted the definition pages added back. That first appeared in the 1994 General Recommendations. I took it out just -- I don't know why, but several people wanted them back, so they are back. If anyone has any additional -- I updated it a little bit. If there are any particular terms that any of the members or liaisons or anyone else feels should be defined, please let me know and I'll be happy to add them.

One thing that has changed several times now is the continuing contentious issue of wording surrounding the grace period. In draft three, which was the February draft, there was a -- and this wording is now on page 12 of your document. This was the wording that was in there and it was intended to try to give some guidance about the relative relationship of the grace period, the four-day grace period, to existing state and local immunization requirements. This was the

note that was there, and the important parts I've highlighted here in yellow.

"While health care providers must comply with existing state laws and regulations, the ACIP hopes that individual states and local areas will consider the new ACIP four-day grace period rule and the grace period recommendation in reviewing and evaluating their state and local vaccination recommendations or requirements."

Subsequent to that draft, we received -- actually, Dr. Snider received a letter from the director of ASTHO asking that there be more clarification be added. I've added that letter, the letter we received from Dr. Hardy, as page two of your handout so you can see it for yourself. But in essence, Dr. Hardy requested that they encourage ACIP to expand the footnote to clearly indicate that practitioners should vaccinate according to recommendations of ACIP, in accordance with applicable state requirements. Uniform grace period is commendable. We would like to see an affirmative statement deferring to specific state requirements where they apply.

As a result of that request from ASTHO, I tried to change -- I changed the footnote to add -- the way it currently exists in draft five on page 12, and that last phrase now says simply that: "ACIP recommends that physicians and other health care providers comply with local or state vaccination requirements when scheduling and administering vaccines." And hopefully -- That is not exactly the same note as was in the draft that was distributed in February, but I think that does essentially comply with what was requested by ASTHO. So if there are any thoughts on the wording of that or if you would like it worded in a different way, it basically says that the grace period -- I think the implication here is that the grace period does not necessarily supersede existing state immunization requirements. And that, to me, was what ASTHO was asking us to do. So any thoughts on that? If not, I'll move along.

**DR. MODLIN:** You're getting a thumbs up.

**DR. ATKINSON:** Okay. Thumbs up, I like it. Next, there are three more things that are relatively minor that I thought I would at least tell you about.

You recall last time -- Well, there were several comments that came in, particularly from people from DOD who suggested because of their unique schedules that rabies and anthrax vaccines be specifically mentioned as exempted or not applicable when the four-day grace period is there, mainly because of the very close scheduling of this. You could essentially be getting doses on the same day. So there was a footnote added on page 12 that specifically mentions that because of their unique schedules and spacing that rabies and anthrax vaccines should be exempted -- does not apply, or should not be applied to the four-day grace period that is discussed earlier.

There were -- There's a section on page 13, and I -- a lot of the careful readers noticed this -- that with one slip of a word I essentially changed ACIP policy. And several people noticed this. They picked it right up, and it basically is at the bottom of page 13. And at least three people pointed out that I had, with one word, made major changes to the schedule. That had to do with down on line 33 and 34, which said, in the previous version, the IPV -- this

was in the discussion of how to reduce the number of injections at the second-year visit. I had written the IPV series should be completed before the first birthday, which was de facto recommendation that it should be give at six to 12 months. Several people noticed that one word, and so that line now says that the IPV series may be completed before the first birthday. And hence, I have not mucked around with ACIP policy.

So that's the main thing that was changed there because actually numerous people noticed that, that one word.

The next thing is on page 15. I've added basically one exemption. We discussed at the last meeting, or in several meetings, actually, the issue of the non-simultaneous administration of live vaccines. And the decision was to put into the document that vaccines -- live-attenuated vaccines -- parenteral live-attenuated vaccines not given simultaneously should be separated by at least four weeks per previous recommendations, and that those given less than four weeks apart should be repeated. A second dose actually should be repeated.

There actually are data now -- actually, they existed at that time and I just missed it -- that indicates that this should probably not apply to the combination of Yellow Fever and measles vaccine, based on a paper that was published in Vaccine in 1999. I show you here just for -- briefly, that there actually was a specific study that is unique, as far as I know, to any looking at this issue to determine the interference or lack thereof of measles and Yellow Fever vaccines. It was done by a group in Brazil. For what it's worth -- I wouldn't have known the significance of this till yesterday -- this was DD Yellow Fever vaccine and they used Schwartz strain measles vaccine in this trial, and they looked at the seroconversion, basically, to yellow fever vaccine following varying intervals after a dose of measles vaccine given at nine months of age. And the bottom line of this is about 300 people involved -- children involved in this, there was no difference in the seroconversion rates, even though they were less than the investigators anticipated there in the third column. But, then again, these were nine-month-old

children given the measles vaccine. And the GMT's were of -- not statistically different, nor were the seroconversion rates.

So based on those data, which is really the best specific investigation of this phenomenon of interference or lack thereof since the data from 1960, I went ahead and put an exemption for the -- since it appears that these -- at least, if you believe that Edmondson Enders [phonetic] equals Schwartz and that at 204 equals DD, then, in fact, I think you could make a case that Yellow Fever and measles probably do not interfere with each other. Hence, I put an exception to that in the repeat rule that was introduced because in that nonsimultaneous part.

So assuming that DD equals 204 and Enders equals -- Edmondson Enders [phonetic] equals a Schwartz strain, I think I'll just leave that exemption in there -- that exception for Yellow Fever and measles in there, unless there are problems with that.

**DR. SMITH:** Bill, just the Yellow Fever statement needs to be changed then to --

**DR. ATKINSON:** Yes, we probably need to add it to the

Yellow Fever statement, as well. I'll make a point of that.

By the way, I'll add -- it just occurred to me that I will be talking to Hal and others concerning the congruency of the General Recommendations and the new hepatitis statement, so just in case you're wondering about that. So I'll make sure that the two are consistent when it comes around to getting those two published.

**DR. PETER:** Parenthetically, and I'm not suggesting a change, but we have one study that suggests that two live virus vaccines given within 28 days parenterally interfere and one that indicates they do not. The only data that indicates interference is the vaccinia measles study, I believe, in the 1970's. We now have another study. So I think the data for interference is pretty weak. I mean, it's one for and one against. I'm not suggesting change after all the work you've done, but I think we should be aware of that concept.

**DR. ATKINSON:** I'm happy to change it. You know, that was a new -- that's a new recommendation. There's never been a statement in there to say what to do. And

this arises frequently. We say don't do it, don't give them within four weeks of each other, but there was never any direction as to what one should do if that were to occur. And that's why we sort of forced the issue and asked ACIP to consider it.

**DR. PETER:** Well, I would make one other point, too, is that we know that if a child has had a recent viral infection, within four weeks, this certainly is not a contraindication for administering the vaccine. And that may be just a vigorous immune response. In fact, we know that mild viral infections do not interfere with the response to at least some viral vaccines. That was pointed out to me by a person -- a very thoughtful person well known to all of us in California.

I mean, for example, a child could have measles, the way the recommendations are written today, and two weeks later, according to your current recommendations, receive varicella vaccine. And yet if the child happened to get measle vaccine, varicella vaccine would be said to be theoretically better to be postponed. So I think we have a certain contradiction that we've never really adequately resolved.

**DR. ATKINSON:** Oh, a serious contradiction. And it actually, the opposite is actually more common these days that a child has varicella, and we are -- they want to know when they can give MMR and they extrapolate logically from the recommendations that are here, and it doesn't make any sense. And I have a hard time explaining to people why you don't have to defer it after varicella but you do after varicella vaccine. So I'm happy to strike that.

I'm happy to strike that sentence out if you would like. I mean, that was something we pressed, and there were some moderately strong feelings about it from the Committee and other folks in the audience. And I'd be happy to drop that out and basically not have that repeat indication in there if that's what the Committee wishes. It's not --

**DR. MODLIN:** My recollection of a very extensive discussion that we had about this topic, probably about a year ago, was that, given that nobody was comfortable with the nature of the information, but the only information we had was that one study. And therefore, I think the consensus, at least at that time, was just

to leave things as they are. But it may very well be that perhaps introducing some expert opinion and common sense here may make more sense.

Melinda?

**DR. SEWARD:** Jane.

**DR. MODLIN:** Jane Seward.

**DR. SEWARD:** There is a study that's been done in the VSD datalink project looking at simultaneous and nonsimultaneous -- or administration within 30 days of MMR and all vaccines. And interestingly, of all the vaccines -- you know, old childhood vaccines used, giving MMR within 30 days of varicella vaccine only did lead to an increased risk of breakthrough disease -- of vaccine failure for varicella vaccine. So that's going to be published in MMWR fairly soon. The study was actually designed to look at some other issues -- asthma and risk of vaccine failure for varicella vaccine -- and it came up with this finding, that MMR

**DR. MODLIN:** Jane, did the study include seroconversion or --

**DR. SEWARD:** No, it --

**DR. MODLIN:** -- was it just looking at efficacy?

**DR. SEWARD:** No, it was efficacy, effectiveness in terms of breakthrough disease reported to the HMO system. But we didn't imagine there would be biased reporting based on vaccines administered.

**DR. MODLIN:** So you think the data from that study are sufficiently robust that we should be concerned about where we're going here with --

**DR. SEWARD:** The data -- you know, the risk is significantly different with a 95 percent confidence and if we're not including one, and it's the only vaccine -- you know, MMR -- within 30 days. Given on the same day, no difference. Within 30 days, there's an increased risk of varicella vaccine failure.

**DR. MODLIN:** Other comments?

**DR. LEVIN:** Jane, Myron Levin.

Was that the only live virus vaccine given with MMR?

**DR. SEWARD:** OPV was another one, and that did not -- I mean, this was looking at varicella vaccine and then other vaccines given simultaneously or within a month, a month preceding. And OPV within a month did not cause -- was not associated with an increased risk of

varicella vaccine failure, only MMR.

**DR. LEVIN:** Although that's given orally as opposed to injected, yeah.

**DR. SEWARD:** Yeah. So that was the only -- that was all the others are cured.

**DR. MODLIN:** Gary, did you have a comment? Sam?

**DR. GALL:** In your -- on page 45 and 46 on vaccination and pregnancy, it's totally silent on pneumococcal vaccine. In the ACIP recommendations, basically, pregnant women that have high-risk medical conditions shouldn't receive pneumococcal vaccine. So there's not -- there isn't any -- any -- it's totally silent on pneumococcal. I think that needs to be -- have a paragraph on that.

**DR. ATKINSON:** No problem.

**DR. MODLIN:** Let's resolve the live vaccine potential conflict issue here because I think you clearly need some guidance.

Myron, did you have anything else to say about that?

**DR. LEVIN:** No, that's it.

**DR. MODLIN:** Jon?

**DR. ABRAMSON:** I think it was in JAMA, but I may be wrong

about that, there was this article that if you had a viral illness and then you got your immunizations, that you had lesser response. And we didn't know what to do with it. I honestly think we probably need a working group that looks at all the data at one point, you know, at where we are now, and comes back with a recommendation. Because we clearly are at a disparity. We're saying ignore it if it's a real viral infection. We're saying not ignore it -- don't ignore it if it's a vaccine. It doesn't make any sense.

**DR. MODLIN:** For the purposes of the statement, would your suggestion be to leave it as it is now --

**DR. ABRAMSON:** At the moment, because I would not --

**DR. MODLIN:** -- and then -- and then address the issue as an update --

**DR. ABRAMSON:** Yeah.

**DR. MODLIN:** -- which I think is excellent suggestion.

**DR. ABRAMSON:** I don't think we can resolve it.

**DR. MODLIN:** Peggy?

**DR. RENNELS:** Suggestion of another approach, and that is, since we really don't have the data to make a well-informed decision, leave the recommendation as it

used to be. Don't introduce change now, then study it, then maybe have another change.

**UNIDENTIFIED SPEAKER:** So you're saying --

**DR. MODLIN:** That's what we're suggesting.

**DR. RENNELS:** Oh, I'm sorry. So take out the repeat immunization.

**UNIDENTIFIED SPEAKER:** Right.

**DR. MODLIN:** That's what we're suggesting.

**DR. ATKINSON:** Well, unfortunately, that puts us back in the position we've been in since 1994, is that when this happens, we have no direction with which to give to the people who are trying to make the decision about what to do. That's the reason we forced the issue in the first place, because I -- we ended up having to make these things up as they came. I mean, this issue comes up a lot, and so we need to have something to tell them, do they repeat it or not, and if we want to say no -- you know, just being silent forces basically us -- somebody else to make the decision what to advise them to do. So we were hoping that you all could make -- give the advice rather than me having to do it.

**DR. RENNELS:** I think to change the policy based on

really little to no data is not a good idea. I mean, we're forever having to give advice without data on the phone in individual cases.

**DR. MODLIN:** I think Jon's suggestion is an excellent one, that we leave things as they are and that we form a group to look at this and to examine the data that are available in a much more careful and detailed way. And we can make updates if we change our mind. We do it all the time.

**DR. ATKINSON:** So you're saying leave it as they are or were? Were was no comment, no -- were was no comment. Are is that two -- basically MMR and varicella, if given within four weeks, not on the same day, the one given second should be repeated. That's as it is now in the statement. So you want to leave that in or you want to drop it out and just have nothing?

**DR. MODLIN:** Peggy?

**DR. RENNELS:** I say drop it out and have nothing and study it.

**DR. MODLIN:** Rich?

**DR. CLOVER:** But given the last comment of --

**DR. MODLIN:** Dr. Seward?

**DR. CLOVER:** Yeah.

**DR. MODLIN:** We haven't seen those data yet, Rich, in all fairness.

Myron?

**DR. LEVIN:** I would leave it in. Based on the old data that you were quoting from, I think, Tom Merrigan [phonetic] in smallpox and measles, I would leave it in, where there was -- where there was interference.

**DR. MODLIN:** In other words, you would leave the statement as it currently reads. Neal?

**DR. HALSEY:** Some of us on the margins are a little confused, because it sounded like Jane reported that if MMR was given after varicella, it led to a decreased response or decreased protection or an increased breakthrough rate with varicella vaccine.

**DR. SEWARD:** Before varicella.

**DR. HALSEY:** Before. So that's what we needed clarification on.

**DR. SEWARD:** Thirty days -- with -- 30 days before. Within, you know, 30 days before, it gave an increased risk of vaccine failure for varicella vaccine.

**DR. HALSEY:** Thank you very much.

**DR. SEWARD:** Enough that the MMWR will say that these data support the recommendation of not -- you know, of administering on the same day or else at a greater interval than the 28 days.

**DR. MODLIN:** Okay. We're at a bit of an impasse. Other comments? Committee members?

(NO RESPONSE)

**DR. MODLIN:** Let me ask this, if the Committee would be willing to leave the statement stand as we currently have it and that we go ahead and try to adopt the -- I mean, we have another option, which of course is to delay this yet one more meeting, which I would prefer not to. But that's option B. To leave the statement as it currently stands in the new statement, but we put together a work group to study this issue and that we do an update in a timely fashion. Timely probably means six to 12 months.

Peggy, are you --

**DR. RENNELS:** Well, my only --

**DR. MODLIN:** -- discontent with that?

**DR. RENNELS:** Well, I am, because you may do a flip-flop. I mean, you're changing policy now. Then

you're going to study it. You may change policy again. And I guess unless you've got compelling reasons to change policy now, I'd say study it first before you change policy.

**DR. MODLIN:** Rick?

**DR. ZIMMERMAN:** It seems that if it's one study that you're talking about looking at -- Right? It's the one study that Jane's talking about. And so if there's one study, that could be reviewed pretty quickly.

**DR. MODLIN:** Jon?

**DR. ABRAMSON:** No. There are more data -- one can look at both from basic science, translational and clinical. I mean, there's viral-viral interaction. There's viral-bacterial interaction. There's all sorts of data out there that one can look at. I think you're going to have to do a serious review of the literature and come up with the best recommendation. It won't be clear-cut.

**DR. MODLIN:** Yeah, I think that's right. I don't think we can be focusing on any single one study or bit of information to address this. And we are inevitably going to see what appears to be data taking us in both

directions. There's no question about that. So I do think it needs a thorough review, but we need to address what to do with the current statement.

Let me ask for just sort of a straw vote, a show of hands, of those who would prefer to leave the statement the way it is currently proposed to us and, if necessary, maybe having to make a change later on.

(SHOW OF HANDS)

**DR. MODLIN:** That's one, two, three, four, five, six. And those that would prefer to not make any change here but go back to the 1994 statement?

(SHOW OF HANDS)

**DR. MODLIN:** Looks like there's three.

So it looks like the consensus is to leave things as they are in the statement as Bill has presented to us with the change.

**DR. ATKINSON:** If you would like to look at it one more time, it's lines 26 through 30 on page 15. And it says: "If parenterally administered live vaccines are separated by less than four weeks, the vaccine administered second should not be counted as a valid dose and should be repeated. The repeat dose should

be spaced by at least four weeks after the last invalid dose."

And that's basically the new wording. The rest of that paragraph is essentially the same. Remember, in the '94, there was no guidance at all. There was no direction as to give it again, don't give it again. This was -- those were the only two sentences that are new.

**DR. MODLIN:** Yes?

**DR. TOMPKINS:** The reason I think we should retain Bill's statement is that it's safer. It errs on the side of safety. Whereas, it's not such a big deal to say, well, it's no longer a problem. We can drop it from the recommendations the next time around. I think it's a safer thing to do, recognizing that this may well be a significant problem with the varicella vaccine, at least.

**DR. MODLIN:** And we certainly do have some information that this is more than a theoretical --

**DR. TOMPKINS:** Right.

**DR. MODLIN:** -- issue. And so I think --

**DR. TOMPKINS:** Right.

**DR. MODLIN:** -- given that -- well --

**DR. TOMPKINS:** And I also do not want to revisit these.

**DR. MODLIN:** Well, we're inevitably --

**DR. TOMPKINS:** And I'm sure Bill doesn't want to revisit them.

**DR. MODLIN:** Dennis?

**DR. BROOKS:** In addition, it gives guidance to the providers who always have this question and have, you know -- don't really have too many sources to look at to get it answered.

**DR. MODLIN:** Okay. Jon?

**DR. ABRAMSON:** I would add one thing, just to help Peggy's concern because I think it's real, is to know that it will be -- the tentativeness of this, in other words, that this is our recommendation right now but it will be looked at again, just so that people are clear that we're not doing this because we know, you know, there's 18 studies that say this is the way it has to be.

**DR. MODLIN:** Perhaps we can add some language to the

effect that there is considerable fuzziness around this issue, Bill --

**DR. ATKINSON:** We'll do that.

**DR. MODLIN:** -- and we'll continue to examine it.

**DR. ATKINSON:** No problem. That will be added.

**DR. MODLIN:** Terrific. Okay, let's move on.

**DR. ATKINSON:** I'll move along. Page 17. Several reviewers requested that I add at least some statement about palivizumab and its exception to interferences in the IG live vaccine section. I added a paragraph. There is technically a new section. It's actually a fairly long one that starts on page 19 and goes to page 22. It's actually not new. It deals with contraindications and precautions. And what I did, basically, was to combine pieces of things that were concerning contraindications and precautions and moved them really up into a more prominent part of the statement, up toward the front of the statement rather than buried in the back where some of this information was and basically combined the information on precautions and contraindications and invalid contraindications and precautions. And with that

came Table 5.

Now, Table 5 is that giant table of contraindications and precautions you see here. It's on page 75 of your document. And at the last meeting in February, the decision as to whether or not to keep Table 5, the large contraindication and invalid contraindication table, was tabled, pending discussion at a later date. I have left it in because it seems like it makes sense to me. The discussion, if you recall, was whether it should be updated more frequently in a different forum, a different format, perhaps published with a scheduled, perhaps something else. I went ahead and put it in, updated it as people suggested, and left it in because it sort of goes along with the -- that whole contraindication and precaution part. So I don't know if you would like to just leave it there or if there's if you want to take up this discussion again about publishing it in some other place.

**DR. MODLIN:** Let me ask Natalie Smith if -- whether or not what -- where we are -- we're anticipating a discussion that we're likely to have this afternoon on the Harmonized Schedule. Natalie, what's the intent

with respect to contraindications?

**DR. SMITH:** We haven't reached any decision about that. We just discussed it very briefly. Melinda, I don't know if you have any --

**DR. WHARTON:** Yeah, I think there wasn't a clear consensus from the working group from my recollection about including it in the schedule. There is a proposal from the working group about including another item that we'll present this afternoon, but the working group, as I recall it, still will -- deliberations did not come forward with a recommendation to the Committee to include this material in a Harmonized Schedule.

**DR. MODLIN:** Myron?

**DR. LEVIN:** Myron Levin. I think it fits in very nicely with this document and it turns out to be very valuable for people in the field. I think it should stay.

**DR. MODLIN:** Other comments? Bonnie?

**DR. WORD:** I was going to say I actually did like it in there. The question I had -- I know looking at the format generally is always say -- you know,

contraindications, serious, allergic reaction, et cetera. But on the forms that -- particularly with measles and influenza and all, many times they ask specifically about eggs, and I don't know -- on the forms -- when you -- the practitioner or whoever the provider is, they will say, are you allergic to eggs or something like that, and I don't know -- in those particular ones do you want to just be more specific instead of that general? The -- I mean, I know eggs isn't a contraindication for MMR -- for influenza if children have it -- oh, and actually even in the regular recs for influenza, it's not recommended to give it.

**DR. ATKINSON:** Some of that's discussed in the allergy section.

**DR. WORD:** Okay.

**DR. ATKINSON:** There's some wording that has to do with components and what components, and egg and neomycin and thimerosal and other things are actually discussed to some degree in the -- actually quite a bit -- in the section on allergies.

**DR. WORD:** I think that because people tend to go -- if you have a table listed, people tend to just go to

that as your reference. And if your reference just says contraindications to, you know, a component of it, sometimes they may not remember. It's just that on certain vaccines they always ask for something specifically, and I think it's on most of the forms.

**DR. ATKINSON:** I guess the problem with something like that is that you then have to decide which components are you going to add, and you could end up with a long litany of things that people never even heard of, you know. And whether or not you put in certain ones that are commonly known or you put in all of them, at some point you sort of get into an issue of listing every single component of every vaccine. It kind of gets a little out of control.

**DR. WORD:** No, I'm not going -- I don't want to go there. It's just that if I recall, I just think on those two they always have that check spot about eggs and things. That's the only reason why I'm fixated with.

**DR. MODLIN:** Georges?

**DR. PETER:** Well, I think an important point that Bonnie is indirectly raising is that the contraindications and precautions change. And this

is the last -- this is the first reiteration of the General Recommendations since 1994, so that if a person happened to be using a table in 2006 that was published now without some knowledge of revision, a change might not be acknowledged. So I don't have any objections to publishing it here, as long as there's some mechanism for issuing and disseminating it widely, a table of precautions and contraindications, that's up-to-date. With the Red Book, for example, we publish the same list, but the Red Book is issued every three years. So I think we need a mechanism for dissemination of contraindications and precautions that would supplement this particular table more frequently.

**DR. MODLIN:** That's the section we had prior to that. I haven't heard any opposition to including it here. So I think probably the benefits are likely to outweigh the downside, but I think we need to continue the discussion about having a mechanism by -- where we can publish a similar table in another format more frequently.

Myron?

**DR. LEVIN:** Myron Levin.

While we're on the same page, I just want to point out that the unknown or uncertain vaccination status is really very similar to the immigrant problem that comes later. And in the latter case where it comes later, you really spell out for people what to do. So either putting these in juxtaposition somehow might be helpful, or at least referring to page 48 where you tell them what to do, and they should be consistent. Here you're -- it's not quite telling them as much as you tell them later on page 48.

**DR. ATKINSON:** What I'll do is put a reference like we did in the -- the middle of the schedule has dropped out of this for the reasons of noncurrency. And what I can do on the table of contraindications is add a reference to say that -- basically that contraindications and precautions do change over time and providers should always have the most current version and that's always available from us from the website. And that's what we've done with the schedule to send people to the website to get the most current version, and that might work here, as well, the same way we've done with the

schedule.

**DR. MODLIN:** Also on the top of page 20 we see national standards for pediatric immunization practices have been established and include -- and I think we now have standards for adolescent and adult immunization, as well.

**DR. PETER:** You've changed the name.

**UNIDENTIFIED SPEAKER:** You have to change the name.

**DR. PETER:** They're now called the Standards for Child and Adolescent Immunization, but I think it's important in the document to acknowledge that both the adult and the pediatric --

**DR. ATKINSON:** Right. And that actually does -- that wording does come up in other places. It's just not quite all together, so I will revise those. I knew those were under revision. Hopefully, they'll be to a point that I can include them, reference you think they'll be out -- published by the end of the year?

**DR. PETER:** Well, I hope so.

**DR. ATKINSON:** Maybe? Okay.

**DR. PETER:** Will this document be published by the end

of the year?

**DR. ATKINSON:** I'll get to that in a minute, so -- Okay.

(LAUGHTER)

**DR. MODLIN:** We'll get it taken care of.

**DR. ATKINSON:** So I'll leave it in and put a reference to the website.

Some wording on aspiration. This was discussed last time. It's on page 24 of your script. There is -- I basically with -- this was discussed, if you recall. There was lots of opinions about it. What I did is basically -- this was the old draft. It was a fundamental -- essentially, a recommendation to aspirate -- remember we had a lot of -- anyway. This was the old recommendation in draft 3.0. The syringe plunger should be pulled back. Basically, it says aspirate. In the spirit of harmony, I basically cloned the Red Book statements, which basically made it much more vague, which says that although -- well, it just says that -- it's not a direct indication to aspirate. I put the same wording in, basically, that although some experts advocate aspiration, there are no data to document the necessity for this procedure

which isn't as definitive. So it leaves it more open that people are going to decide is that something they wish to do or not, and then went on with the rest of it the same.

So I think that's a reasonable thing. It's not a directive to aspirate. It doesn't say you have to. It doesn't say you don't have to. So people can make up their own mind -- since we couldn't decide here. And I don't think you really want to revisit that again, do you?

(LAUGHTER)

**UNIDENTIFIED SPEAKERS:** No.

**DR. ATKINSON:** I didn't think so. So I thought this would -- this is wording like -- it just will allow people to basically make their own decision. So just FYI.

You all probably notice -- I hope you notice -- that there's a new big section on jet injection. This came compliments of Bruce Weninger. You've heard his jet injection lecture here before. Frankly, several reviewers have already told me that it's way too much for something that's not used hardly

at all in the United States.

So I will ask you, what would you like me to do? I put it in because I asked Bruce if he would revise it. He did, extensively, and added 30 references and a whole bunch of other stuff. If you would like, I can really collapse that down to a few paragraphs. In the '94 document, it was literally three or four paragraphs. I can really make it very short.

It's a comprehensive -- it's a very nice piece, if you read it. It's a very nice review of jet injection and adverse reactions, lots of things. If you would like me to really -- really severely cut it down, it's five and a half pages, the actual longest piece in the entire General Recommendations now. I'd be happy to do so if you'd like me to do that.

**DR. MODLIN:** Bill, it's more than we want to know. I wonder if it would be wise to have that available at some other source. Perhaps a website would be --

**DR. ATKINSON:** It's on the website. That's where --

**DR. MODLIN:** -- available to --

**DR. ATKINSON:** Bruce has got a lot of his stuff --

**DR. MODLIN:** -- reference the website in the document

would be the way to do that, I would think. Myron?

**DR. LEVIN:** Yeah, I noted it as five and a half pages, also, and I would certainly -- and I think it's very comprehensive. But I think you can do it all with the references and have it basically two paragraphs or less.

**DR. ATKINSON:** I kind of thought you would say that. So I will work with Bruce and we'll condense it down to some -- to a few paragraphs of key information and reference the website, which is quite extensive.

**DR. MODLIN:** Okay. Dr. Overturf?

**DR. OVERTURF:** Well, I suggest -- it's such a nice piece that I would suggest maybe you just make it a footnote that all this is available by request at some site or just make a website available.

**DR. ATKINSON:** How about an appendix? Would anybody have any interest in an appendix and actually add it as an appendix at the end?

**UNIDENTIFIED SPEAKER:** It doesn't belong here.

**DR. ATKINSON:** Okay, good. So I will add it and put it up as a summary document on the website in one way

or another.

I have added the -- we discussed last week some -- or last meeting and actually a couple of meetings before that, page 31 and 32, just to remind you what the end result of our discussion about non-standard routes and sites was at the last meeting. It was first a statement that variance from recommended -- this is on page 32 -- recommended -- variance was not recommended. And that unlike all previous general recommendations, which essentially said if it was given by non-standard route or site, don't count it, this is 180 degrees different in that we're asking for -- we're only accepting -- we're only recommending repeat of those vaccines for which immunogenicity is known to be compromised if given in a not-recommended route or site. And that essentially currently is limited to rabies vaccine and hepatitis B vaccines given in the gluteus and hepatitis B vaccine not given intramuscularly. Those were the two exceptions for which there are data to support lack of immunogenicity. And in fact, there are some data to support non-traditional sites like DTaP given subcu, et

cetera, in the literature. So this is the wording that's in there now. Just wanted to let you know this is what it was and if anybody had any thoughts before it leaves. This is quite a departure from -- from what has -- it's been discussed before. I don't want to drag it out again, but just to let you know this is the wording. And lots of people will notice, this is one of the biggest changes in this document that is going to affect the way people do business.

**DR. MODLIN:** We discussed this extensively and I think we are pretty much in agreement that we like the way it is.

**DR. ATKINSON:** There was a request, page 33, 34, that we add wording on syncope. Syncope has been added. We did some VAERS runs. We used some of the published literature. There's now a couple of paragraphs, and I must say that there is something here also that is a policy change that has never been done before. And again, in the spirit of harmony, I mirrored what's in the Red Book, and that is at the bottom of page 33 that it does include, as has never been done before, a suggestion to hold the person and observe them for 15

to 20 minutes after the vaccine has been done, mainly in case they should fall down, have an allergic reaction, whatever.

This is functionally the same wording that's in the Red Book. There's never been a waiting period after vaccination recommended, or even discussed in the general recommendations. I just wanted to make sure that you knew it was there. It is consistent with the Red Book wording. And so just be aware that that's there. This is a fairly big change from previous documents.

**DR. MODLIN:** My recollection was, when we discussed this at the last meeting, that we would take a look to see what data are available that pertains to these. Bill, I don't know if you have anything new to present.

**DR. ATKINSON:** We put it all in. There basically is one published paper and some VAERS data. And the one published paper was fairly -- came from the -- it was generated by VAERS data that report a series of reports to VAERS, including some with permanent disability as a result of skull fractures after having had syncopal episodes. Most of these do occur, 90 percent of them

do occur, within 15 minutes of that, hence the 15- to 20-minute observation period, if possible. So what data exists is really in that paragraph that's in the bottom of page 33, 34.

**DR. OFFIT:** But Bill, just educate -- Sorry. Just educate me about one thing. Were those who were prone to syncope --

**DR. MODLIN:** Just one second, Paul. I don't think they can hear you. Okay.

**DR. OFFIT:** Bill, were those who were prone to syncope greater than a certain age?

**DR. SMITH:** Were they adolescents?

**DR. ATKINSON:** It was mostly adolescents. It was a higher frequency in adolescents, actually.

**DR. SMITH:** The skull fracture in California was definitely -- it was an adolescent.

**DR. ATKINSON:** Adolescents. But it really was -- there was a -- syncope had been reported in all age groups but primarily was in adolescents.

**DR. SMITH:** Not two-month-olds.

**DR. OFFIT:** Not two-month -- not infants, presumably.

**DR. ATKINSON:** No, not too many syncopal episodes in

infants.

**DR. MODLIN:** Melinda, did you have a comment?

**DR. WHARTON:** Yeah. Well, it's on this same issue about vaccination of infants and whether or not this recommendation is actually being applied to an age group in which it's not going to really be applicable and whether or not some consideration should be given to this in this wording. An awful lot of childhood vaccines are given to children who are not walking around, and perhaps this should reflect that.

**DR. MODLIN:** Jon, Gary, do you have any opinion about that?

**DR. OVERTURF:** I guess there's a more global use of the word "syncope," but I suppose it could be, you know, unconsciousness or a lapse of consciousness or something else. So I -- I probably would leave it in because it's a general -- I think most times we use it in the Red Book as a general precaution throughout, and I'm not sure it's always applied just to syncope. It's applied to other reactions that may occur acutely.

**DR. ATKINSON:** Yeah, there is wording that talks about serious allergic reactions, as well. So that's sort

of part and parcel of the sentence that that occurs in.

**DR. MODLIN:** Okay. Geoff?

**DR. EVANS:** Having just reviewed an IHS claim having to do with an adult who had a syncopal episode and broke their -- some facial bones, it's just the idea that you inject the idea into people that give the immunization that they should at least elicit a history, any problem with being -- feeling faint after they've gotten previous immunizations, because the person that gave this immunization basically gave it and then left the room.

**DR. MODLIN:** Jaime?

**DR. DESEDA:** I'm just wondering if there's a massive immunization campaign, how would this operate? Because you cannot keep people -- large number of people

**DR. MODLIN:** Yeah, I don't think this applies to mass campaigns and almost certainly not to administration of OPV. I think they're talking about injected vaccines.

Myron?

**DR. LEVIN:** But are we creating a legal requirement to

have people observed for this length of time? You sort of -- you made it a suggestion, but is it going to give some legal force to -- to lawyers?

**DR. MODLIN:** It's a good question. I think we're obligated to include the data that are available, and maybe -- of course, this is a guidance document rather than a scientific document. I don't know.

Eric?

**DR. FRANCE:** I did just want to point out that this document says some experts suggest that persons be observed. So there's really no recommendation here that this become some new standard of care. It's just bringing up the information and folks will make decisions accordingly. I imagine for 95 out of 100 practices, nothing will change. It's just a FYI.

**DR. MODLIN:** I guess, Myron, you could take the point that there would be the legal issue of not including this information, knowing that we know that it exists. So that you could play that -- you could --

**DR. LEVIN:** I wasn't worried so much about us. I was worried about the people in the field who are -- who might feel they have to do this and if they don't, they

would be at risk. Eric's view of it may soften that somewhat because of the way it's worded.

**DR. ATKINSON:** It's a pretty soft comment. It says although syncopal episodes are uncommon, allergic reactions are rare. Some experts suggest persons be observed for 15 to 20 minutes after being vaccinated, if possible. Reference Red Book.

So the some experts are, in fact, referenced to the Red Book.

**DR. MODLIN:** Would it be reasonable to indicate that most of the syncopal episodes have occurred in older children and adults -- or adolescents and adults?

**DR. LEVIN:** Yeah, I think that's a good idea.

**DR. ATKINSON:** We could add that.

**DR. MODLIN:** Other comments?

(NO RESPONSE)

**DR. MODLIN:** Okay, let's go on.

**DR. ATKINSON:** There was a brief -- I added a brief section on acute vaccine reactions at the request of a couple of reviewers, essentially a very short discussion of -- this is on page 34 -- a very short discussion of anaphylaxis, that epinephrine should be

around, that -- you know, it's a very general statement about epinephrine and airways and what-not.

There is a new section that was suggested. Bruce Weninger also contributed to this in association with some folks at NIOSH. A brief discussion, a lot shorter than the jet injector part, on occupational safety regulations, basically addressing the issue of safety needles and reduction of injection injuries. And you can see that it's fairly straightforward, and NIOSH has signed off on it. We asked them to look at it and they agreed with it.

I rewrote some of the thimerosal allergy section that's on page 42 to basically clarify it and to add a little bit more information about the nature of allergy to thimerosal. We do hear this question endlessly about people allergic to thimerosal. So we just basically beefed that up a little bit, talked about what kind of sensitivity has been recommended and that -- again reiterated the fact that local and non-IG mediated types of allergies are not contraindications to vaccination. We say that several times in the document.

**DR. WORD:** I've got a question. Are you on page 42?

**DR. MODLIN:** Bonnie? I'm sorry.

**DR. WORD:** Is he on page 42?

**DR. MODLIN:** Yes.

**DR. WORD:** I mean, this is just a simple word -- that thimerosal as a preservative has been removed from pediatric vaccines but is present in some vaccines given to older children, I guess my question was should the wording -- it hasn't been removed from pediatric vaccines. You might want to change it from routine pediatric vaccines because -- I mean, children do get influenza.

**DR. ATKINSON:** No problem.

**DR. WORD:** And right now we still have thimerosal in that.

**DR. ATKINSON:** Happy to add that. Not a problem at all.

**DR. MODLIN:** Jon?

**DR. ABRAMSON:** What I would like somebody to comment on, is the trace amount of thimerosal that's still in

some of the routine vaccines a problem from an allergic standpoint? I know it's not a problem from a standpoint of toxicity, but is it a problem from an allergic standpoint?

**DR. MODLIN:** Oh, boy. Karen, did you catch that?

**DR. MIDTHUN:** Yes. I would assume you would have to assume that it still is. I mean, you know, allergens is, you know, very, very small amounts can be a problem, so. . .

**DR. MODLIN:** There's probably more thimerosal than there is egg protein.

**DR. ABRAMSON:** Right. Well, if that's true, then I think the statement is misleading, because there is thimerosal -- there is still trace amounts of thimerosal in some of the pediatric routine vaccines.

**DR. MODLIN:** For delayed type of hypersensitivity --

**DR. ABRAMSON:** That's what I'm asking.

**DR. MODLIN:** -- I think that the amount of antigen required is quite a bit more typically than for IGE mediated. Isn't that the case? Rich, you -- where are our immunologists? Paul?

**DR. OFFIT:** I think that's fair to say.

**DR. MODLIN:** Okay.

**DR. OFFIT:** One would require more antigen for a delayed as compared to acute hypersensitivity, that's true.

**DR. MODLIN:** So I think the answer would be we just don't know here.

**DR. OFFIT:** But what that number is and what that quantity is is less than. . .

**DR. ATKINSON:** I can add a phrase in there that says even though it's been removed as a preservative, it may be present in very trace amounts. That would probably cover it, I think.

**DR. MODLIN:** Okay.

**DR. ATKINSON:** So not to give the impression that there was zero in there, because you're right, the IGE stuff might still be an issue.

**DR. MODLIN:** That's good.

**DR. ATKINSON:** I will do that.

I don't intend to revisit the immigrant and international adoption section. This is on page 47, and it's the second -- second to jet injections, it is the second-longest piece because of all the if-thens

that we have discussed at some length in this forum. What I did do, and I basically added -- we've sort of lost the spirit of what this section was about in 1994. The reason it was added in 1994 was basically to try to give guidance for not just adoptees, but anyone given a vaccine outside the United States. That was -- In fact, the section was acceptability of vaccines given outside the United States. So I added back in immigrant and put it back in, just so the readers wouldn't think that this section only dealt with internationally-adopted children because really it is a more generic issue that deals with anyone getting a vaccine outside the U.S., and not just immigrants, not just adopted kids. So to try to move it back a little bit toward a more generic feel, I added those words in. Didn't really add -- change the text very much, but did add some -- just added that to make it a little broader than just the narrow focus on international adoptees.

**DR. MODLIN:** Natalie?

**DR. SMITH:** Yeah. I was just -- I know why you were doing that, but I was concerned that we're taking data from, you know, a couple of adoptees studies which

actually have conflicting results and somehow -- I think it may just be wording changes, but I don't want to imply that that applies to immigrants in general. I mean, certainly in a large state with tens of thousands of immigrant children, you wouldn't want to recommend serologic testing or revaccination if you have a documented immunization with a date on it. And that becomes more apparent in the sections on the individual antigens where it says, you know, serologic testing is reasonable and that sort of thing. And I just don't want to imply that we're having some mass change in policy to a kid that's coming from Japan or Mexico or wherever.

**DR. ATKINSON:** The front end of that section still does emphasize written documentation, dates, that sort of thing --

**DR. SMITH:** Right.

**DR. ATKINSON:** -- and we could tweak the words around a little bit.

**DR. SMITH:** Maybe it's just the formatting. Yeah.

**DR. ATKINSON:** We can tweak the words around a little bit and sort of -- because it -- sort of the approach

to all the individual vaccines basically if -- it says if there's a question as to whether vaccines were administered to an international adoptee or immigrant were valid. So it's -- everything that follows that is based on whether or not the provider has some question about whether the record is actually valid. So we can play around with the wording of that and make it not seem like that's what we're recommending, that everybody get tested for rubella antibody.

**DR. MODLIN:** Dr. Overturf?

**DR. OVERTURF:** I'm going to have to look at this carefully and see how it is going to look with the 2003 Red Book, because this is being consistently revised and reviewed. And maybe I'll just send you the copies of what we are looking at for 2003 because I think it's going to be important that these things line up pretty well.

**DR. MODLIN:** I agree.

**DR. OVERTURF:** And I'm a little bit concerned that there is -- there have been no recommendations for serological testing in the past, with the exception of DTaP. So -- particularly with pertussis. So I can't

get a feel for that. There's no table in here, but there have been tables in prior publications that we've looked at that have suggested serological testing and specific approaches to that.

So this may make -- this may not be internally consistent with other things that CDC's written. I'll be -- might hear some comment on that from other people around the room.

**DR. MODLIN:** Gary, you probably don't -- weren't here at our last meeting, unfortunately, and didn't have the benefit of a very extensive discussion that we had on it, specifically on this topic. And I think that the language in the statement now very accurately reflects a fairly strong consensus based on having the experts present and discussing the topic at some length. And so I think that most of the Committee are pretty comfortable with the --

**DR. OVERTURF:** My only concern is that there's a lot of disagreement among the experts. So --

**DR. MODLIN:** We're well aware of that.

**DR. OVERTURF:** So the -- you know, the question is a little bit -- making sure that we have a consensus, at

least among our groups, about this from that expert opinion.

**DR. MODLIN:** Ben?

**DR. SCHWARTZ:** At a previous ACIP meeting, I participated in the discussion of these recommendations and then also presented those materials at the Red Book Committee with the AAP. And after the discussion at ACIP, as we looked a little bit more into the laboratory methods that had been used in the various studies, I think it became clear to us that the data that suggests that vaccination records usually are adequate and that serological testing of those who have documentation of vaccination generally shows that they indeed are protected. And so what I presented at the AAP meeting and what I feel is the correct interpretation of the data is one that is generally reassuring. And I don't see in this current draft that that reassurance is reflected, that basically the data are presented which are concerning, saying that some may have a very, very low rate of evidence of seroprotection and then leaves really open which of the two interpretations are most likely

correct. And I think that issue, to a large extent, has been resolved. So what I would propose is that, as was presented at the AAP meeting, that we provide a little bit more reassurance based on those data that are available. And perhaps, Bill, we can work with you and also with the representatives from AAP to come up with the appropriate wording for that.

In addition, the text here is fairly long and dense, and if it could be put back into the tabular format that it was earlier, it may be clearer and may be easier to pull out of this document and use elsewhere. Because I know that from folks that I've talked to, this is an issue that does frequently come up. And having a table that you could put on the wall or somewhere in the office might be easier than referring back to the large document.

**DR. ATKINSON:** Some of the background material was taken out in an attempt to shorten up that -- what was a very long section. It was actually about eight pages long in its previous iterations. So some of that may have -- I may have been a little too aggressive with my editing, but we can certainly add some of that

material back. The discussion about nutes [phonetic] and EIA's and various pros and cons of lab things, we can certainly add that, and I can put the table back.

**DR. LEVIN:** John, can --

**DR. MODLIN:** Myron?

**DR. LEVIN:** Myron Levin.

Can I ask Ben a question?

**DR. MODLIN:** Sure.

**DR. LEVIN:** So, Ben, are you saying that the original data that Peggy Hoffsteder presented to us may have been misinterpreted because of the type of lab data that she presented?

**DR. SCHWARTZ:** That's correct. When Peggy presented her data, she didn't clearly describe the type of testing that was done on those specimens. We communicated with each of the laboratories that she had used in her studies, and she had changed labs halfway through the studies, and talked with them about the types of tests that they were doing. It turned out that those were not neutralization assays and that there was some concern that those weren't the optimal tests that could be done.

Mary Stadt, in the data that she presented, had used the ELISA assays, and after a number of discussions between the various participants in this, we decided that Mary's data was more likely to represent the actual situation because of how the lab tests were done and interpreted.

**DR. MODLIN:** Other comments, specifically about foreign adoptees?

(NO RESPONSE)

**DR. ATKINSON:** Okay. The two other things that I'll just mention that are really not quite complete, in sort of a rush to get the meat in, there will be a resource directory added. It is incomplete in the document you have. We will try to put together a succinct listing of relevant web and telephone resources for individuals.

Also, you can see that the reference list needs to be tuned up a little bit. I'll be working on that over the period of the next month. And those are really the changes that I had made based on feedback that I have gotten since February. I did notice the issue about putting in references to pneumococcal vaccine for

pregnant women. I'll do that. If anybody has any other comments on any part of the document, speak now.

**DR. MODLIN:** Myron?

**DR. LEVIN:** Myron Levin.

The one question that I wondered about is the comment on conjugate pneumococcal vaccine after children have had the pneumococcal polysaccharide vaccine or -- this is a question that is asked to me all the time, and are we going to make a statement about it? Or have we?

**DR. MODLIN:** We do have extensive information about that in the pneumococcal -- in the conjugate pneumococcal statement.

**DR. LEVIN:** Okay. Well, it's not in here then.

**DR. MODLIN:** Okay.

**DR. LEVIN:** Should it be?

**DR. ATKINSON:** It wouldn't be difficult to put it in.

**DR. LEVIN:** Well, you tell people what to do with the conjugate vaccine in a lot of other situations. Might as well add that, or refer to something, whichever.

**DR. MODLIN:** Right. I think referring to the recent statement on -- revised statement on pneumococcal vaccines, which includes both for use in children.

Yes, Tom?

**MR. VERNON:** Tom Vernon from the Merck Vaccine Division.

In a recent meeting with a group of pediatricians, I was impressed that a couple of pediatric offices which have their own websites have listed on their websites those websites that they would choose -- they would most want their patients to go to for good information on vaccine safety. And I want to ask Bill and the Committee if that would be possible in the resource directory to put in such websites as the Academy of Pediatrics and --

**DR. ATKINSON:** Absolutely.

**MR. VERNON:** -- vaccines info dot -- and so on and so forth?

**DR. ATKINSON:** Definitely. We'll add a lot of resources on the -- we'll probably use Debra Wexler's excellent compilation of resources and try to strip out the -- you know, the top 20 or so of those, and they'll all be in there. And it'll be heavy on vaccine safety. So we'll put lots of vaccine safety things in.

**DR. MODLIN:** Bob?

**DR. CHEN:** Along those lines, there's just a couple of suggestions which are pretty non-controversial and I'll work with Bill to incorporate them, and that is, in the definition area to include something about what we mean by reaction versus adverse event, kind of a programmatic error versus et cetera, all those things. And then in this new section on the management of acute vaccine reactions, to cross-reference the reporting to VAERS he has later in the document.

**DR. MODLIN:** Any comments, questions? Jon?

**DR. ABRAMSON:** Yeah. Just to let you know that the Red Book is actually formulating a process by which websites will be picked out. And I guess I'm not clear on how the CDC does that, but I'd be most comfortable if I understood a process by which -- because you can get, as you know, tremendously variant information. So I think there should be some process by which you decide a website is adequate to list or not.

**DR. MODLIN:** I think I can assure you that the National Immunization Program will be pretty careful in their discreet in their selection of websites, I'm sure. Eric?

**DR. FRANCE:** In the back section of this document it talks about vaccine programs. It talks about vaccine programs and how to best promote vaccination. And as I read that, I wondered if there may be an opportunity to say something more about payors and the impact of vaccine coverage. I know I've heard from managed care organizations that when there's a specific recommendation from the ACIP regarding a vaccination, then it becomes covered, a covered benefit. And we heard yesterday about some of the difficulties in flu vaccination not being adequately reimbursed, and I've heard also that some -- some managed care organizations will only cover a vaccination for hep A and hep B if they're done in primary care offices versus specialty care offices. And so the GI docs aren't allowed to be doing hep A and hep B for patients with hepatitis C. So knowing the managed care organizations look to the ACIP, is there a place, in general, where the ACIP can be making some statements about the importance of adequate reimbursement and is there a potentially a place towards this end in the vaccine program sections for just a simple paragraph talking about

reimbursement and encouraging health payors to actually pay for adult vaccinations?

**DR. MODLIN:** Marty, would you like to -- I just wonder if that isn't something that we should be addressing on the NVPO side --

**DR. MYERS:** Well, I guess I'm not --

**DR. MODLIN:** -- as opposed to the ACIP document.

**DR. MYERS:** I was going to say, I'm not sure this is the right document for it. There is that process going on at the NVAC working group and NIP is planning on having an IOM committee consider the issue of financing. And so I'm not sure if this document would be the --

**DR. MODLIN:** Georges?

**DR. PETER:** Well, the NVAC has issued a statement two years ago in JAMA, strategies for sustaining success, where indeed that very recommendation was made. So it's already consistent with the Advisory Committee's recommendation. I don't think it needs to be included in ACIP statement.

**DR. MODLIN:** Kristin?

**DR. NICHOL:** I'm not sure if such a statement exists

in the current general recs or elsewhere. On the flip side, would it be helpful if there were a very explicit suggestion that not only primary care practitioners but some specialty practitioners administer immunizations to their patients?

**DR. MODLIN:** That's a good point. Yes, absolutely. Geoff?

**DR. EVANS:** I hesitate to add this suggestion, but under patient information, we're missing anything on vaccine risk communication and how to deal with patients that have questions or why patients have resistance or concerns about getting a vaccine. And it's something that we -- that was worked on with the Red Book. I know Dennis Murray and I put some narrative in on that.

So I'm wondering if we could, without having the Committee need to look at every sentence, put something in that reflects the thinking that's already in the Red Book.

**DR. MODLIN:** Where would you suggest we put it?

**DR. EVANS:** Page 61 under patient information.

**DR. MODLIN:** Bill, do you think you could put together

two or three sentences that addresses that issue, maybe taking a look at the Red Book?

**DR. ATKINSON:** Absolutely. Particularly, if Geoff already wrote it.

**DR. MODLIN:** Okay.

**DR. ATKINSON:** Even better. I'll be happy to put it in.

**DR. MODLIN:** Terrific. Other comments or questions? Bonnie?

**DR. WORD:** This is just something minor. It's not --

**UNIDENTIFIED SPEAKER:** We can't hear.

**DR. MODLIN:** Well, her microphone is not on. Just a second. Okay.

**DR. WORD:** This is something minor. It's not anything major. On Table 4 in the back, just -- when you talked about suggested intervals, it's just very difficult to read. I don't know -- you have the numbers going across. I don't know if you can just --

**DR. ATKINSON:** That was it. That messed up in the formatting.

**DR. WORD:** Oh, okay, because it went through and --

**DR. ATKINSON:** Yeah, that messed up when we printed the

document. So, be assured, MMWR will do a very nice job setting these tables up and making them much more readable. That was an error. I just didn't look at every page when we printed it out. I don't know how that happened, but --

**DR. WORD:** The only other comment is can you just double-check, I'm not sure, about with the blood transfusions with packed red blood cells. I wasn't -- I thought it was five months and not six months.

**DR. ATKINSON:** I'll recheck that with the tables. I think it's six, but I'm not certain. I'll -- I don't remember that, but I will recheck all these numbers before they go in to make sure they're consistent with our previous publications.

**DR. MODLIN:** Even though we are hopefully going to vote on the statement today, I think there still will be an opportunity to get comments regarding -- particularly small things -- editorial issues, errors and so on back to Bill. It's unlikely that this will be published immediately. So there will be some editorial opportunity.

**DR. ATKINSON:** Here's the time line that I would

propose. If it is approved today, I will spend the next month doing any edits that you-all suggest, adding in the things that were suggested and putting it through formal NIP clearance. I have already spoken to MMWR. The publication process at MMWR now ranges from 90 to 120 days from intake. They can't intake this document until September right now, which means that, in theory, they couldn't take it from me till September, which means it won't be published until November. I'm hoping to have it done and in their hands by August so that if a slot does open, I can take advantage of it and can get it in if there's an opening.

If this schedule looks all right and if they can't, in fact, intake it until September, my hope actually is and call me romantic, I guess -- is to publish it on or about November 12th, which would be the 25th anniversary of the very first publication of the very first general recommendations of the organization, which anecdotally was published in the weekly and was three pages long and had no references.

(APPLAUSE)

**DR. MODLIN:** Bob Chen?

**DR. CHEN:** Just to follow up on Geoff's -- I don't know, I haven't seen your statement on the vaccine risk communications. Does it deal with the issue of exemptors? And if not, I wonder if the Committee -- there is now some research in terms of the risk of VPD among people who are exempt and whether we want to include something in that area or not.

**DR. EVANS:** The problem is that every sentence you write, you need another sentence and another sentence. Why don't the three of us work on figuring out what it is that we can say in the shortest amount of space?

**DR. MODLIN:** Thank you. Other comments? Questions? Concerns?

Yes, Tom?

**MR. ZINK:** Hi. Tom Zink with Glaxo SmithKline. It goes to definitions, definitions around what "trace" means when we talk about thimerosal and other agents, and it goes to the allergy conversation that occurred, as well. And since you're going to be addressing that, I'd like to just point out that when we talk about a thimerosal-free -- preservative-free vaccine and that there may be a trace that -- we're

actually being very open about the fact that very, very early on in the production of the vaccine, there may be a chemical reaction that produces the thimerosal agent or chemical or molecule that is eventually, we think, completely removed through the process of purification. And so in the spirit of full disclosure, we talk about thimerosal-free preservative vaccine with potential trace amounts that are not detectable by our current scientific analyses. So when you go about talking about thimerosal trace and trace elements, it might be interesting to put in a statement from the ACIP -- what exactly do we mean when we say trace -- so we don't bring up a whole new worry about allergies, about something that we think is purified and is so early in the process of manufacturing as to be not even detectable at the -- in the final product.

So I thought I'd bring that up in terms of perhaps future definitions or a comment in regards to the allergies.

**DR. MODLIN:** Thank you. Lucy?

**DR. TOMPKINS:** I wanted to make a motion.

**DR. MODLIN:** Terrific.

**DR. TOMPKINS:** Is it time?

**DR. MODLIN:** You bet.

**DR. TOMPKINS:** I move that we accept the General Recommendations as proposed.

**UNIDENTIFIED SPEAKER:** Seconded.

**DR. MODLIN:** So moved, and seconded that we accept the general recommendations. I'm going to assume that, for purposes of this vote, no one is conflicted. Okay. Those in favor of the motion for accepting the General Recommendations?

(SHOW OF HANDS)

**DR. MODLIN:** Those opposed? Those abstaining? It's the unanimous vote of the Committee. Thank you.

(APPLAUSE)

**DR. ATKINSON:** There will be more edits. Obviously, we have some things to add and some things to change. Is the Committee interested in seeing -- and it's got to be cleared and, you know, other little things we need to do before it needs to go to MMWR. Is there interest on the part of the Committee to, say, get it by e-mail and have another draft they could look at before -- at the time that it's cleared by NIP and, you

know, sort of the penultimate version which will then be given to MMWR for editorial work and clearance? Would you like to see another version of it? Should we send it out just FYI and you can delete it from your e-mail if it comes because you don't want to think about it anymore?

**DR. MODLIN:** Why don't we ask individual members of the Committee, and for that matter, everybody else here, that if individuals are interested in seeing it prior to production that they ask Bill specifically and you can send it to them.

**DR. ATKINSON:** Yeah, just drop me an e-mail. My address is there on the front.

Also one other little minor issue. There's a lot of this has been a highly-anticipated document from a lot of different places, and I've been given the long production cycle -- granted, most of it is -- much of it is because MMWR has such a backlog. There was a request that we start releasing this in draft form after it is cleared by NIP and to put -- to start, say, sending the program managers and other people who have a real vested interest in this information a draft form of it

before it's formally approved -- formally published by ACIP -- or by MMWR.

So I guess the question is, do you have any feelings about that? Do you think it's a bad idea? Should we wait till it's formally published before we actually sort of let it out of the box, or can we begin -- granted, it's out in the public now with this draft, but do you have any problem with us distributing this in the time between formal clearance by NIP, final version by ACIP, and the time that MMWR actually publishes it?

**DR. MODLIN:** I think I can speak for the Committee. I don't think there would be any concern. I mean, the document is intended to be used just in that manner. I think that the sooner that it becomes useful, the better.

It's 10:20. Let's take our break and return at 10:45 if we can, perhaps make up a little bit of time. We'll start with the rabies vaccine discussion at 10:45.

(BREAK FROM 10:20 A.M. TO 10:55 A.M.)

**DR. MODLIN:** Could I ask everyone to please take their seats.

The next item on the agenda will be a discussion led

by Dr. Chuck Rupprecht on -- updating the Committee on discontinuation of human rabies vaccine for intradermal pre-exposure use. Chuck?

**DR. RUPPRECHT:** Thank you. I appreciate the opportunity to update you in regards to this item and hope to enter into some discussion after the fact. It came as a bit of a surprise to us after the last ACIP meeting and, hence, was one of the reasons why we wished to bring it up for discussion at this meeting. As you're aware, rabies is the most significant global viral zoonosis, if not the United States, as well. And human rabies cases in the United States remain low, predominantly because of the prevention of exposure to rabid animals, as well as prompt and proper post-exposure prophylaxis after exposure occurs and, in addition, to pre-exposure vaccination of those considered at risk.

Although human rabies in the U.S. is uncommon, we also feel that it's under-reported, as our collaborative investigation this month indicated with the Department of Health in California in a gentleman who succumbed to rabies in February but was not diagnosed

retrospectively until this month.

Beyond post-exposure prophylaxis, human rabies prevention is also supported via the immunization of those considered at risk, such as veterinarians, those on the front lines of protecting your pets, the nation's food supply; acquiring rabid animals and preventing exposures to people, such as animal control officers; as well as those diagnosticians, laboratory workers, et cetera, that come in contact with the rabies virus directly or rabid animals or the virus indirectly.

The rationale is to simplify the post-exposure management of those at risk of exposure since it would not entail the utilization of rabies immunoglobulin and similarly would only entail two booster immunizations intramuscularly on days zero and three.

Pre-exposure vaccination consists of three doses on days zero, seven, and 21, given either intramuscularly or, with one product, the one under discussion today that's been discontinued, intradermally. It may be somewhat misguided to think that it also provides some level of protection against inapparent or inadvertent exposure due to occupational risk, but that is not its

primary rationale. It's to simplify post-exposure prophylaxis by priming the immune system for the development of an amnestic response, either when prompted by the virus's antigen itself or, more appropriately, when boosted by the intramuscular route.

Also as a caveat, as I'm sure might be raised, we have to recognize that this is a specialized niche. This is a zoonosis. We're not talking about viral contagions like polio or flu or hepatitis, and so from the outset, because it's a zoonosis, we're talking about a relatively small, specialized cadre and, hence, immediately fits into the orphan biological category. It's for that reason why it causes us some great concern because we feel it's just one more nail in the coffin of what we call rabies prevention and control.

Most of the boomer generation grew up with either nerve tissue vaccines or poorly immunogenic duck embryo vaccines, and, hence, it was the licensure of the human diploid cell vaccine in 1980 that was the first cell culture vaccine to come into the market, as well as the

first cell culture vaccine licensed in the United States. And it was really the first immunogenic and efficacious product that became available and it's the one we grew up with. I was trained by the scientists at the Wistar Institute in a former life that gave rise to this product for marketing by the then institute [inaudible], which was a name that was renowned in regards to rabies control and prevention.

It was shortly thereafter with the development of HDCV as a whole that -- unfortunately due to the expense in cell culture of that vaccine, somewhere around $100 a dose, needing three doses, making it one of the most expensive, if not the expensive viral vaccines offered in people -- individuals started looking for alternative routes. And it's been a long time, more than a quarter of a century, that the skin has been recognized as an immune organ, and hence, the utility of the intradermal route whereby one could take small doses, 0.1 amount, and infiltrate them intradermal, safely and effectively, which our colleagues in the U.K. demonstrated, which has been supported to date by WHO and which was advanced by this Committee back in

1982, even before licensure of that product in 1986, for single-use application.

Similarly, after much discussion of intradermal for pre-exposure vaccinations, individuals also started thinking about it for post-exposure but, for a variety of reasons, that was never extended into the United States. Obviously for those at risk in developing countries hailing from the U.S., it was also seen as a cost-effective means of vaccinating Peace Corps workers. But concomitantly, it was also shown the potential for interference by those traveling to developing countries for the utilization of malaria prophylaxis and, hence, the recommendation at that time that if the intradermal route was utilized in Peace Corps workers or those utilizing antimalarial chemicals, that intradermal vaccination be concluded before that was initiated or travel was begun.

Similarly, into the '90's and the current time, Arguin and Murray showed that economically the serological monitoring of those at risk continuously and boosting ad hoc only when serological detection became undetectable by the intradermal route was a very

cost-effective measure. Hence, we have more than a quarter of a century of experience with the intradermal immunization, not only by pre-exposure, but in developing countries and through CDC-supported enterprises in developing countries, as well, for post-exposure prophylaxis. Hence, we were quite surprised when we were one of the recipients of this letter from Aventis, that it was through a business decision that the intradermal vaccination would be discontinued in the United States. The United States is the only country in which ID rabies vaccine is licensed.

Obviously, this caused us some deal of concern because of those populations at risk. In fact, state health care workers are usually one of those groups that is considered -- diagnosticians, animal control officers, et cetera -- and those staff are utilizing the ID vaccine in order to obtain pre-exposure vaccination. Significantly, as been pointing out to one of our Ferguson summer fellows that the veterinary schools in particular, more than 80 percent of the veterinary schools in the United States and probably

elsewhere, utilize ID rabies vaccination pre-exposure.

Obviously, this is a financially disadvantageous group. If you consider that veterinarians today are coming out of veterinary school, as opposed to medical school, with a mortgage and no house and pay is not compensatory, this is going to be a significant population whereby ID withdrawal is going to impact. Similarly, there are concerns about the return to practices of taking multiple vials out of a single-use vial for ID. Obviously that was how ID was first realized and how, in post-exposure in developing countries, it is still practiced to the current time. Similarly, one has to wonder immunologically about the utilization of now only intramuscular vaccination routinely for those once serological titers become undetectable, IM versus ID, as well as those financial costs. Obviously, it puts out some suggestion of lessened public health flexibility in an already orphan product. It suggests some disregard commercially for a specialty niche. And it obviously, in preparedness, causes some grave concern because of

the global crisis in rabies immune globulin availability. And if ID vaccine can so disappear overnight due to a business decision, obviously because of the problems with the production and availability of rabies immune globulin, be it human or equine heterologous products utilized in the developing world, similarly what's going to happen tomorrow's business decisions suggest that RIG similarly disappears from the market.

It's somewhat ironic, if one considers in the need for paradigm shifts into this next century, that WHO is considering, rather than focus attention on reservoir and vector controls, i.e., dogs in the developing world, the potential for utilization of intradermal vaccination of children, obviously a population, a select population, at risk. But there are some serious dilemmas with this idea using it as a paradigm shift as opposed to tried and true methods of rabies prevention and control in the developing world.

With no surprise, it was one of the reasons why at the recent Council of State and Territorial Epidemiologists they passed unanimously their concern

over the discontinuation of RIG, as well as calls for alternative techniques, methods, or strategies to alleviate both our and their concerns.

Possible solutions which could be considered obviously would be the default, to have the manufacturers reconsider their decision, as we've asked personally. Additionally, one could consider the offering of their intramuscular product at the intradermal price. We know that new vaccines for the last decade, in theory, have supposedly been coming down the pike. And with the new varicella vaccine, perhaps consideration for it via the intradermal route, since it would invest a cost savings by that mechanism as opposed to intramuscular.

There are also some suggestions that not only should impact at the level of NIH and FDA, CDC, NIP, et cetera, such as renewed requests for proposals for alternatives, more economical biologicals for rabies prevention and control as a whole, additional support in RFP's for innovative small business grants, perhaps consideration -- thinking out of the box a little bit for FSS schedules whereby, should the Federal

government become a broker and potentially a supplier to end users, be they state health departments or subcontracts to other in the broadest sense by medical professionals such as veterinary schools and veterinary students.

Similarly, it probably harkens the previous discussions for other orphan biologicals as to how serious the Federal government should become involved in the vaccine process, either with production or specialized contracts, for such orphan products.

And lastly, it really does call for the need for renewed communication for rabies prevention and control, not only here but also abroad, and at the very least will necessitate a supplemental MMWR statement, which we'll be happy to work with ACIP Committee members to get out the information to those end users.

And we look forward to any discussion that one might have. Thank you.

**DR. MODLIN:** Thanks, Chuck. Paul?

**DR. OFFIT:** Chuck, thank you. It's my understanding that in the developing world often they will use the intramuscular product, dilute it, and then give it

intradermal. Is that true?

**DR. RUPPRECHT:** That's correct. That is a WHO-sanctioned process, particularly now with the shortage of rabies immune globulin and because of the issues in regards to nerve tissue vaccine in the developing world.

**DR. OFFIT:** Then, so is it -- do you think it's a realistic fear then that by discontinuing intradermal route in this country that we would send a message that intradermal route is not as acceptable and that we would perhaps drive those developing countries to the nerve cell vaccine, which would be less safe?

**DR. RUPPRECHT:** I think that's a very interesting and important point, particularly if you consider that for the last decade, working with WHO as a collaborating center, we've been pushing towards the discontinuation of nerve tissue vaccines, particularly actively here with the Pan American Health Organization in Latin America with replacement of the [inaudible] vaccine. Previously, there was a very strong message that, look, this is a safe and effective product. We have had no deleterious effects from its use in the United States.

We should then send a message via WHO to developing countries in Latin America and sub-Saharan Africa and Southeast Asia that the intradermal route is a safe and effective means, that it is a WHO-sanctioned mechanism. We have a meeting next month addressing this issue, and so we are concerned about misguided messages that this may send inadvertently, perhaps questioning the utility or safety of this mechanism.

**DR. OFFIT:** Do you think, John, that it would be possible to get a representative from Aventis Pasteur to stand up and discuss the possibility that they would consider the intradermal use vaccine in this country? Because -- is there a big difference, Chuck, in the price between intradermal and intramuscular here?

**DR. RUPPRECHT:** That's a very good question, and from our surveys, particularly in the states whose end users are the veterinary school, and this price differential, interestingly enough, has been creeping ever closer within the last few years. But on the average, we're talking about -- it used to be a doubling of difference, and somewhere in the orders of 65 to 70-ish for the intradermal, recognizing three doses,

as opposed to a $100 to $120 per dose for the intramuscular.

**DR. MODLIN:** Phil?

**MR. HOSBACH:** I'm going to try to break down the situation for you. This is something that -- a decision that we didn't take lightly. First of all, we knew that there was a product to fill the gap with the need here, and that is the IM product, which is essentially the same vaccine.

What we did in terms of a business decision was -- as you know, manufacturers have to continually comply with GMP and we're continually doing maintenance and upgrading our facilities. With this particular product, it's a very small customer segment. There are not that many customers that buy the product and it's a very manual process in filling the vaccine, and we're having more human interaction with the vaccine in the process of manufacturing and filling the product. So we also want to try to stop those interventions where the -- where there's human intervention involved, too, try to limit those types of things.

In making our decision, we took a look at what the potential investment would be for upgrading that facility to become more of a mechanized type process, and we found that by the time we would get that accomplished, upgrade the facility, the cost of the ID vaccine would far exceed the cost of the current IM product.

In addition, while we sent out this letter to all of our customers who received ID product, we allowed them to also buy in the IM vaccine initially at the ID price, in particular to address the needs of the veterinary students, and we're also aware that many schools also buy their vaccine for them, and they're all required to carry insurance in those situations and they all -- many of them are reimbursed for a rabies-type vaccine.

**DR. RUPPRECHT:** I'd have to correct the last statement, at least from our Ferguson fellows investigation this summer. The majority of those costs are borne by the students at the 27 schools we investigated.

**DR. MODLIN:** Chuck, you referred to the product as an

orphan drug product. Does it truly have that status or are you just referring to it in the way in which it's -- because of its relatively small market?

**DR. RUPPRECHT:** No. We believe it is both in regards to its small market, in addition to the time and attention that's spent with either nationally or internationally, commercially or otherwise.

**DR. MODLIN:** And again, as someone who's very naive with respect to the issues of financing around orphan drug products, would that make a difference if it really truly were designated as such? Karen, do you have any

**DR. MIDTHUN:** The main thing that orphan drug status refers to -- Can you hear me?

**DR. MODLIN:** Yes.

**DR. MIDTHUN:** The main thing that that refers to is to products which are being considered for licensure and, for example, you know, you don't need to pay a user fee for an orphan drug product. Nonetheless, the standards for safety and efficacy are the same.

**DR. MODLIN:** Yes?

**MR. REILLY:** Kevin Reilly.

I'm not involved in this actual situation, but let me clarify the orphan drug issue a little bit. I don't believe that any biologicals fit within the orphan drug definition. There is a -- the orphan drug is a specific piece of legislation to encourage pharmaceutical drug manufacturers as criteria of exclusivity and a sole presence on the market for a certain period of time. I don't believe that applies in this situation.

**DR. MODLIN:** Thank you. Paul?

**DR. OFFIT:** Just I guess I would feel more comfortable if somebody who I guess is closely in touch with the way that vaccines are administered in the developing world could -- could stand up and reassure me that by saying that we're not going to be using an intradermal vaccine here, that that won't drive the use of nerve cell vaccine elsewhere. It worries me that that may be the outcome.

**DR. MODLIN:** Chuck, you're probably the closest to this. Either you or Stan Plotkin could best address Paul's concern.

**DR. RUPPRECHT:** I'll defer to my senior colleague.

**DR. PLOTKIN:** Thanks. Well, the evolution of intradermal vaccination against rabies has been driven essentially by cost issues in the developing world. I do think there is a risk of sending the wrong message, but I think that we should tailor the message to the situation. That is, the message being that the decision to discontinue intradermal vaccination was based essentially on the cost of production of the intradermal vaccine if the manufacturing facility were to be upgraded.

I think that intradermal vaccination is here to stay. It's going to stay in the developing world -- and the issue before the Committee, I think, is whether to recommend off-label use. That's what it boils down to. Because the manufacturer, as you've heard, is offering intramuscular vaccine at -- I understand at some reduction in price but, nevertheless, the issue of cost will remain. And in the developing world, I believe that they will continue to use intradermal vaccination.

I do think actually -- Chuck, I think that the vaccine is licensed intradermally in Thailand but, basically,

it's the intramuscular vaccine that is used in, you know, multiple doses from a single vial. I'm not sure that it's licensed anywhere else in the world for that route, but it is used extensively in Asia certainly by that route.

So will it impact on the developing world? It will if the wrong message is sent. So I think it has -- whatever message is written by this Committee has to be very specific as to why the intradermal is no longer recommended, if that's the decision.

**DR. MODLIN:** It's clear to me that we're going to have to have a revision to our current statement, an update in there for it. We're going to need to put together a group to -- hopefully, a relatively small group to work with Chuck on this.

Let me ask now -- I don't believe that we have a standing working group on rabies or -- we haven't had one, at least in my recent --

**DR. RUPPRECHT:** Since 1999.

**DR. MODLIN:** '99, thank you. Let me just ask for a quick show of hands of individuals who might be interested in working on a rabies vaccine work group.

(SHOW OF HANDS)

**DR. MODLIN:** Dr. Offit, Dr. Brooks -- anyone else, liaisons, ex officios, anyone else in the room that would be interested in working with -- Dr. Marchessault, Dr. Plotkin. I'm sorry?

**UNIDENTIFIED SPEAKER:** Jane [inaudible], Chiron Vaccines.

**DR. MODLIN:** You're with who?

**UNIDENTIFIED SPEAKER:** Chiron Vaccines.

**DR. MODLIN:** Chiron Vaccines. I regret that -- we would love to have your involvement but, of course, with our new policies and procedures, we do not have manufacturers' representatives as members of work groups. We certainly will invite them and would invite you to a meeting, should you have an interest a specific interest in the agenda.

Anyone else?

**DR. SNIDER:** Let me just, to clarify -- the vaccine manufacturers, certainly, we want their input as consultants to the work groups. So that's what John's referring to. There may be some members -- if we are going to be able to have the new members come on board,

which would also increase the size of the Committee, we may have some members there, John, who would be interested in serving.

**DR. MODLIN:** That's a good point. Okay, we'll take that. And of course -- how about the Academy?

**DR. ABRAMSON:** Well, I think we're going to have to be involved because if you approve -- if the decision is approval of off-label use, then

we -- it could be used in children that way.

**DR. MODLIN:** Of course, again, this is pre-exposure prophylaxis --

**DR. ABRAMSON:** I understand, right.

**DR. MODLIN:** -- which I don't know if we have any indication for that in childhood in this country.

**DR. ABRAMSON:** It's a question of -- for travel.

**DR. MODLIN:** For travel, good point. Karen?

**DR. MIDTHUN:** I mean, I guess I would just say that I think that the thought of sanctioning off-label use and using a multi-use for a single-use vial is something that I really would not, you know, want us to endorse.

**DR. MODLIN:** At the very least, it sounds like we need to have somebody from the FDA on the work group.

**DR. MIDTHUN:** Yeah, I'll --

**DR. MODLIN:** You'll let us know who that's going to be?

**DR. MIDTHUN:** Yeah, I will.

**DR. MODLIN:** Okay.

**DR. SNIDER:** I think it also would be useful if we could get some input from WHO since they have a policy and presumably some process that led up to that policy. I don't know, Chuck, do you know someone we could contact?

**DR. RUPPRECHT:** Yes.

**DR. SNIDER:** Wouldn't necessarily be a part of the working group, although that's a possibility, but at least could provide us some background information.

**DR. RUPPRECHT:** Yes.

**DR. MODLIN:** Melinda?

**DR. WHARTON:** The state public health veterinarians might also be another group that would have useful input.

**DR. MODLIN:** Good point. Okay. Thanks very much, Chuck. We appreciate the update and the information. Let's go on to the next item on the agenda. We have asked to have the Committee brought up-to-date from time to time on the progress and development of HIV

vaccines. Dr. Tim Mastro will be presenting this morning.

**DR. MASTRO:** Thank you very much. Good morning. I'm from the Division of HIV/AIDS Prevention at our National Center for HIV, STD, & TB Prevention. And I very much appreciate this time on the agenda of the Committee to actually update you on these current ongoing trials and help us think through a number of issues from the public health arena about what we should be doing now to get ready for the results of these trials, and then what to do after that, particularly in the area of communication.

Twenty years into this epidemic there have been some 60 million HIV infections globally, with about 25,000 deaths globally. And currently WHO and UNAIDS estimate there are 36 million people living with HIV infection globally. That overwhelming number, as you know, is disproportionally infected sub-Saharan Africa, with currently about 25 million people infected, with some southern African countries having adult prevalence rates in the 30 percent range.

Here in North America, we estimate there are some

900,000 prevalent HIV infections. And as you may know, we just celebrated the 20th anniversary of this epidemic and we've had about 750,000 AIDS cases reported in the U.S., and about 450,000 deaths. Despite everything we've known about HIV and HIV prevention, in the last ten years the epidemic accelerated. We weren't successful really in containing it in many parts of the world. We have had considerable success here in the U.S., but our record in the last ten years has really not been so good in controlling this epidemic. And I think everyone globally now has really be convinced of the need for a safe and effective HIV vaccine to really slow down this epidemic.

Looking at HIV incidents, last year there were about five million new infections. That works out to 15,000 new infections every day of the year throughout a year. Here in North America, we think there are about -- in the United States about 40,000 new infections annually. Again, more than 100 new infections a day. We don't have an HIV vaccine 20 years into the epidemic, and it looks like it's not going to be an easy virus

to control with a vaccine. Natural HIV infection does not confer protective immunity. There's lack of an ideal animal model for evaluating products. The correlates of human protection are not defined and not known. And there's great HIV strain variability within HIV sub -- HIV type 1. There's a variety of genetic subtypes distributed around the world, and we actually don't understand fully the importance of these genetic subtypes for a protective immunity. There have been more than 70 HIV vaccine human clinical trials in the Phase I and Phase II, including 12 of these in developing countries. A variety of products have gone through Phase I and Phase II, but only one product has advanced to Phase III clinical evaluation. And we'll talk about two trials of the gp120 vaccines today going on here in the United States and in Thailand. Today I'll be talking about the AIDS vaccine efficacy trials, the two ongoing trials of similar products. These are preventive vaccine trials among HIV negative persons, as opposed to therapeutic trials in HIV infected persons. These trials involve recombinant gp120 envelope protein products. The gp120 is

expressed in mammalian cells. These are Chinese hamster ovary cells. They're both made by VaxGen, Incorporated, in California, and VaxGen is a company headed by Dr. Don Francis, and it was spun off from Genentec [phonetic] about five years ago and VaxGen went out and got investor capital to actually get the resources to take these trials forward and is the trial sponsor of both trials.

Both trials employ a bivalent product, each with 300 micrograms of each antigen in an alum adjuvant. Both bivalent vaccines employ both a CXCR4, a T-cell trophic strain, as well as a CCR5 using a macrophage trophic strain of the virus. The VAX004 trial is being conducted primarily in the U.S. with sites in Canada and the Netherlands. The product is AIDSVAX B/B. There are two B-clave viral strains used in this product. And in Thailand, the VAX003 trial is using one of the same B strains and a subtype E strain is used for formulating this product. Subtype E is the predominant HIV strain circulating in Thailand. Both of these trials are randomized, double blind, placebo-controlled trials.

This is a schema from VaxGen which actually is important to put into perspective of where these Phase III trials are, and there are only two other Phase III trials that are currently on the drawing boards in the world. To walk you through this a bit, the AIDSVAX gp120 vaccines primarily induce antibody. We're here in 2001 and these two Phase III trials are ongoing. These red bars indicate the first formal interim analysis for efficacy. So this trial is being conducted with the AIDSVAX B/B in North America and the efficacy look will be later this year and then the trial will be completed a year later at the end of '02. The Thai trial is running about a year behind that, the AIDSVAX B/E, and that'll be having its efficacy look at the end of '02 and be completed in '03.

The only other two Phase III trials that are currently being planned both employ the Aventis ALVAC canarypox vector, which is, again, a canarypox vector that delivers HIV antigen and is designed to induce cytotoxic T lymphocytes. In addition to that, the AIDSVAX B/E and B/B will be used as a booster in these. So these are prime boost vaccine strategies with a

canarypox prime, with the same VaxGen AIDSVAX boost in these.

The U.S. Army is currently doing a Phase II trial of B/E in Thailand and the ALVAC product, and they will reach later this year a go/no-go decision, both on epidemiologic and immunologic bases of whether or not to take this product to Phase III. And given the epidemiology in Thailand now, they're looking at a sample size of 16,000 to 20,000 people in a community-based Phase III trial, and that may get started next year.

The NIH's HIV vaccine trial network is conducting a large Phase II trial of an ALVAC product that's a B clade, along with the AIDSVAX B/B boost currently in the United States and again, based on immunogenicity data coming out later this year, will decide whether or not to proceed with a Phase III trial in North America, as well as Latin America perhaps. And again, that'll be an ALVAC B product with an AIDSVAX B/B boost, and that trial -- the site preparation would wrap up next year and the trial would perhaps start in '03.

So there won't be any other Phase III trials yielding

efficacy data for a few years after this. And of course, since these products here are being envisioned for boosts in the next trials, the outcome of these trials will impact potentially what happens with the next trials.

This is a schema from VaxGen about the hypothesis or the rationale for using gp120 which is the envelope of HIV. gp120 is then cloned. It's a very safe strategy. Synthetic gp120 is created by genetic engineering in mammalian cells. The gp120 is purified, put into a vaccine, injected and it induces antibodies to gp120 that hopefully will block the HIV infection. And there's been a great deal of controversy over whether or not these antibodies will work to prevent infection and what the merits of this product are. And we're pleased that the Phase III trials are going on because they will resolve the controversy over whether or not gp120 antibodies are going to be effective in controlling HIV infection. gp120 appears to be very safe. Again, it's in an alum adjuvant that safety now has been demonstrated in more than 5,000 HIV-negative volunteers, more than 500 HIV

infected persons. It's been evaluated as a therapeutic vaccine, as well. There've been really no - there's no evidence of serious adverse effects related to this product. There's been minimal reactogenicity. Fifty or 60 percent of the people get pain at the injection site, and there's been, to date, no evidence of enhancing antibodies that's been raised as a potential concern for gp120 immunization. These data were used to end up with the final trial design that's being used, and the current trials are very much a proof of concept for gp120 immunization. And they involve seven immunizations with boosters every six months after the primary series. These data are from MN, which is a monovalent strain of gp120 and one of the AIDS evaluation group trials. What it shows is the pink dots are the neutralizing antibody titers just before a dose, showing that at 12 months the neutralizing antibodies are here. After you boost them at 12 months, they jump up quite a bit and then come down. So based on this falling neutralizing titers, the trial was designed to have boosts every six months after the primary immunization.

So this is an overview of both of the AIDSVAX efficacy trials. The trials involve a screening phase with information and HIV testing. People pass a comprehension test to demonstrate that they understand the outline of the trial, it's placebo-controlled nature, and the possibility that the vaccine will not work. They have education and informed consent. The vaccination schedule is zero, one, and six months as the primary immunization, and then booster doses at 12, 18, 24, and 30 months. The full trial takes about 18 visits. There's a visit and a blood draw with each injection, and then two weeks later, as well as a follow-up visit and three screening visits, and the trial is completed in 36 months after enrollment. If someone becomes HIV infected or HIV positive as determined by EIA and western blot, they receive no more injections and they shift into step B, which is the term for the HIV infected persons' part of the study. The trials involve extensive risk-reduction education

**DR. MODLIN:** Tim, could I interrupt you just a second? I apologize. Gloria's just handed me a message that

there's an emergency message for Karen Biscardi, if she would see Gloria please, if she's in the audience. Thank you. I'm sorry.

**DR. MASTRO:** Getting back to the overview of the conduct of the trials, people receive extensive risk-reduction education and counseling, hopefully to ensure that there would not be an enhancement of risky behaviors during trial conduct. There's an ongoing evaluation of the safety of the product and the possibility of social harms previously determined as trial-related discrimination, that indeed someone could actually suffer from having been in this trial, and that's being monitored in the trial. Community advisory boards have been established at most of the study sites, and in Thailand there's a community advisory group. Participants who become HIV infected during the trial are linked to care by the local sites. The study and the local sites did not actually provide that care, but they linked them to a system in their local site.

HIV infected participants are followed under the step B special procedures for the assessment of their

clinical progression and care. They get an evaluation and a blood draw as soon as possible after their first seropositive test, and then at months one, two, four, eight, and then four-monthly thereafter. At each of these, they get immunologic assessments, including viral load, CD4 determination, and the ability to look at the viral characterization of these breakthrough viruses.

The primary endpoint for this trial is HIV infection and that's determined by an EIA and western blot. The vaccine-induced antibodies from gp120 are readily distinguished from true HIV infection and really a western blot can do that. A small proportion of gp120 vaccines will seroreact on an EIA. On a western blot, they would simply have a gp120 band and it would not be positive.

The secondary endpoints are looking for the possibility of transient HIV infection, as well as possible reduction in viral load and the slowing of disease progression related to that. Other objectives, of course, looking at safety of the products, a HIV strain selection. There's a

hypothesis that the vaccine will protect against strains very similar to the vaccine strain but not other ones. It's called the sieve analysis. And we'll of course be looking at the behavioral effects of being in the vaccine trial.

Now I'll go through the trials one by one. VAX004 is the North American trial. It's being sponsored by VaxGen and it's being conducted at 61 local sites, mainly in the U.S., with a few sites in Canada and one in Puerto Rico and one in Holland. CDC joined the trial about a year after it got started, and I'll describe our contributions, and the NIH is funding the collection of lymphocytes from the HIV-negative people in the trial in hopes of getting a better handle on the correlates protection, if indeed there is protection in the trial.

The study is almost exclusively men who have sex with men, 5,190 high-risk gay men and 300 high-risk women in the trial. And again, the bivalent vaccine with an MN B strain and a GNE8, the other macrophage trophic B strain. With this seven-dose immunization schedule, the vaccine/placebo ratio is two to one.

The trial started just three years ago. It was fully enrolled after about 16 months, with a duration of three years. It'll be completed in October of '02. And again, the first formal look at efficacy will be in the fall of this year, probably in November.

This is a map showing the 61 trial sites, again with three sites in Canada, one in Puerto Rico, and Holland. Again, these were individual sites that VaxGen directly funds to conduct these. So, on average, each site has somewhere around, you know, 100 participants in the trial. And there's a centralized data management system and a centralized specimen handling, as well.

These are the statistical power and sample size calculations for this trial. For the primary efficacy endpoint of infection, the study is powered to have 90 percent power, to reject the null hypothesis if there's a vaccine efficacy of 30 percent, if the true VE was 67 percent using a two-sided test. That assumes that there's no vaccine effect until after the third immunization, projecting an HIV incidence of 1.5 percent in this high-risk population, and assuming an

annual loss of ten percent in the first year and then five percent in the second and the third year.

CDC, in hopes of learning as much as we can about this trial and hoping to inform future trials, funds six of the sites in the trial, what we call the VISION vaccine substudies network. So we're funding a site in Boston, two in Chicago, one in Columbus, San Francisco, and Seattle, and one of the sites in Chicago enrolls exclusively high-risk women. So these are 800 participants, or about 18 percent of the full trial. And each of these sites will also be enrolling a comparison group -- a population with similar risk characteristics who are not in the trial -- to be able to make some comparisons behaviorally of those in the vaccine trial and those who are not in the trial. And those studies are ongoing.

Some of the key elements of these substudies are looking at behavioral aspects of participation, what are motivations for enrolling in a vaccine trial, what are determinates of risk behavior and how does risk behavior change in relation to a trial. We want to know if people un-blind themselves. In the U.S., it's

quite possible that you could go outside the trial, get a gp120 on the market some -- get a western blot on the market and figure out if you're in the vaccine or the placebo arm, and that would have a profound effect on the conduct of the trial if people perceived that vaccination did confer some kind of protection. So it's important that we ascertain that. We're also interested in what contributes to good retention in the trial, and also figuring out if people use post-exposure prophylaxis for sexual exposures, do people actually then go and use antiretrovirals as post-exposure prophylaxis, and it would be important to know if that's happening systematically in the trial, as well.

Through a series of in-depth interviews and focus groups, we're exploring a number of qualitative issues to understand perceptions of being in a trial, decision-making, motivations, and trying to understand the trial experience.

Virologic aspects of these substudies are determining antiretroviral resistance in those strains that do break through, as well as the genetic characterization

of those viruses. We're looking at mucosal immunity in both men and women, cellular and humoral, in two of the sites. And at all 61 sites we've put in a module to assess care to determine how people get into care after they get infected, when they access the antiretrovirals, and what their experience is to getting into care. And again, thinking of future trials, we have another part of this looking at individual site and community-level factors that contribute to high levels of enrollment, retention and protocol compliance -- essentially trying to identify what makes a good study site.

Shifting now to Thailand, a very different setting, the collaborators in this trial are the Bangkok Metropolitan Administration, which is the city government of Bangkok, Mahidol University, VaxGen, the sponsor, and CDC's HIV/AIDS collaboration in Bangkok, which I had the privilege of directing for seven years, up until the year 2000.

The population in Bangkok is 2,545 injecting drug users in treatment programs in Bangkok. Again, the bivalent vaccine has a B and an E clade virus, the same seven-dose

immunization schedule with a one to one ratio.

This trial started in March of '99. Again, it took 16 months to fully enroll and, with a three-year duration, will be completed in '03, with the first formal look at efficacy a year after the U.S. trial.

This is a map of Bangkok. Bangkok is a city of some eight million people. It's had an explosive epidemic among injecting drug users, starting 12 years ago. The prevalence of HIV among the drug-using population is about 50 percent. There are estimated to be about 40,000 active injecting heroin users in Bangkok, and the BMA has maintained a large drug treatment program since the 1960's, mainly based on methadone detoxification. So these 17 clinics have been able to engage these drug users and enroll them into the trial.

As this was the first international Phase III trial, it went through a very extensive review and an approval process, starting with the Ethical Review Committee of the Thai Ministry of Public Health, the HIV Vaccine Subcommittee of the Thai National AIDS Committee, and the IRB's of the BMA, Mahidol University, and the U.S. CDC, as well as approval by the U.S. FDA, our Office

for Human Research Protections, and the UNAIDS HIV Vaccine Advisory Committee. And believe it or not, this all did happen in less than one year.

This chart just provides an overview of these two studies with nearly 8,000 people in these randomized trials. Again, the North American trial will assess sexual challenge to the vaccine, primarily among men who have sex with men, with a parenteral challenge in drug users with needle-sharing among drug users. In North America we estimated there was about a 1.5 percent annual incidence of HIV based on prior studies. And in Thailand a preparatory cohort study actually measured a six percent annual incidence in drug users in treatment, and the study was powered with a more conservative four percent.

These are the vaccines, the ratios, and again, the interim analysis for the Thai trial will be just about a year after the North American trial. This will coincide with the final analysis in the North American trial.

So how are the trials going? Just very briefly, in the North American trial with 5,400 people enrolled --

Again, 94 percent are male with a median age of 37 -- follow-up has been quite good overall, with a successful follow-up rate of 91 percent of people retained in the study. There've been only two serious adverse events thought to be related to the injection, and these were both cellulitis, but they resolved and allowed the people to continue. Encouragingly, there has been observed to be actually a reduction in reported risky behaviors. The important sexual behaviors we know that are related to seroconversion have actually reduced since baseline of enrollment in the study. And the social harms that have been reported have been minimal to date and they've all been resolvable.

In Thailand, to enroll 2,540 drug users, nearly 5,000 were screened at the drug centers. Of those screened, excluding known positive drug users, 34 percent were found to be HIV seropositive, reflecting the nature and the breadth of the HIV epidemic in this population in Bangkok. Ninety-three percent of these drug users are male, and that's reflective of the drug use population in Bangkok. It's actually -- in contrast to the United States, it's quite unusual for women to be injecting

heroin users in Thailand, a younger population with a median age of 26, and again, so far follow-up has been quite good, with only three percent lost to follow-up. And there have been no vaccine-related SAE's. And also in terms of the frequency of heroin injection and needle-sharing, risky -- reported risky behaviors have decreased since enrollment. Minimal social harms observed.

One problem that was anticipated, based on our preparatory cohort, that incarceration is common. Of course, people enrolled in the trial are not incarcerated, and they're participating in drug treatment programs, but we know that drug users in Bangkok get arrested at a fairly high rate, and they are incarcerated. And this was dealt very forthrightly with the IRB's and the oversight committees, and while incarceration has been common, it has been possible to continue to follow up people in a voluntary nature, allow them to either decline participation or to continue to participate in the trial.

There's a single data and safety monitoring board

overseeing both of these trials. It's chaired by Dr. Walter Dowdle. It's a ten-member multi-disciplinary committee of both Americans and Thais. They meet every six months to oversee the conduct of the trial and the safety data. They've had five reviews to date, shown here most recently just two months ago. To date, they've found that there've been no serious problems with trial conduct. The trial is proceeding well and they've advised the trial to continue.

At each visit, they look at the SAE's by treatment assignment, make sure that the HIV infection rate is not higher in the vaccine arm compared to the placebo, and that there's no apparent disease progression differences -- in the bad sense -- for vaccine related to placebos. They've not formally looked at efficacy yet. And again, the first interim look for efficacy will be probably November of this year.

These are the stopping rules for the efficacy analysis coming up in November. To stop, there would have to be a high level of protection, with a vaccine efficacy, lower bound exceeding 30 percent at the .03 level and, of course, the trial could be stopped for any safety

concerns of SAE's, increased susceptibility, or rapid disease progression associated with vaccination. But again, all these serious events have been observed in the last five reviews and have not been observed so far. So, really, we're looking at whether or not the trial could be stopped based on what would have to be probably a very high level of efficacy at this interim analysis. If it doesn't stop, the trial will proceed for one more year until it's completed.

Again, just looking back at this time line again where we are, we're now here in the middle of '01 coming up on this efficacy analysis, which we're going to discuss it today and again a year later for the Thai trial. There are some very interesting scenarios if one trial reaches a stopping point, what do you do with the other trial, given the fact that it's a different challenge and a different product. The implications of that would be -- require a fair bit of discussion. And again, as the two other trials in the world that are planning to go forward are planning to use these AIDSVAX products as a boost, certainly the planning of these is very much looking at what happens with the efficacy

outcomes of these trials.

As we think about vaccine efficacy, I think it's important to prepare for and think about a partially effective HIV vaccine. And HIV vaccine efficacy could be characterized in a few ways. Probably the most traditional is its protection from infection, so it's vaccine efficacy for susceptibility. It's also conceivable that a vaccine, even if it doesn't protect you from getting infected, may change your infectiousness. Therefore, you could have a reduction in transmissibility or infectiousness and having a VEI or a vaccine that lowers your infectiousness, and that would have profound effects on an epidemic, perhaps not on that individual. But also if you were less infectious, there's a good change with HIV that your disease progression would be slower. So it's quite conceivable that an HIV vaccine will actually render you potentially less infectious and have a less severe course of HIV disease.

We now, of course, can measure plasma HIV viral RNA levels, known as the viral load. And with natural HIV infection, a viral load's set point is established

about six months after primary infection. And we know now very well from clinical and epidemiologic studies that HIV viral load is directly related to the rate of disease progression, as well as the rate of infectiousness. People with very high viral loads progress rapidly and they're more infectious. People with low viral loads are much less infectious and they have a much more slow rate of progression.

This is a schema for natural HIV infection. Following infection there's a very high peak of viremia. Once the immune response kicks in, it pulls this down. And then some homeostasis or steady state is established between our immune system and the virus, and you get a virus set point that's this level range here. And associated with disease progression is your eventual decline in CD4, and as CD4 declines the virus takes off. But during this stage here, this steady state, this is quite variable. And with natural infection, some people have a virus load of 1,000 copies per milliliter and they tend to progress very slowly. Other people have as many as half a million viral copies per milliliter and they tend to progress very rapidly.

And without treatment -- of course, now we're in the treatment era and this is greatly changed -- but we would see about an average of ten or 11 years from infection to AIDS onset, but that can vary tremendously, from two years to more than 20 years. It's conceivable with vaccination that you could get a vaccine effect as shown here. A placebo recipient could have a normal peak of virus with a viral load established at a relatively high level, but a vaccine recipient with pre-existing antibodies could have actually a blunted viremia and establish a viral set point. And if this happens systematically, this could have a profound effect on both the progression of the disease as well as infectiousness in people, and would be one of the partial vaccine effects.

So a partially effective vaccine might reduce your change of getting HIV infected if you're exposed. It might protect against some modes of transmission, such as mucosal and not parenteral. It might protect against some strains of HIV and not others, strains within an HIV subtype or across different subtypes. And a vaccine might lower your viral set point, which

would result, we think, in slower disease progression and decreased infectiousness.

So at this juncture, with where we are with these trials and the possibilities of a partially effective vaccine, we would very much invite discussion and what we should do and how to prepare for the results of these trials, with the interim analysis coming up in just six months in the U.S. trial. And that trial will either stop in six months or it will continue, and then it will be finished 12 months after that, in the fall of 2002.

I think as public health officials we need to get ourselves together on the interpretation of these results and make sure that all the involved parties, including VaxGen, CDC, FDA, and NIH, have a joint interpretation of these results. And then move forward with the communication planning for how to communicate these results, which we should start now before the trial finishes, as well as afterwards, and have a coordinated message in what these results mean and communicate that with the general public, as well as affected communities, and as well with the medical and public health communities.

As we think about the possibility of a partially effective HIV vaccine, we're planning now to convene a CDC consultation in September here in Atlanta, and we're just putting together the planning for this and what we hope to be a multi-disciplinary group to consider use of a partially effective HIV vaccine, to actually identify some of the issues important in this and outline future areas or areas for future research and things that need to be sorted out as we get ready for the results from this trial.

And related to that, we need to prepare -- there certainly will be future HIV vaccine trials. If this product is licensed or if it's not licensed, you know, where do we go for the planning. If this product is licensed, it will, of course, have profound effects on future trial designs. It's likely there won't be placebo-controlled trials after this. If this product is not licensed, it's important to communicate to the public health community, as well as affected communities, that the trials need to go on and have realistic expectations for this one and not be discouraged about conducting future HIV vaccine

trials.

Thinking about HIV vaccine implementation, a large number of issues -- what would the demand for this vaccine be. It's very enlightening to think about what we do or what this Committee does with very highly efficacious vaccines and how challenging it is to get them ready for people. And when you think about getting an HIV vaccine ready -- there's very little production capacity now for gp120 vaccines, and there would not be a ready supply of these vaccines sitting on the shelf ready for use if they're licensed immediately.

What would be the implications for HIV prevention, having an HIV vaccine as part of the armamentarium. There's great concern about behavioral enhancement. If you vaccinate people, then sort of safe-sex behaviors may wane. How do you plug a vaccine into counseling, testing, or referral strategies. Of course, international implications beyond the U.S. for how you use this vaccine internationally, as well as a host of ethical and legal considerations.

It's very easy to come up with a long list of needs for

additional research. Just a few. Certainly, a continued safety assessment of the people that are in these trials. We need to define safety in other populations. Both of these trials are overwhelmingly men, and there's no children involved, certainly no pregnant women, and we have to learn more about the safety in other populations. We won't know very much about the duration of protection with a vaccine that's boosted every six months. There would have to be studies to extend, to figure out how long the duration of protection is, what's the breadth of protection in other population groups, the mode of transmission, whether it's sexual and whether that's regular or vaginal sex, blood or perinatal transmission, and the effects on HIV diversity, how to use this vaccine with other vaccines. And Hal Margolis has reminded us that, you know, you might want to use hepatitis B vaccine along with HIV, and we don't know how those two vaccines would interact, and a large number of operational issues that we could come up with.

So, with that as an intro, I would be happy to answer questions and would very much welcome the Committee's

thoughts on all these thorny issues. Thank you very much.

**DR. MODLIN:** Thanks for presenting a lot of information in a very comprehensive way in a very short period of time. Thank you. I'm sure there are comments and questions.

Dave Johnson?

**DR. JOHNSON:** Tim, thank you for the presentation.

There's been a fair amount of media interest in these vaccines and sort of the fits and starts with various vaccines. In the process this fall to look at possible stoppage of the trial, if the stopping criteria are not met, what kind of public communication do we expect at that point?

**DR. MASTRO:** That's an excellent question. We're discussing that now, both within CDC's communication offices as well as linking with VaxGen's communication people on that. Up until now, every DSNB meeting they simply issue a report saying the trial is going well, proceed. And it's conceivable they'll do that again in November, that the trial is going well, you've not

reached the stopping point, continue with that. I think there is a need now to adjust expectations for what that means, and that's very likely that would be the outcome. But we actually don't have the communications all lined up, but we certainly need to do that in terms of that the trial didn't reach the stopping point. We don't know what the incidence is - or I don't know what the incidence is in the trial. Therefore, we don't exactly know what power there is. You could try to figure out what the efficacy might be to exclude a 30 percent efficacy with a lower bound at 03, but you would have to do a fair amount of guesswork to figure out how low or high it could be.

**DR. MODLIN:** Sam Katz?

**DR. KATZ:** I realize that this presentation is for information and this Committee has no role in recommending clinical trials or approval of clinical trials. It seems to me that science has moved so rapidly that any optimism that antibodies to gp120 are going to be effective are very pessimistic, and that the science is increasingly integrated that it's cytotoxic lymphocytes, CD8, CDL stimulation that we're

looking for. And I'll be a pessimist and say I don't think this trial is going to show anything positive. And my question of you is, what effect do you think a failed trial is going to have on the implementation and the initiation of trials with more promising antigens? It seems to me that if you have a terrible disappointment, you're going to have a hell of a time trying to interview and enroll people with products that may be much more promising.

**DR. MASTRO:** Those are, of course, very, very tough questions. I think a trial would really be a failure if it didn't yield interpretable results, and I think if this trial evaluates the merits of gp120 antibody and resolves once and for all are these -- do these have value, then it's a successful trial. The efficacy may be zero or close to zero, but I think we've done a successful trial that's actually at least resolved this issue of what gp120 antibodies do.

I think with the absence of animal models and protection, we actually really don't know. Your pessimism is, of course, shared by many of what the outcome's going to be of this.

**DR. KATZ:** I think it's Don Francis's optimism.

**DR. MASTRO:** Well, I think -- I think over the last several years, I think there's a need to figure out how to do HIV vaccine trials, and I think there's going to be a tremendous amount learned operationally from these trials of how do you enroll people in trials, how do you conduct a HIV vaccine trial. And I think the information from this trial will inform future trials very well, and so they'll be in a better position to conduct those future trials.

Your point is very well taken, though. We need to communicate this in a way that, yes, this was the first try. I think it's not a realistic expectation that the first time out you're going to hit a home run with an HIV vaccine trial and suddenly come up with your definitive vaccine. And that expectation should be addressed publicly, that there's a good chance this will not be highly efficacious or, as you're suggesting, any efficacy. But I think it is important to plan for that communication, that if there's not efficacy that will lead to licensure, to say that this was a try, it's time to move on with other products.

The time line, though, is very -- is very sobering. And when you think of my first couple of slides, there were five million HIV infections last year. I think we need to move the pace of vaccine evaluation forward more quickly. The other products that are on the drawing board are the ALVAC canarypox products. Of course, there's new things coming down like DNA vaccines that are behind those. And the question is going to come up in one or two years, do the current canarypox products have enough merit to go forward to Phase III evaluation, or do you wait for the other product that's a few years up the pipeline to test those because you have a high enough chance of high-level efficacy.

So I guess to answer your question, we do need to do a good communication job with that. I think the main thing is to do these trials well so they yield interpretable data, and we'll know what happens with gp120, and we know what happens with people in these trials, and try to present that in a way that it will be, I think, an iterative process to develop our eventual safe and effective HIV vaccine.

**DR. MODLIN:** Kristin?

**DR. NICHOL:** I'm just curious to know what your power is to exclude a vaccine efficacy of zero, given the fact that you've powered the study to have a very -- a rather precise confidence interval around your point estimate of vaccine efficacy, given the assumptions that went into the original power calculation. And also, how will the results be interpreted if the confidence intervals are wider than they were for the power calculation?

**DR. MASTRO:** Well, two issues. It'll be easier to exclude zero than it'll be to exclude 30.

**DR. NICHOL:** It must be essentially 100 percent to exclude zero.

**DR. MASTRO:** So there's more -- well, it depends on what that point estimate is, can that -- did the one scenario -- of course, in the protocol, there's a table of various assumptions. This was the one that I chose to show of a VE of 67 percent excluding -- that's just the stopping rule. That's not the -- and then there would be a series of discussions, of course, with the FDA of what outcome

might lead to, you know, licensure of this kind of a product. So there's more power to exclude zero with a VE that might be down in the 30 percent range, certainly more power than that.

And the second part of your question was the --

**DR. NICHOL:** It was related but. . .

**DR. MASTRO:** Thanks.

**DR. MODLIN:** Other questions for Dr. Mastro? Jon?

**DR. ABRAMSON:** Yeah. How strong is the educational effect and will it likely have an impact on the speed by which you can determine outcome?

**DR. MASTRO:** You mean, how effective is education --

**DR. ABRAMSON:** I mean are you slowing --

**DR. MASTRO:** -- in the --

**DR. ABRAMSON:** Are you slowing down the rate of HIV infection in the placebo groups?

**DR. MASTRO:** Yeah. That's, of course -- you know, the issue of, you know, the study effect. But if you do such a good job with your prevention, education, and interventions that you essentially have no incidents in your trial population, you'll have no power to evaluate your vaccine. I actually don't know what the

incidence rate is in the trial, and that's not a piece of data that's shared with investigators in the trial. What I understand, though, is the incidence rates are substantial and they're consistent with the trial design, which is an unfortunate reality that with HIV we're unable to -- even with people in clinical trials getting extensive counseling, there still is risky sex going on in the U.S. trial and there still is injecting drug use and needle-sharing in the Thai trial. And so we understand there's a fair bit of -- there's a substantial amount of incidence that will provide power in the trial.

**DR. MODLIN:** Yes, Lucy?

**DR. TOMPKINS:** Tim, I had a question about the therapy of patients who do convert. Will there be a standardized approach to that or will that be individualized? And then, if it is a standardized approach, what is it going to be?

**DR. MASTRO:** Again, in the North American trial, the study did not assume responsibility for care of people that became infected in the trial, thinking that was due to risk behaviors that led to that. So the trial

sites linked people to care in their own setting, and that varies based on their setting -- some of the university settings, public health departments -- and so there's not a standardized treatment. What is standardized is the way they're followed up under study protocol for assessment of viral load and CD4 counts. We do have a module -- well, from the basic study instruments, we'll know when people get on antiretrovirals because at each visit there's a concomitant medication form and we'll know what their viral load and CD4 counts are, but there will not be a uniform antiretroviral or other care strategy for that.

In Thailand, it's more -- it's more regulated, in that all of these people are managed by the Bangkok Metropolitan Administration, again, essentially the city government of Bangkok. And they assume responsibility for care, and people are cared for under the BMA treatment standards, and those are actually evolving. At the time the trial was put forward, it included a two-antiretroviral regimen for a CD4 count below 500, and that's actively being re-evaluated now.

The reality in Thailand, with -- I think Thailand is a country of 60 million people that has more HIV infections than North America. There are about a million prevalent infections there with an adult prevalence of two percent. The BMA drug treatment clinics, with about 8,000 or 10,000 IDU's coming through their system, they see alone 4,000 to 5,000 HIV infected drug users, not to mention their other populations. They cannot afford providing antiretrovirals for everybody in their system. The people that are in the trial actually are getting a higher standard of care than the other people in the BMA, and most people are getting on at least a two-antiretroviral regimen during some course of their treatment.

**DR. MODLIN:** Bob Chen?

**DR. CHEN:** Yeah, Tim, one of the potential shortcomings of data safety monitoring boards that we've been trying to highlight and overcome is that historically their composition has been by relatively or been by infectious disease epidemiologists, whereas the safety part skills really are rare disease

epidemiologists, and I'm just curious. Of your ten members, do you have folks who actually have expertise in rare disease epidemiology?

**DR. MASTRO:** I'm trying to think who -- Walter Dowdle is the Chair. There's an ethicist, a couple of, you know, statistician folks, clinicians, Thai clinicians, community -- someone who sort of represents the community interests. I'm actually not sure if there's someone that covers the domain of rare disease epidemiology, specifically.

**DR. MODLIN:** Dr. Severyn, did you have a question?

**DR. SEVERYN:** Yes, sir. Dr. Christine Severyn, Vaccine Policy Institute.

Over the past year, I've been researching the history of vaccine development. As I'm sure Dr. Plotkin and some of you may be aware, the late Dr. Albert Sabin was an outspoken opponent of developing an AIDS vaccine. His views were published a little bit before he died in the early '80's in the proceedings of the National Academy of Sciences. A recent speaker from the Vaccine Research Conference that was held in Bethesda excuse me, Arlington, Virginia just about -- oh,

let's see, mid -- third week of April just this year, also expressed a similar pessimism and thought that he -- Dr. Sabin was probably right on in his criticisms, I guess you could say -- pessimism for developing an AIDS vaccine. Would you care to comment?

**DR. MASTRO:** Well, I'd like to be optimistic, but I think the world needs an HIV vaccine that's safe and effective, that can protect people from HIV, and I hope we can make progress to eventually have one.

**DR. SEVERYN:** It might be a good education to maybe look up what maybe Dr. Sabin had to say.

**DR. MASTRO:** Thank you.

**DR. MODLIN:** Other comments or questions?

(NO RESPONSE)

**DR. MODLIN:** Tim, thank you very much.

We will be getting -- well, we actually have been discussing what the responsibility and the role of the ACIP will be. I think we'll probably begin to accelerate that thinking in the next few months and, obviously, I'd be very curious and anxious to have the input of all the members of the Committee, and anyone else for that matter, as we engage in this process.

It's 12:00. We're a little ahead of time, fortunately. Let's reconvene at 1:00 to begin the Harmonized Schedule discussion. We may -- well, let's reconvene at 1:00.

(LUNCH RECESS FROM 12:00 NOON TO 1:09 P.M.)

**DR. MODLIN:** Could I ask people to take their seats, please.

We're going to go on to discuss two issues regarding a Harmonized Schedule. This is a topic that we usually don't get to until October, but this year we're doing things a little bit differently in having a work group not only look at the Harmonized Schedule itself but to consider some other issues about how the Harmonized Schedule is formatted and distributed. And we're going to start off with a look at the traditional Harmonized Schedule, which has been devoted to -- for the most part to childhood and adolescent immunization, and then go on and discuss the possibility of developing a Harmonized Schedule for adults.

We'll lead off with Natalie Smith, then Melinda. Natalie, you're in charge.

**DR. SMITH:** I'm ready. I'm just going to make a couple of brief comments, and then turn it over to Melinda Wharton from NIP.

First of all, I'd like to thank the Harmonized childhood working on the childhood schedule working group for their work so far. And let me -- I've just got this one overhead. We did discuss frequency of updates, and we decided -- the consensus of the working group is that we should continue to just publish a schedule annually, and if there's anything major or very urgent, we should consider those on a case-by-case basis. But in general, we should stick to an annual schedule and continue to publish hard copies in journals and CDC does their hard copies, and continue to also have it on the web.

As far as the format of the Schedule, I think you-all remember that we had an excellent presentation by Diane Peterson from the Minnesota State Health Department who presented their schedule, and we've essentially just changed theirs around a bit. So that's why it's called "Change to the Minnesota design." And Diane is actually here if you have any questions about how well

this format is working out in the field there.

Just a few of the things -- obviously, the schedule and footnotes are now on the same page. We would also mention that the most recent version is actually in your books. The one that we mailed out was revised in the last couple of days. So look at the schedule in your books. The recommended ages extend through 18 years. We do have that purple column to indicate the 11- to 12-year-old assessment. It's been pointed out that we, of course, need to do assessment at every visit. So it's been suggested we change the wording of that to something like need for the adolescent assessment or something along those lines.

And then you'll see below the dotted line the vaccines for selected populations, such as influenza.

We have made, or NIP has made, both color and black-and-white versions, and I think everyone agrees we should have both of those available. And you'll see on the schedule that the CDC website information and the hot line number are at the bottom.

On the schedule -- the Minnesota schedule that Diane Peterson had presented, on the flip side of that

schedule, was a schedule for children that start late, and Melinda is going to get more into that discussion about whether we should include that on the schedule you're looking at on the back side. We did not have time to come up with a schedule by this meeting. And then, as far as content changes Melinda can discuss, we don't think there are really any significant changes. So, of course, this is a great year to change the format because we can concentrate on that more than content issues.

So with that, I'll turn it over to Melinda.

**DR. WHARTON:** Are we on? Okay. If you go to the MMWR on the CDC website, we print out the Harmonized Schedule that was published in January of this year, the 2001 schedule. This is what comes out on your printer if you're using a color printer, just to remind you what the current format looks like.

This format was developed by a -- by actually Jacqui Cindler and a number of other people quite a few years ago and has served us well over the years. But as Natalie mentioned, there have been, I think, some improvements in presentation that some of our partners

have developed and we would like to present one of those to you today.

So this is the scheduled which is published on one page of MMWR in a current presentation and these are the footnotes, which are perhaps the worst graphic presentation I have ever seen in a publication. And this is the format that the harmonized -- the Childhood Harmonized Schedule Working Group would like to present to the ACIP as a proposal for your consideration today.

We are not focusing on the wording of the footnotes, which still need some work and I notice some errors there, so you can tell me about that later, all the ones that you caught in addition to the ones we've already caught and fixed. But what I'd like to focus on is the upper part of the figure where there are a number of new conventions that have been used in presentation. Now, I will point out, though, that the -- that pretty much all of the text that was in the old schedule actually is included here one way or another, but by putting the footnotes in two columns and putting the whole thing on an eight-and-a-half-by-11 sheet of

paper, you can actually get it on one page and it looks a whole lot nicer.

Now, in terms of what MMW -- what the constraints are of publication in the various journals and other publications where this schedule is carried, it would be possible to put it on two pages if there was a smaller page size, but MMWR is moving toward an eight-and-a-half-by-11 format, although I'm not completely sure about the time frame for that. But I think it will be by next year, so it could even be presented in MMWR on a single page if they're on the larger format.

By using the colors that are used here, if this is printed out on at least the black-and-white printers we've tried it and the colors can be distinguished. The yellow comes out a light color, the wine color in the columns comes out a dark color, and the green is a medium color with darker stripes. So the three can be distinguished, which was something that the group was worried about. We also have a black-and-white version which uses similar conventions, with white bars, the dark column and striped bars for catch-up.

Some of the differences between this schedule and the previous format are explicit indication of catch-up vaccination for some vaccines, and those are, of course, indicated by the green striped bars. So catch-up is indicated for the hepatitis B series, for MMR-2, for varicella, and for pneumococcal conjugate vaccine.

The adolescent assessment visit is highlighted, although I think we need to change the name on the column. And as Natalie already mentioned, additional vaccines are included for selected populations, as opposed to the single hepatitis A for selected populations that is included in the present schedule. The ones that are included in the proposed schedule are influenza and pneumococcal polysaccharide vaccines, vaccines to be considered for selected populations. There are a number of issues for consideration, and some of these are larger issues and some of them are smaller issues. They're mostly pretty small ones. One of them has to do with just -- for hepatitis B catch-up. I think this was taken from the Minnesota schedule, but it's -- because of the way it's set up, it ends up being

a lot wider than the others and we probably want to change that. We've got pneumococcal conjugate vaccine as the title and then pneumococcal vaccine line. We may need to change that. And we want to include pneumococcal polysaccharide vaccine, and where exactly does that diagonal part of the dotted line go?

There's the issue of how to numerically indicate multiple doses, and I think there are some copyright issues with using MMR-2 that the Committee has previously addressed. There's currently a -- the recommended age column is labeled acceptable ages. I think we need to change that to recommended. There is the previous convention of do we use placement of the dose name to indicate preferred age, which came up yesterday in a discussion about administration of the first dose of hepatitis B vaccine at birth, and the working group would like some guidance about does the Committee wish to do that.

And which vaccines do we want to indicate for use in selected populations. There are only a couple listed here. There's other vaccines which are recommended

for use in selected populations and should they be included, as well.

Are there comments that anyone would like to make regarding these issues?

**DR. MODLIN:** Maybe the best thing to do here, Melinda, would be just to go from the top down on specific ones and ask if there are comments, from bar size on down, and maybe just do it that way.

**DR. WHARTON:** Well, I mean, perhaps -- actually before we do that, it may be useful just knowing the people like the basic idea of the change, because if they don't like the basic idea, maybe the rest of this is immaterial.

**DR. MODLIN:** I don't think you're going to get any argument there. I think we can just go on to get into specific issues.

**DR. MODLIN:** Okay. All right, fine.

So what -- I'll just go through and sort of say what we are -- what Natalie and I talked about doing. We have discussed changing the bar widths so they're all the same, so the hepatitis B would be the same as the others. And we also talked about changing the

pneumococcal conjugate title here to pneumococcal vaccine so it would be more general and include both vaccines. Does that seem like a reasonable thing to do? And so that would keep pneumococcal polysaccharide in and have it appropriately labeled. This issue about where to place the line has to do with where that diagonal jump-up is, and it doesn't seem to me that really this is terrifically critical, but it has been raised as an issue. If anyone has any thoughts on that, I would welcome them.

As far as the numerical indication of multiple doses, again, I think the problem with doing the hyphen and the number has to do, as I recall, with copyright and with trademark issues. So here I think there may be some problems, in fact, with using that MMR-2 and the same with hepatitis B doses.

The way this is dealt with in the current schedule was to actually -- with the hepatitis B, to use a little number sign and a one, and so we could do it that way if you guys want to. And we would propose changing the label here for range of acceptable dose to range of recommended dose, given that lots of things are

acceptable but they're not recommended.

We would like some guidance about whether or not you all want to use this placement of dose convention. I know that the schedule had employed that for some time, but I think it wasn't widely understood and it was never written down anywhere. So I'm not sure how much information it conveyed. So, for example, if we want to say that it is preferred to give first dose hepatitis B vaccine at birth, the label would be moved over here. Is that a convention you want us to adopt, and are there additional vaccines that you would propose be added for use in selected populations or really the things you would like to see back on at this time.

**DR. MODLIN:** Why don't we throw this open for discussion and try to focus on these issues that -- if we can, that Melinda has highlighted for us, so we'll just go around. Jon?

**DR. ABRAMSON:** I do have some concern about putting down the ones under selected conditions and then not putting others, because I think people will then forget for instance, meningococcal vaccine --

**DR. WHARTON:** Right.

**DR. ABRAMSON:** -- would be a good example of something that's not on there. You know, to list some and not list others, people are going to forget about. They're going to think this is it. And so -- and I don't -- I haven't sat and thought about how many we would have to put up there, but a good example is meningococcal vaccine is indicated in selected circumstances, and whether that would make it so crowded as to make it, you know -- I'd have to see it.

**DR. WHARTON:** Well, I think that was Natalie's and my concern, as well, and it -- you know, at some point one has to draw the line. And part of the reason I like the way this is is it does include influenza and it highlights it. And if what we want to do right now is to make sure that people are aware that children -- that influenza vaccine is going to be recommended for routine use in children in certain high-risk conditions, that's a good way to emphasize that recommendation.

**DR. MODLIN:** Well, we certainly have already had hepatitis A on the current schedule for selected populations, and we make a distinction. And this

could be something in which we could add vaccines on an annual basis, kind of based on a judgment as to where they rise to sufficient level to be used in a general population or not. It seems to me that there's more to be gained from adding than there is to -- than to exclude, say, influenza immunization.

Gary?

**DR. OVERTURF:** A couple of issues. One has to do with -- I don't quite understand why DTaP's fifth dose and IPV's fourth dose is not in a gold bar, because it says the range of acceptable ages, and that is -- those are the acceptable ages for that -- for those recommended doses. I don't quite know why they were excluded from the color. That's one issue.

The second issue is about pneumococcal conjugate vaccine. And you've got it -- you've got a bar for conjugate vaccine as a catch-up vaccine up to -- looks like about five years of age. And I know this is a problem because there are somewhat conflicting ideas about -- the vaccine itself is actually licensed for safety up to a higher age group. And for certain high-risk groups, they are -- I can tell you, they

already are electing to give the dose up to some of those higher age groups. And I don't know -- I don't know whether this really -- is really completely consistent with the recommendations because I forget a little bit, but we need to examine that very carefully and make sure that that bar doesn't prevent people from using the vaccine if they want to, up to ten years of age, in selected high-risk groups, because it's below that bar, as well.

**DR. MODLIN:** Gary, it's certainly consistent with the recommendation. I don't think there's any question about that. Our recommendation does not include the use of conjugate vaccine beyond five years of age in any group, even though it's licensed for use in a higher group. So I think it's quite consistent.

I guess the other issue that you raise really gets beyond the Harmonized Schedule issue as to whether or not -- how we should be addressing it, the potential use of the vaccine in older kids. It's probably not an issue for this schedule.

**DR. OVERTURF:** It's an issue that once you make these schedules up, this actually gets referred to a lot more

than the original document, which discusses some of these issues a lot more. So when you put the bar at five years of age, you're putting the bar at five years of age. And it will generate more questions, and I think you need to go -- I know that the AAP's -- we also didn't recommend routinely for doses over five years of age, but we also noted that the vaccine has been given safely and that some people may want to elect to do this in selected high-risk groups, specifically.

**DR. SMITH:** I guess I --

**DR. OVERTURF:** I think the language was similar in the ACIP's recs.

**DR. SMITH:** I guess I would be concerned it would generate even more questions from all these people that would think five to nine years of age is now routine or -- I'm concerned about the confusion that might introduce on the other hand.

**DR. OVERTURF:** Well, one of the problems here is you've got an overlap in indications, because one indication is for catch-up and one indication is for continued use of the vaccine in high-risk groups. So I don't know how you resolve that, but it's a -- and I don't have

a good solution. I think this is going to have the effect of actually defining that cut-off, at least in everybody's mind here, a lot better than perhaps the actual documents.

**DR. MODLIN:** Again, the issue is dealt with in the footnote, as well, and it may very well be that there's an additional way in which we can word the footnote that might help address some of your issues. And that's something we could certainly address for when we actually adopt the schedule in October.

**DR. OVERTURF:** Yeah. The other question then was about the DTaP and the IPV. Is there a reason why those are not in bars?

**DR. WHARTON:** Well, they're not in bars because they don't span multiple columns. The ones that are in bars all span multiple columns. So that's why.

**DR. JOHNSON:** But to that point, if you're going to call that the, let's see, recommended age -- I know we didn't do it previously, but I wonder if we shouldn't put a lightly colored bar around each of those -- DTaP, HIB, IPB, and PCV, in the two, four and six-month columns.

**DR. MODLIN:** Yeah. Melinda, the problem comes with up at the top with the legend of that range of acceptability.

**DR. WHARTON:** Right. I'll see what we called it before. Well, it says "Range of Recommended Ages for Vaccination" on the previous schedule. So this is actually quite consistent with what we said before, but we could change it if you-all want.

**DR. MODLIN:** Rick?

**DR. ZIMMERMAN:** Several comments. One is, under the age four to six, and maybe you were getting to this -- under four to six there's a little inconsistency with DTaP and IPV, and then the second dose of MMR. And actually if you look back on your old schedule, we didn't have, on MMR, an extra symbol where -- and so there is -- this is a little different with MMR than it is on the old schedule.

**DR. WHARTON:** And I believe the reason -- I believe the I think this was taken from the Minnesota schedule that way, and I believe it is there to distinguish the second dose of MMR routinely from MMR catch-up. And in this schedule, that distinction is made by use of

the ovals. I mean, if you-all don't want those numbers there, we can take them off. I think -- We put them on. We thought that made it clearer.

**DR. ZIMMERMAN:** Two other comments. One comment would be to list the websites of all the organizations that are endorsing this schedule instead of just the CDC's, and --

**DR. MODLIN:** I think that's a decision we actually made at the last meeting, to do just that, and that was the plan. Unfortunately, at the October meeting when this came up, it was a bit late.

**DR. ZIMMERMAN:** And the other question that I would have is, I think I understand the rationale for having pneumococcal polysaccharide, but it is getting you know, the question of where you call the point, and I guess I favor influenza, and I'm wondering if we're pushing it a little too far with the pneumococcal polysaccharide. It's not indicated in pure asthma or simple asthma. So if you're really getting to more of the children with sickle cell and other things, then, again, where do you call the line? I wonder if we're going to get more confusion with adding that --

**DR. MODLIN:** How do others feel about including polysaccharide -- pneumococcal polysaccharide vaccine? Rich?

**DR. CLOVER:** Well, one advantage of having it on there is, for those practices that stock both, it clearly delineates where one should be used and where the other one shouldn't. And from that perspective, I think there's an advantage of listing both.

**DR. SMITH:** Yeah. I think it's a reminder that there are two different pneumococcal vaccines.

**DR. MODLIN:** It's one of the most common questions that come up these days with -- since the licensure of the conjugate vaccine as to how the two vaccines are used in different settings and vis-a-vis one another in the same patient. So I think at least for a period of time, there's probably more to be gained than to be lost in the realm of confusion.

Stan?

**DR. PLOTKIN:** This is another issue.

**DR. MODLIN:** Sure.

**DR. PLOTKIN:** Is that all right?

**DR. MODLIN:** Sure.

**DR. PLOTKIN:** I'd like to ask the Committee just how serious are they about recommending a birth dose of hepatitis B. Because if the Committee is serious about that, this is an opportunity to so indicate. And there -- I mean, there are several graphic ways this could be done, but I'd just like to point out that in -- I think looking this over, in every case where there is a bar that is indicating a range of recommendations, it really makes little difference, either programmatically or immunologically, which -- at which point the vaccine is given. In the case of the first dose of hepatitis B, there is both programmatic and immunologic implications. So if you're serious about it, now is the time to do something about the way this schedule looks.

**DR. MODLIN:** That's a good point, and we raised this issue yesterday, of course, when we were talking about the hep B statement, which is not finalized yet. But there's no question that this will need to be consistent with -- at least from the ACIP standpoint, consistent with the language in that statement. I think already consistent with Red Book Committee policy.

Rick?

**DR. ZIMMERMAN:** This is related just to that point. It used to be, if I recall correctly, in previous years where hepatitis B was moved over within that column -- not in 2001, but I think back in 1999 -- and I think the reason that some of us, including myself, spoke for putting it in the middle was that we have existing policy that prefers combination vaccines, and then you end up with an inconsistency. If you prefer a birth dose, and yet you also prefer a combination vaccine, you have an inconsistency. And so by moving it back in the center, it kind of resolved that potential inconsistency.

**DR. MODLIN:** I think this is an inconsistency that's going to be resolved when we make our decision regarding hep B vaccine with the hep B statement, which, hopefully, we'll be doing when we finalize that at the October meeting. So I think we kind of need to be prepared to do it at that time.

Other comments? Deb Wexler?

**DR. WEXLER:** Debra Wexler, Immunization Action Coalition. I have four comments.

The first one is, I would really like to see on the table the bar going across that every age is reflected, so that we don't forget to assess seven- to 10-year-olds. Currently -- you know, you could take space out of that first column where it's really wide where other vaccines are listed, and add a seven- to 10-year-old so that doctors remember to do catch-up at the seven- to 10-year-old visit, as well. And then I would like to suggest that you change the 14-to-18-year-old range to 13-to-18, and that way all the ages are reflected from the five-year-old to the 18-year-old.

My second suggestion is that I think we're being a little inconsistent -- and I'm on the working group. I would like to see, for catch-up vaccination, that the Td be extended for catch-up to 18 years of age, because we're still catching up kids who haven't had their doses when they come from other countries or whatever, for whatever reason, and that IPV should be extended to 17 years of age, through 17, so there should be a green band there, and that Hib, for kids who need catch-up, go up to age five.

**DR. WHARTON:** Could I -- do you want me to comment on

that or you want to go on --

**DR. MODLIN:** Yes, please. Please do.

**DR. WHARTON:** This was an issue which did come up on the working group conference call about, well, what do you mean by catch-up, for how long is catch-up in order and when should we be caught up. And the catch-up bars are confined to vaccines that either have relatively new recommendations or relatively new emphasis on -- on policy implementation. And given that we've been recommending either DTP or DTaP at four to six years of age for a long time, for example, was -- that Td, there's been a longstanding recommendation for use of Td boosters, and so there isn't a green bar. What we've got here is a yellow bar, which is the first Td dose. It is not catch-up. This is a routine recommended booster.

You know, we could put more catch-up in there, but I think if we do that it will -- you know, we could have hepatitis A catch-up, too; we can have catch-up for anything -- it will decrease, I think, the impact that those vaccines that are highlighted would have, but it's up to you-all how we do it.

**DR. WEXLER:** I just think that by not including it, it gives a message -- I mean, doctors don't know that the reason that you're not putting it in is because it's an old recommendation and -- and I just think we should be consistent throughout the table.

**DR. MODLIN:** Melinda has a good point. If you look at hepatitis -- I'm sorry. With Hib vaccine, it doesn't make a whole lot of sense to be catching kids up after five or six years of age in the sense that almost all of the disease that we see, at least in normal individuals, is confined to under five years of age.

**DR. WEXLER:** Right. You would stop it at five for kids who didn't get any previous doses of Hib. I mean, that's why I thought the green band would just go from the -- where the Hib dose four stops to five years of age, and that's all the further it would go on Hib.

**DR. MODLIN:** I see.

**DR. WEXLER:** My last -- Can I make my last comment? I'll make my last comment.

I think it's confusing to have the PCV7 overlaying the PPV23. I think it's -- and that diagonal line is hard to look at, and I really understand, and I think if

there's any way you can squeeze an extra line in there for PPV23 so that they're not overlapping and confusing providers, I think that would be really helpful.

**DR. SMITH:** I think it might also be helpful to hear from Diane Peterson, because I guess this format has been essentially -- or some of it has been tested in the field in Minnesota this past year, at least.

**DR. PETERSON:** Yes, I'm Diane Peterson from the Minnesota Department of Health. And we have used this format now since 1995, and I presented this to the group last year. We haven't -- I mean, the comments that Debra makes I think are good, and we've found over the years with our hot line that if there's anything that can be misinterpreted, it will be.

For example, under the hepatitis B footnote where the third group of infants born to mothers whose status is unknown, where it now says that they should get hepatitis B vaccine within 12 hours of birth, there's no information about when you give dose two and dose three. And I know that this is the way the Harmonized Schedule has read the last couple of years, and we did actually reprint it once -- one year in that manner,

and I personally took a call from a clinic where everyone in the clinic interpreted that to mean that they only get one dose of vaccine, even though up in the top table it has all three doses indicated and these are just the footnotes, because in the first two groupings, it does talk about timings of dose two and three. So that's just an example of how something can be misunderstood if it's not very, very clear.

In terms of adding the additional columns, I will say that what we've done here is to try to conserve as much space as we can because you know it's getting smaller and smaller font size as we keep adding more vaccines and more age groupings, having added the 24-month column just in the last couple of years. And I'm not sure -- we've not had questions about persons -- providers misunderstanding that they're not supposed to be doing assessment at other ages or not being -- doing catch-up at other ages, but I'm sure that some of that could be out there. And as much as we can emphasize that, I think that's important that we do that.

**DR. MODLIN:** Georges?

**DR. PETER:** Yes. Well, I think one of the issues here is we are trying to determine just how much information we can include, and we've very definitely reached the point of diminishing returns when we remember that the vast majority of people who look at the schedule do not look at it in the detail that this Committee does. And I am very, very concerned that our attempt to be all-inclusive and to perhaps take the place of some of our detailed recommendations, we would indeed lead to confusion and lose some of the initial purpose of having a universal schedule.

So, you know, I think, you know, it's not only questions of lumpers versus splitters, and I have my own viewpoint. It's interesting that we hear the disparity in viewpoints as to just how much can we include, and that's a philosophical issue we need to decide.

**DR. MODLIN:** Walt, did you have a --

**DR. ORENSTEIN:** I was going to say something very similar. I think the whole purpose of this and the major criticisms have been that the previous schedule is just so complex, and I think we've never designed

this to handle every situation. And I think we need to be frank about that and keep it as simple as possible. And the more we add columns of vaccines, the more concern I have and that's one of the concerns I have. For example, even though I'm very supportive of the influenza, putting it in I think just opens up the door to a whole variety of other selected use vaccines, as much as I would love to have it in there. And I think it probably ought to wait -- we ought to think about universal kinds of -- hepatitis A is universal in the whole population in whole states.

**DR. MODLIN:** Geoff?

**DR. EVANS:** I may not get high marks for timing, but I'm wondering if we might consider putting something in about safety, that is, the legal requirements as far as reporting and the Vaccine Injury Compensation Program. Because all the vaccines that are listed above the line have those requirements, and there's -- nowhere is it mentioned, and this is the most widely-circulated document, that's what I understand, having to do with immunization each year. So perhaps two, three, four lines having to do with both VAERS and

the compensation program, just so providers can be alerted to their existence, and websites or telephone numbers.

**DR. PETERSON:** Could I make a comment?

**DR. MODLIN:** Yes.

**DR. PETERSON:** On the Minnesota schedule, we do have on the back side catch-up schedules, which Melinda alluded to the work group hasn't had a chance to deal with, and on the very bottom of it we talk about reporting vaccine reactions, the VAERS number, the website, and also reporting disease.

**DR. MODLIN:** Dr. Seward?

**DR. SEWARD:** Are you taking comments on footnotes or are we not doing that?

**DR. MODLIN:** No, on everything.

**DR. WHARTON:** No.

**DR. MODLIN:** Oh, we're not? Okay.

**DR. WHARTON:** Well, you can tell me later.

**DR. MODLIN:** Let's see -- Jon?

**DR. ABRAMSON:** Yeah, I would have a suggestion, and that is, can we take the stuff under the red dotted line and move it to a second page? The reason I would prefer

that is this

is -- it's -- I can see how dense this is going to get. If you move it to a second page, if people want that second page, they can paste it up. I mean, there's nothing stopping them. But then the heart and soul of this whole -- of this whole thing is above that dotted line.

**DR. WHARTON:** That would take hepatitis A off.

**DR. SMITH:** Which has been on there.

**DR. ABRAMSON:** My problem with it, as I say, is if you think -- people are going to look at this and think that's it. That is not it.

**DR. MODLIN:** How do others feel about that? Natalie?

**DR. SMITH:** Well, you know, obviously, the discussions were held in the past when I wasn't a member of this Committee, so some of you may know, but why you chose to put hep A on last year's schedule, as well. I think it's going to cause confusion if you suddenly take hep A back off again, for instance.

And I am -- I do think it's important to emphasize flu. Whether we need more language

in -- at the top saying this isn't -- you know, there

are other vaccines that may need to be considered or something else, we could consider, but . . .

**DR. MODLIN:** How do others feel about the dotted line? Dennis?

**DR. BROOKS:** I actually like the format. You know, usually in our settings, the nurses have it up on one board and, you know, they don't want to have a second page. They don't want to have anything else. They just want to look at that and deal with that. So the dotted line doesn't really bother me. And you know, influenza is a key component of our preventative health in our setting and, you know, I'm glad it's on here, actually.

**DR. MODLIN:** Yeah. I think we have to be listening to the people on the front lines who are actually using this document. It's a whole lot different than -- and Okay. Richard?

**DR. JACOBS:** Richard Jacobs, Little Rock. I'm a member of the Academy's education program, here as a guest, but I'd make two comments. We get a lot of feedback through our educational process at the Academy, but if you change the language on the hep B

or you move the bar, I think it's going to cause a great deal of confusion to the practicing pediatrician who has finally come to understand my practice has no surface-antigen-positive women or a very low rate. I can look at this schedule and start my schedule at two months, and that's within the guidelines. The more you change it back toward a mandatory feature for the birth dose for all those populations, I think you're going to create a tremendous amount of confusion and frustration.

Second, the Prevnar conjugate pneumococcal vaccine in the green, could you not also argue that you should have a green catch-up by the Hib at the same -- if you have no one who's previously not immunized? I think that's confusing and I would like to see at least that component moved to a catch-up table where it is preferred for select populations, but you could also argue for the 23-valent unconjugated. And I think that is going to be confusing, and I think a lot of pediatricians at least are going to look at that and say, I should be giving this at this age group. And like was mentioned earlier, maybe they don't like to

tape the second page up, but that second page in the current handout has got all the footnotes that explain everything. So if they don't want to put a second page up in public health or doctor offices, that table has got to be clear and free-standing. And I think that the conjugate pneumococcal, the 23-valent, and if you change the hepatitis B, I think it's going to cause great confusion and immense frustration.

**DR. MODLIN:** Other comments?

(NO RESPONSE)

**DR. MODLIN:** Melinda, fortunately, we have one more meeting before we have to -- I don't think that there I don't think that there's any question that the Committee is -- and all the comments have been positive with respect to changing the format and, obviously, going in the right direction there, except for maybe Dr. Zimmerman.

**DR. ZIMMERMAN:** No, I think we're in the right direction. I think the question -- since there's other groups to work with this, obviously, there's going to be an iteration that comes back. I think it would be helpful if we could get the next iteration and

have a conference call in July, rather than waiting till October.

**DR. MODLIN:** That's the whole point. And clearly, I think that will be the plan and that's what we'll do, and we will have to finalize this, at least for this Committee, in October. So I don't hear any further discussion.

Melinda, is there anything else, feedbacks on specific issues that you would like at the moment?

**DR. WHARTON:** I guess what I would -- I'd like to just present a proposal for how we're going to deal with these things on the next round, based on the discussion I just heard. And if I have heard it wrong, please tell me. We will, I think, try to keep the pneumococcal polysaccharide vaccine there, and we will keep influenza and hepatitis A there with the dotted line. And I'm not sure what we're going to do about hepatitis B bars and name placement, but I guess we can wait till the hepatitis B statement is finalized to see what that final wording is.

Do those seem like reasonable decisions for this next iteration? Okay?

The other issue is -- that I would like some guidance from the Committee on is, the working group did like the idea of having a catch-up schedule that, if it were developed and improved in time, could be published concordantly with the Harmonized Schedule. Now, catch-up schedules are complex and we've collected them from a number of locations. I think that the most aesthetically pleasing one is the one that Diane just held up. And I don't have it on an overhead, but it looks pretty nice. Of course, there's the same problem with catch-up schedules we have with the Harmonized Schedule in that they cannot capture all the baroque complexities of existing recommendations, and it's easy to find things that are not -- that do not -- that don't cover every situation.

But how does the Committee feel? Does the Committee wish the work group to attempt to develop a catch-up schedule that potentially could be published concordantly with the Harmonized Schedule?

**DR. MODLIN:** On a second page or on the back? Yes.

**DR. WHARTON:** No promises we're going to be able to do this. But who wants to try?

**DR. MODLIN:** It looks -- there seems to be -- the answer seems to be nods yes.

**DR. WHARTON:** Okay. So that's it for us.

**DR. MODLIN:** Terrific. Melinda, thank you. Obviously, we'll be revisiting this in October. Shall we go on to the discussion of the Adult Harmonized Schedule? And Dr. Sneller is going to lead the discussion.

**DR. SNELLER:** Good afternoon. During the past several years, the Adult Immunization Working Group had considered a harmonized immunization schedule for adults, very similar to the one that -- that's for the childhood vaccinations. A subgroup representing the provider organizations and the NIP staff have initiated discussions on the harmonization process. And during the next few minutes, I wanted to summarize the efforts of this group towards developing a harmonized adult immunization schedule.

The partners in this effort were Dr. Kathy Neuzil and Dr. William Schaffner representing the American College of Physicians, Dr. Richard Clover representing the American Academy of Family Practitioners, and Dr.

Stanley Gall representing the American College of Obstetricians and Gynecologists. I apologize for the mistake. These three provider organizations had issued immunization schedules to their membership at least once since 1991 when ACIP had published their update on adult immunizations in the MMWR. Now, Dr. Bill Schaffner and Dr. Clover are also members of the ACIP Adult Immunization Working Group, so they indirectly represented the Adult Immunization Working Group of the ACIP, as well, in this effort.

Establishing standard immunization schedules for adults provides standard guidelines for adult vaccination providers nationwide, improving visibility among private providers. And as you know, most of the adult immunizations are provided in private doctors offices rather than by state organizations or state health departments.

Now, in addition, the process of harmonization itself increases the focus of provider organizations on the adult immunization issues, hoping that it will motivate these organizations to update immunization recommendations to their members. Including an

annual review and revision like the childhood immunization schedule, the adult immunization schedule could provide an opportunity to highlight the most important messages and changes in adult immunizations that the media could carry to the public and providers on an annual basis. Again, as with the childhood immunization schedules, harmonizing the recommendations for adult immunization by provider organizations and presenting this information in a single and simple format could increase adult immunization services by private providers.

The U.S. Public Health Service has new and more ambitious targets for the next decade. During the next decade, we want to achieve a vaccination rate of 90 percent of the persons 65 years and older and 60 percent for persons 18 to 64 years of age for whom these vaccinations are recommended. If you will recall that of the HP 2000 targets for adults, the only one that was achieved was the influenza vaccination among persons 65 years and older. And this, too, was not achieved among African-American and other minority populations.

We failed to reach the other adult health targets, including that for the pneumococcal polysaccharide vaccine among older adults, regardless of their ethnic group. We need to be more aggressive, perhaps, in getting the providers to include vaccinations for their adult patients. NIP is committed towards increasing adult immunizations, and developing a simple, structured, harmonized schedule is an important step.

The process of harmonizing the adult immunization schedule is proceeding in the following manner. First, we conferred and identified a working group representing the provider organizations that had issued immunization schedules to their members. This has been completed.

We are now at the second step, comparing the published immunization recommendations for adults in order to determine what needs to be harmonized. When step two has been completed, we will produce a template or a format of a schedule for the approval of the ACIP and the provider organizations.

In the final step, the working group would also develop

a process for an annual review, revision, and publication of the harmonized adult immunization schedule, similar to that one being used for the childhood schedule.

We compared the recommendations of the ACIP, the ACP's Green Book, and the ACOG's technical bulletin on the immunizations during pregnancy and rubella in pregnancy. ACIP's recommendations titled "Update on Adult Immunization" was published in November, 1991, and other vaccine-specific recommendations have been published subsequently. ACP and the Infectious Disease Society of America published the guide for adult immunization with the green cover in 1994, and that's why it's called the Green Book. The ACOG has published technical bulletins in 1991 and 1992, and their recommendations were adopted from the ACIP's recommendations, so they are fairly well harmonized. For the most part, ACP's Green Book and ACIP recommendations were identical or harmonized. So we're concentrating on the differences, either real or perceived by virtue of the written text.

Now let me highlight some of the harmonization issues

that we are considering. In this first example, the recommendations of the ACIP and ACP are truly different. ACP offered two options for the Td booster, the decennial booster for all persons or, for persons who have evidence of completing the primary three-dose series, a single booster at age 50. ACIP does not offer the option of a single Td booster at age 50. The process of harmonization then could provide the opportunity for ACIP and ACP to discuss the Td booster schedule and come up with something that is harmonious to both, and to all of us.

Here is an example where ACIP and ACP statements are conflicting and confusing. Regarding the revaccination of older adults with a 23-valent PPV, ACIP recommends a second dose of vaccine for all persons 65 years and older if they received the vaccine five years or more previously and were less than 65 years at the time of primary vaccination. ACP recommends that revaccination should be strongly considered at age 65 for persons with high-risk conditions if the initial vaccination was more than six years earlier. Not only is there a difference in the strength of the

recommendation ACIP has recommended, which is stronger than the ACP has strongly considered, there are differences in the indications for revaccination. For example, in the time upon -- since initial revaccination, ACIP says five or more, ACP says six or more; ACIP specifies age at first vaccination, ACP's recommendation is not clear whether it refers to a single revaccination or not.

Another form of disharmony is where ACIP and ACP differed in the strength of recommendation. For example, the ACIP and ACP recommendations for measles vaccination of persons born prior to 1957 using MMR differed in the wording used. ACP [sic] is stronger. It says should be offered. ACP was more permissive. It says may be considered. This difference changes the strength of the ACP versus the ACIP recommendations for measles immunity and MMR use among health care workers who were born before 1957.

In this next example, it highlights the differences in recommendation which may no longer be relevant for -- this is revaccination of persons with the 23-valent PPV for persons who have been vaccinated

with the 14-valent PPV. ACP -- ACIP recommends patients who have received the earlier pneumococcal polysaccharide vaccine containing [inaudible] from only 14 types of strep pneumonia should not be routinely vaccinated with the 23-valent pneumococcal polysaccharide vaccine as the increased coverage is modest, but both groups agree that people with high-risk conditions should receive at least one dose of the 23-valent vaccine. So, generally, there is agreement, but the wording is just a perceived difference.

In the ACP, it says revaccination with the 23-valent vaccine is recommended for all persons who received 14-valent vaccine if they are at highest risk for serious or fatal pneumococcal infection. So ACIP and ACP recommended vaccination of -- I'm sorry.

So this may be a moot point at this time because most of the people who have been vaccinated with the 14-valent are probably already vaccinated, at least revaccinated with the 23-valent, but these are the issues that are being considered during harmonizations.

In addition, ACIP has issued recommendations for hepatitis A, meningococcal vaccine, varicella, and Lyme disease since 1991, and ACP had not published additional recommendations for adult immunizations, and these probably should be included in their messages to the ACP membership.

Several formats are available to present the immunization schedule for adults, and these are being considered, and these are already in the packets that were on your table this afternoon. One is, of course, the graphic representation used adapting the format that the Minnesota State Health Department has been using. Thank you, Diane Peterson and the Minnesota State Health Department. And the handout that you have will show you that the only -- the main difference that we are considering is the collapsing of the first two columns so that it reflects ages 19 through 49 so that we don't have to change it every year when people age out of the age when measles vaccine should be considered.

There's a tabular format that's also there which is specifically for people with high-risk conditions,

making it easy for the subspecialty practitioners to be able to look for their patients by their chronic disease or condition and be able to look at the vaccinations that are indicated. And there is another tabular present summary of vaccinations for special populations. This is the graphic format that the Minnesota State Health Department is using, and the -- what we are actually considering is collapsing the first two columns.

The advantage of this would be to develop a one-page schedule very similar to the childhood schedule that has been presented before. And by having formats that are very similar, perhaps distinguishing them by the colors used or even harmonizing on the colors used, might make it more user-friendly for the people who are actually providing these immunizations.

One of the key requirements to make adult immunization schedules successful is to make it easily available to the public, as well as to the providers. The most successful channels for publication of the immunization schedules are the channels that have been successful already in promoting childhood

immunization schedules that are indicated above. These are the Immunization Action Coalition's mailing list, the state health departments also have their communication channel and mailing list of newsletters, and the medical specialty groups newsletters that are available on the web or through the membership by mail. Once available, it is conceivable that the adult immunization schedule would also be published by the media and other community-based organizations serving older adults, or those organizations that are committed to prevent and manage chronic diseases such as diabetes and smoking-related disorders.

So, in summary, a harmonized schedule is needed to vitalize the adult immunization services by private and institutional providers. We believe that the collaborations with provider organizations and ACP are very crucial in motivating the members of the provider organizations to vaccinate their adult patients. A single format is needed to make the schedule user-friendly and wide publication of the harmonized schedule and annual revisions are needed to improve the adult immunizations as part of the regular clinical

care.

This morning when the Subcommittee of the Adult Immunization Working Group had met and discussed, there was a general feeling that we should -- that we should not -- we should not wait until the entire harmonization with the provider organization -- if there's going to be a substantial delay in harmonizing a schedule, that we should work with the provider organizations to publish an article or a report showing a table indicating the areas of harmonization and then describing the areas of disharmony or the areas that are being negotiated at the present time, and then provide updates later on.

**DR. MODLIN:** Terrific. Very, very, very nice work.

**DR. SNELLER:** Thank you.

**DR. MODLIN:** Congratulations.

Bill Schaffner, Kathy Neuzil, did either one of you want to add anything at this point before we open things up?

**DR. SCHAFFNER:** Well, I think we're in debt to Rich Clover, as well as all the folks who were indicated on the slide. Vishnu, thank you very much for bringing this forward. This could be a milestone in adult

immunization activities. I think it will be the focus whereby we will gain the attention of many of the scholarly and professional societies that relate to adult patients and their practitioners. And I like the idea of going ahead, getting as much harmony around the table initially, and then using that subsequently to gain the support of the other organizations. And I think everyone who's participating in this is very committed to the success of this project.

**DR. MODLIN:** Terrific.

**DR. SCHAFFNER:** I guess I might add that probably -- almost all of the documents that have been mentioned are a bit aged, and I think they're virtually all, except for maybe our own here, our ACIP document on adult immunization -- they're all under revision presently, including a -- the documents from ACOG.

**DR. MODLIN:** Rick?

**DR. ZIMMERMAN:** Three comments.

First, there is -- on the American Academy of Family Physicians website, there is an immunization schedule, and that will be another one that has to be harmonized. I don't think there will be major problems, as it's not

as detailed, but that'll have to be brought in. The second one, I guess I would encourage maybe a slightly different tact. I think that agreement potentially could be reached on something that looks like the Minnesota schedule, which is just an age-based, by the organizations in time for this. I think working out the details -- revaccination, high-risk groups, et cetera -- is a major effort that would take years. But I think on the issue of something that looks just as simple as the Minnesota schedule, not giving a great deal of detail but here's your vaccines by age, I think we could achieve harmony on that part fairly quickly, given -- you have to have a little footnote, this organization does Td different than that one, but otherwise we're pretty much in harmony. It's just the high-risk and revaccination where I think there's differences.

**DR. MODLIN:** Stan, anything you want to add? Okay. You've been part of the process.

Ray?

**DR. STRIKAS:** Ray Strikas, NIP.

I want to commend the work group for a nice beginning,

and it's very encouraging to see this. My only thought is to consider, when would you publish this? And the ideal time to put another burden on the flu season is publish it around August or September would be one thought, not the only one, but the more significant suggestion is don't publish it at the same time as the childhood schedule because the Academy of Family Physicians and CDC have plenty to do at that time and I would shoot for a different time of the year. And again, perhaps August, September is a better time. And I don't know if it's possible to get it done, as Rick Zimmerman suggests, a simple schedule. I would differ, though. The Td issue is a significant one when one group said booster at age 50 is sufficient when we have a Td shortage. I think that one has to be resolved before you publish anything about Td boosters.

**DR. MODLIN:** Maybe it will be that in the future we could plan on completing the harmonization process annually at the June meeting, which would certainly achieve that goal and put us out in a different cycle than the childhood immunization schedule.

Other comments? Questions?

(NO RESPONSE)

**DR. MODLIN:** I think you have general enthusiasm for proceeding, and I'm sorry that Trish Gardner is not here to see this happen.

Is Nancy Rosenstein here? We're running considerably ahead of schedule at the moment.

**UNIDENTIFIED SPEAKER:** Neither presenter is here. You may want to take a short break.

**DR. MODLIN:** Okay. Let's break until -- I guess 2:30 and try to start at 2:30 if we can.

(BREAK FROM 2:08 P.M. TO 2:35 P.M.)

**DR. MODLIN:** All right, could I ask people to please be seated so we can continue. Could I ask people to please be seated.

The next item on the agenda will deal with some relatively new information that has become available regarding meningococcal disease in -- laboratorians? microbiology laboratory workers. This will be led by Dr. Nancy Rosenstein. Nancy?

**DR. ROSENSTEIN:** There have been several reports recently of laboratory-acquired meningococcal disease. These have hit the media really strongly,

and they've also caused a lot of concern in the health care community. Of course, we want to make recommendations not based on these case reports but based on data, and Jim Sejvar will tell you soon about the data.

But the bottom line is that we found that there was a high rate of meningococcal disease among laboratory workers. Based on this, we're recommending enhancement of the current guidelines for laboratory safety, as well as a reinforcement of the current ACIP guidelines for vaccination.

There are actually a lot of stakeholders on this issue, and there have been multiple groups that have already contributed to the development of these guidelines. We're actually not recommending a change or suggesting a change in the current ACIP guidelines, but we felt that the ACIP members should hear this story and be given the opportunity to make suggestions. So I'll turn it over to Jim now.

**DR. SEJVAR:** Thanks, Nancy.

First off, you should have received and should have in front of you an updated draft from the one that we had

circulated previous to this meeting. It differs slightly, and this draft has essentially evolved as we've continued to refine our numbers and our recommendations.

In the United States, approximately 3,000 cases of meningococcal disease are reported each year, and the case fatality rate is about 12 percent. Neisseria meningitidis is transmitted by close direct contact with respiratory secretions. Serogroups B, C, and Y are responsible for most disease in the United States. The current quadrivalent polysaccharide vaccine, the only vaccine licensed for use in the U.S., protects against serogroups A, C, Y, and W135, but provides no protection against serogroup B. In addition, while safe and effective, its efficacy is not 100 percent, and its limited duration requires repeat doses.

For laboratory workers there are recommendations for both laboratory safety and for vaccination. In the CDC/NIH publication, Biosafety and Biological and Biomedical Laboratories, Neisseria meningitidis is classified as a Biosafety Level 2 organism. Guidelines state that personal protection in the form

of laboratory coats and gloves should be worn, and facial protection should be used as appropriate.

The guidelines further state that primary barriers, such as biological safety cabinets, should be used when performing procedures that might cause splashing, spraying, or splattering of droplets. However, the guidelines do not clearly define which procedures carry with them this increased risk.

In 1991, two fatal cases of probable laboratory-acquired meningococcal disease were reported in the MMWR. These were the first reported cases in the U.S. of meningococcal infection acquired in the laboratory setting, and they prompted CDC to recommend that work involving high concentrations or large quantities of organisms should be performed in a Biosafety Level 3 laboratory. Laboratory workers in this setting should be immunized.

In 1997, ACIP recommended that research, industrial, and clinical laboratory personnel who were exposed routinely to Neisseria meningitidis in solutions that may be aerosolized also should be considered for vaccination.

The general assumption of these recommendations was that primarily research personnel would be frequently exposed to these quantities, and we think that many research and industrial laboratory personnel have been vaccinated. The risk among clinical laboratory personnel, however, has been less clear.

Last year CDC was notified of three cases of probable laboratory-acquired meningococcal disease. The close proximity of these three cases in time prompted us to assess the frequency of these infections and to reassess the guidelines for laboratory safety and vaccination.

We placed a request for information to members of various infectious disease, microbiology, and infection control professional organizations via electronic mail discussion groups. A case was defined as a laboratorian with meningococcal disease in which the history was consistent with acquisition in the laboratory setting and in which the serogroup matched a recently-handled specimen.

We collected basic descriptive epidemiologic information and, given the known mechanism of

transmission of meningococcus, we collected information on behaviors and laboratory practices that might have predisposed to exposure to aerosols or droplets.

Including the three cases that prompted this survey, we identified 16 previous unreported cases of probable laboratory-acquired meningococcal disease in the past 15 years from six countries. Among these 16 cases, most were female. About half the cases were due to serogroup B and half were due to serogroup C. Eight cases, or 50 percent, were fatal.

In the ten cases where information was available, the median interval between handling of the probable source specimen and symptom onset was four days. In all 16 cases, the laboratorian was a microbiologist. None of the reported cases occurred among workers in hematology, chemistry or pathology.

This slide shows all cases reported for the past 15 years, including five cases recently reported from the U.K. in blue, ten previously unreported cases, plus the two cases reported in the 1991 MMWR from the United States in yellow, and six previously unreported cases

from various other countries in red. Of the 16 previously unreported cases, six were from the U.S. in the past five years. As there are no accurate estimates of the number of microbiologists in the United States, we had to estimate a denominator of laboratorians at risk.

Approximately 3,000 isolates of pathogenic meningococcus are cultured in hospital laboratories each year. We estimated that each of these samples is handled by an average of three microbiologists in the course of a laboratory investigation. Our time period was five years. This yields an average attack rate of 13 per 100,000 population at risk per year, compared to a rate of 0.2 per 100,000 among adults aged 30 to 59, the age group of most laboratory workers.

Many of the case microbiologists were reported to have been reading plates, restreaking agar plates, and performing serogroup testing at the bench top, all of which are common, microbiologic laboratory procedures. Fifteen of the 16 case microbiologists performed these activities outside of a biosafety enclosure or aerosol screen.

We conclude that in the U.S. rates of laboratory-acquired meningococcal disease are much higher than initially suspected and represent a substantial occupational hazard to microbiologists. In addition, the case fatality rate was high. While this certainly may be a result of reporting bias, it is also possible that this reflects the highly virulent strains and high density organisms encountered in the laboratory setting, compared to natural transmission. All of the cases were among microbiologists, and not workers in other sections of the laboratory, suggesting that exposure to meningococcal isolates and not patient specimens represent the increased risk. And although it does not represent a breach in laboratory safety technique, according to current guidelines for BSL-2 or Biosafety Level 2 organisms, in nearly every case, manipulation of the isolate was conducted on the bench top and not in a biosafety cabinet. Similarly, a recent U.K. study found that there was a high risk of disease associated with manipulating suspensions of Neisseria meningitidis outside of a biosafety cabinet.

All of the cases that we detected were in clinical laboratories, and we suspect that this is because safety guidelines may be stricter in research and industrial laboratories. In addition, a higher proportion of these personnel may have been vaccinated.

Based on these findings, we suggest that the emphasis for prevention of laboratory-acquired meningococcal disease should be on laboratory safety and the implementation of additional safety precautions when manipulating meningococcal isolates. Specifically, isolates of Neisseria meningitidis should be manipulated with the use of a biosafety cabinet. If a biosafety cabinet is not available, other methods of aerosol protection may be appropriate. If adequate safety equipment is unavailable, manipulation of the isolate should be minimized and the isolate transferred to another laboratory.

Because implementation of additional safety precautions when manipulating meningococcal isolates should greatly minimize the risk of infection and because of the limitations of the vaccine, we think that

the quadrivalent polysaccharide vaccine should be used as an adjunctive measure in the protection of microbiologists. Consistent with previously outlined guidelines, research and industrial laboratory scientists who are exposed routinely to Neisseria meningitidis in solutions that may be aerosolized should consider vaccination. Further, microbiologists should be educated about the increased risk of infection and the seriousness of illness so that laboratory leaders and individuals can make informed decisions regarding vaccination.

In instances where Neisseria meningitidis is inadvertently handled outside of a biosafety cabinet, antimicrobial chemoprophylaxis should be considered for the exposed microbiologist.

Therefore, we don't think these recommendations conflict with the current ACIP guidelines, which again state that research, industrial, and clinical laboratory personnel who are exposed routinely to Neisseria meningitidis in solutions that may be aerosolized should be considered for vaccination. We would, however, suggest that these issues be

incorporated into the next ACIP guidelines.

Our next step is to publish in MMWR, incorporating recommendations for laboratory safety and vaccination. We anticipate the endorsement of this MMWR by the American Society for Microbiology, as well as other stakeholders. We plan to initiate prospective surveillance for cases of laboratory-acquired meningococcal disease to continue to assess the rates among laboratorians and the effectiveness of the recommendations.

And finally, we would encourage the assessment of current laboratory safety practices. Thank you.

**DR. MODLIN:** Thanks. Questions and comments for Dr. Sejvar? Lucy?

**DR. TOMPKINS:** I have some questions about what type of exposure was really relevant here. For instance, the vast majority of meningococs that are isolated in the clinical lab aren't in spinal fluid. They're in sputum cultures. And to read all sputum cultures in a biological safety cabinet is clearly not realistic. I wonder if there was any one of these cases where, in fact, all they did was actually open the plate and do

the analysis, or whether it's really the handling of the concentration of the organism when you're doing serological group serotesting or species identification and it's really the aerosol that makes the difference.

And the second point I would make is that I think it's completely unrealistic for you to expect someone to transfer their isolate of suspected mening to another laboratory if they don't have a biosafety cabinet. I think there has to be another way to deal with that.

So could you answer my question about whether it's merely the reading of culture plates, say, of sputum culture plates, that was an increased risk factor or do you think it really was the stuff that took place down the line?

**DR. SEJVAR:** Well, you know, as far as at least from the six cases from the U.S. that we used to calculate the rates, we were able to ascertain that these isolates were cultured from either blood or through the spinal fluid. None of those cases were cultured from respiratory secretions.

**DR. TOMPKINS:** Okay.

**DR. SEJVAR:** I don't have data -- don't have data for all of the cases that we collected, but I'm working on trying to ascertain that.

Again, the -- on the basis of the information that we got back, the common -- the common theme was the manipulation of isolates of culture outside of the use of biosafety cabinets. Again, the fact that -- in terms of handling a patient's specimens, none of these cases were reported among individuals in a lab who handle only specimens.

**DR. TOMPKINS:** Right. No, I understand that. But you know, in reading the blood culture, for instance, most labs -- many labs use automated devices, and you don't know what you're going to get once the bell goes off until you've actually taken the sample out and plated -- and done the gram stain on it. Is that a dangerous step? I doubt it.

**DR. ROSENSTEIN:** You know, we've really struggled with this issue over the past six months, as Dr. Johnson can tell you since he was one of the initial cases. I guess I agree with you --

(LAUGHTER)

**DR. ROSENSTEIN:** He reported one of the initial cases. And what I would tell you is that we've done a great deal of vetting of these recommendations with our laboratory colleagues, both at CDC, the people who write the safety guidelines, as well as state health departments that reported these cases and ASM. And these issues have come up, but they really felt like this was the right thing to recommend, both transferring of the specimens -- although maybe it can't always be accomplished -- and that based on what we know, at CSF, a blood culture that is suspicious for meningococcal disease should not be handled on an open bench.

**DR. TOMPKINS:** Well, you know, I think you're not thinking about patient care if you're suggesting that the laboratory hands this thing off to another laboratory to make an identification. That's a critically important thing to be able to do. So there has to be some other way where a close -- close-fitting N95 mask, if you don't have a biological safety cabinet. But to say it should go to another laboratory, I think

is --

**DR. ROSENSTEIN:** Well, if you read the --

**DR. TOMPKINS:** -- just not acceptable.

**DR. ROSENSTEIN:** I'm sorry. If you read the recommendations, what we say is if there is not appropriate aerosol protection. And we completely hope that somebody will figure out if an aerosol guard or a TB mask is sufficient. But as far as we can tell, nobody has actually examined that. I think that you're correct, somebody should figure out whether that is sufficient. We're trying to make sure that people understand that we're identifying increased risk associated with common practices, such as reading these on the bench top. And then I think it is up to the laboratorians and other organizations to figure out if you really do need a biosafety cabinet or if a simple aerosol shield is actually sufficient.

**DR. MODLIN:** Dr. Hos-- Mr. Hosbach, Phil?

**MR. HOSBACH:** Thanks, John. Phil Hosbach, Aventis Pasteur. Hi, Nancy, how you doing? I just wanted to make a comment and let you know what we do at Aventis. I know there are limitations to the

polysaccharide because it is a polysaccharide and it doesn't contain mening B. However, for all of our workers who are in the manufacturing area, they are all vaccinated routinely every five years. That's within the package insert recommendations of routine boosters every three to five years.

We also draw bloods on these folks and they have adequate antibody responses and they are adequately protected during the course of exposure. So I just want to -- I'm wondering why you wouldn't recommend vaccination rather than saying "should be considered," because it seems to be very safe. We do it with our workers. And you'll also be seeing some data shortly published by Drs. Freshley [phonetic] and Rubin in JID relative to what's done in our area.

**DR. MODLIN:** Dave, did you want to address Phil's comment?

**DR. JOHNSON:** Yes, I'd like to speak to that if I could. I do think that's a relevant question for this committee. Our previous recommendations have been rather equivocal when it comes to laboratorians. And I think if we're in the right ball park for calculating

risk to microbiologists who handle meningococcal specimens, then what we've found is a considerably increased risk, and a higher risk than that for which we recommend vaccine use in outbreak control. Right now our recommendations talk about those who work in laboratories where they expect to encounter meningococcal isolates frequently in solution where they -- where it's likely to be aerosolized, and then we say should be considered for vaccination. So I think, without opening up the entire statement, that's a point that we may want to consider strengthening and being less equivocal on.

**DR. ROSENSTEIN:** Can I respond?

**DR. MODLIN:** Yes, of course.

**DR. ROSENSTEIN:** You know, we're cognizant of the fact that research laboratorians routinely get vaccinated. And in fact, research laboratorians at CDC routinely get vaccinated. But what we're struck by is that in research and industrial settings, laboratorians are exposed to the organism in high quantities and basically every day. And we think that there is a real difference in risk at one extreme between that person

and an individual in a clinical microbiology laboratory who encounters this organism once a year. And although I agree with you about research and industrial personnel, and we're pretty sure they're getting vaccinated, and maybe you -- are you -- certainly that at a busy academic institution where somebody is isolating mening every week, it makes sense to vaccinate them. But we were sort of struck by the fact that you would be vaccinating a lot of microbiologists for a very uncommon exposure and you still wouldn't be preventing serogroup B, which makes up half of these cases.

**DR. MODLIN:** Rich?

**DR. CLOVER:** Not that I want to open up our past recommendation, but when and if that ever happens, there is some wording in there that did strike me as you presented it. One was the word "routine." I don't know how, in a clinical laboratory, you can define what routine is. And I think that's -- maybe be re-looked at.

And the other thing I just want to raise a word is to I believe when we were talking about college students

and their risk of exposure, particularly freshman students, we were talking about an increased rate of around three per 100,000.

**DR. SEJVAR:** Three to four, uh-huh.

**DR. CLOVER:** And now we're talking about a subgroup of people who have, you know, 13 per 100,000. And we're not -- I don't think the wording is as aggressive for this subgroup as it is for college students. And I think there's an inconsistency there.

**DR. MODLIN:** Lucy, you're probably as close to the microbiology lab as any of us. How do you feel about immunizing microbiology -- clinical microbiology personnel?

**DR. TOMPKINS:** Well, I can't speak on behalf of the ASM and the group of microbiologists that you've spoken with. I would imagine they would prefer to see -- to still have the wording be "should be considered for," because I would guess that we can't mandate this vaccination for microbiologists who work in the institution. We only have a couple of mandated vaccines, and everything else is voluntary. So I think that -- for instance, my lab director, Ellen Jo

Brown, would probably highly recommend it for microbiologists and our set-up people. But in another laboratory in another situation, I think someone would just have to say, you know, the number of isolations that we make in the course of the year just doesn't warrant this kind of program where we would have to be vaccinating people every three to five years, including the labs where there's a rotational pool where there may not be, you know, the same cadre of people. So I -- although I completely agree with what Rich is saying. I mean we were -- strongly said, you know, college students should get this with a much lower risk than what you've calculated for microbiologists. I think the critical thing here is that you've opened up a whole can of worms that I never knew existed -- as I gleefully go around and show everybody the plate on plate rounds.

(LAUGHTER)

**DR. TOMPKINS:** And I still don't think bugs can jump off the plate into your nose, but you know, I'm going to be a whole lot more careful next time. And I think that's -- it's the educational effort that's behind

this study that is going to be the most important thing. So I don't think the -- I think the vaccination recommendation should -- personally think it should stay as "should be strongly considered." But it's up to the individual, I think, laboratory to make that decision.

**DR. MODLIN:** I also, Rich, think we have to be careful about this number of 13 per 100,000. I mean, as Nancy and Dr. Sejvar have already admitted, it's a back-of-the-envelope calculation, at best, and we really don't have a good number there to quote very broadly.

Let's go around -- Yes, Gary?

**DR. OVERTURF:** Putting on another hat here, as a medical microbiology director, I -- this has become an issue only because it -- depending on what the wording is here. It talks about whether we mandate this or not, and it also has to do with whether the laboratory then has to provide the immunization or whether it's elective and the person pays for it on their own. There are issues here, depending on how you word this. And for very large laboratories with large numbers of

microbiologists, that can become an issue. This has been a huge issue because it's been on the laboratories network the last six months, and I think most -- most laboratories I deal with are ready to step up right now and give me their right deltoid.

So I think -- my feeling among laboratorians right now is that they very want this -- very much want to accept it. The only issue really is who's going to pay for it right now.

**DR. MODLIN:** Bill?

**DR. SCHAFFNER:** Well, speaking as a former clinical laboratory director, just some recent experiences. This issue was brought to our attention it's received a lot of publicity -- by our laboratorians. And our hospital, on their representation, quickly made the vaccine available to them and they all volunteered to take it. I agree with Dr. Overturf. I think the laboratorians will be very interested in this.

Apropos of which laboratories, I don't think we recommend seat belts only when you're driving fast.

(LAUGHTER)

**DR. SCHAFFNER:** And my last observation is, the piece of this that I'm worried about is that prophylaxis piece. Apropos of the occurrence of meningococcal isolates in the laboratory in different circumstances, we're going to have to stock Cipro in the lab. I think that requires a whole lot of careful thought. Among other things, it opens up the institution's legal liability pretty widely.

**DR. MODLIN:** Chuck?

**DR. HELMS:** This is an interesting situation because I -- let me throw an analogy to you. If we're looking at a water system and we found legionella in it, what would be our response to that situation? Prophylaxis for the patients there, immunization, or would it be to try to find out what's wrong in the water system to account for that? I'd argue here that there's a big impetus here for research as to how these aerosols are generated. Is it simply use of this thing on the top of the table that's important? Is it something else that's going on in the lab? Has there been a change in medium that's occurred? What is the basis of it? I think we've got to look further than simply treating

the disease when it occurs, but it may be something more systematic going on in the laboratory.

**DR. MODLIN:** Other comments? Let me try to get a sense of the Committee as to whether or not the Committee feels a duty to make a change in our current recommendation. I heard some fairly strong opinions, at least in one direction. Is there anyone who feels that we should be revisiting the meningococcal statement, which was, of course, published about a year ago, at this time? Is this something that would require an update or a supplement to change the strength of the recommendation?

(NO RESPONSE)

**DR. MODLIN:** Something you would like to revisit in six months or a year's time to -- Rich?

**DR. CLOVER:** To me, the most important issue -- or maybe -- or an important issue, I should say, is the reliability of the numbers presented. Is there any way we could do a better job of understanding what the denominator is?

**DR. ROSENSTEIN:** We're open to suggestions, but having spent, you know, six months going back and forth with

different laboratory organizations, it's just not a number that's out there.

I should also comment that if you get rid of the three cases in 2000 that prompted us to do this, the number is significantly lower, but it's still seven of 100,000. So I guess I wish that that was true, but -- I mean, we're partly pushed to say something based on how hard this has been, hitting the e-mail and list serves and people sort of calling -- what exactly is the data, and so we felt really compelled that we had to get something out pretty quickly.

I also wanted to comment that, you know, the meningococcal conjugate vaccine is going to be licensed in two years, and I assume that as of next year, we're going to start working on a revised ACIP statement to incorporate the conjugate vaccine. And I certainly think at that time we should revisit the language for laboratory workers and for college students and sort of look at the whole statement. We are going to be doing that anyway, I presume, in about a year.

**DR. MODLIN:** Thanks, Nancy. Other comments or questions? Karen, is it going to be licensed in

another two years?

(LAUGHTER)

**DR. MODLIN:** I knew what her response would be. Phil?

**MR. HOSBACH:** It might take a little bit longer than that. I think -- we're going with the conservative estimates on this, and it might take about a few years. So it could be about three years. Three years rather than two.

**DR. MODLIN:** Okay. Thank you. Thank you very much. The final item on the agenda this afternoon will be some information and some education that the Committee has asked for in the past, and that is to have a -- sort of an introduction, a primer, to economic evaluation, an analysis for setting health policy. And so Dr. Corso will be taking us through this.

**DR. CORSO:** Hello. Thank you for inviting me. Let me introduce myself. My name is Phaedra Corso. I'm a health economist with the Division of Prevention, Research, and Analytic Methods in the Epidemiology Program Office at CDC. I have the dubious task of trying to get you excited about economic evaluation, very late in the day and very late in your busy agenda.

So I'm going to try to make this as dynamic as I humanly can. We're talking about economics here, so bear with me.

I have three objectives for today's session. The first one is just to provide you with a basic understanding of the economic evaluation methods, particularly cost-benefit analysis, cost-utility analysis, and cost-effectiveness analysis.

My second objective is to -- if you don't know already, interpreting some of the results coming from out of these -- coming from the economic evaluations are often very difficult and complex. So I wanted to talk to you about some of those issues.

And, finally, to close I'd like to talk about some of the economic evaluation tools and training opportunities we have here at CDC that you might be interested in.

When we think about setting health policy or making recommendations about national health policy, there are four components that we might think about. The first is biologic feasibility. And this really brings in the basic science of epidemiology, looking at

incidence, prevalence, what is the effectiveness and efficacy of our interventions. So in the vaccine world, this speaks to the question: Is there a vaccine available for the health outcome of interest?

The second component is technical feasibility. Once you've determined that a vaccine exists, you then need to think about how the vaccine might be administered. So that speaks to technical feasibility.

And then once you figure out a way for the vaccine to be administered, you really need to look at the political and social feasibility in that okay, are parents going to be okay with you administering the vaccine. In other words, does the vaccine pose some risks that the parents are not willing to accept or that society in general is not willing to accept.

And then finally, the fourth component of setting health policy is economic feasibility, which is the topic of my presentation today. So we've found out that a vaccine exists. We've found out there's a way to administer the vaccine. We've determined through focus groups or other methods that parents are willing to have their children be vaccinated or society is

willing to have -- to be vaccinated. The next question is, how much does the vaccine program cost and how do we compare the cost to the outcomes associated with the intervention?

So a basic definition of "economic evaluation" is applied analytic methods to identify, measure, value, and compare the costs and consequences for interventions. So let me go through each one of these verbs in turn, because they're each important.

The first one is identify. By this we mean to explicitly delineate the possible interventions or strategies of interest. And then we need to measure the different components of the intervention. So here's where we use our quantitative tools: Epidemiology, decision sciences, meta-analysis, economic evaluation, to value -- this is providing probability estimates, quantifying the costs and outcomes, and then we do a comparison of the different interventions that we're considering.

Economic evaluation in setting health policy can be thought of in a tier of decision-making. Okay? So at each level of this decision-making tier, we may

choose to use a different type of economic evaluation method. At the top tier, we may think of the President of the United States or Congress, who has to make decisions about putting our resources, our very limited resources, into programs that may have to do with defense, they may have to do with health. There are different outcomes associated with the different programs. And so in this case, we may consider doing a cost-benefit analysis because the common denominator or the common outcome measure is converted into dollars, and so you can compare across health and non-health outcomes.

At the second tier of decision-making, a group like ACIP or the Director of CDC, who is considering interventions for different health outcomes, may consider doing a cost-utility analysis. In a cost-utility analysis, the common denominator is a health metric, so it allows you to compare different health interventions. So for example, a CDC Director may be interested in putting funding into a breast cancer screening program or putting funding into an immunization program. The health outcomes themselves

are different, but we can put it -- we can convert this into a common health metric by quality-adjusted life years or disability-adjusted life years in order to make the decisions between the two programs.

And finally, at the bottom tier of decision-making we have a clinic director. This is at the micro level, and this is where a clinic director or someone who's trying to make decisions about immunization strategies to prevent the same disease. And in this case, your common metric is natural unit, cases prevented, but it doesn't have to be converted into a health metric like quality-adjusted life years. Okay?

So it's not to say that at the ACIP level you have to do cost-utility analysis. What it's suggesting, what this tier is suggesting is that if you don't have to go the extra step of converting your outcomes into dollars, then don't do it.

So let's go through each of these types of methods in a little bit more detail. The first is cost-benefit analysis. Now, I've already mentioned the focus here is converting all benefits into dollars. So you're going to be comparing your costs to outcomes in dollars,

dollars to dollars. The advantage of a cost-benefit analysis is that it provides a list of all costs and benefits over time. The key here is all.

Cost-benefit analysis has been used, in particular, in the environmental health field for over 50 years, and it rests on a strong theoretical basis that all costs and benefits can be quantified in dollar terms and included in the analysis.

You can also have costs that occur at different time lines. This is very important in the prevention world because we often see costs occurring when the intervention occurs, but then the benefits -- we don't see any benefits occurring until later in the future. So cost-benefit analysis allows us to deal with this. You can also have different amounts of costs and benefits occurring over time.

Another advantage of cost-benefit analysis is that the summary measure is one single value, and we'll be talking about this a little bit more in detail. That's the net present value, or sometimes referred to as net benefits, or the benefit/cost ratio.

Now, compare this to cost-utility analysis.

Cost-utility analysis does not convert outcomes into dollars. Instead, it looks at a common health metric such as quality-adjusted life years or disability-adjusted life years. The key here with cost-utility analysis is that it incorporates length of life with quality of life, which as you can imagine in the public health arena, we are very interested in quality of life. Cost-utility analysis allows us to compare these disparate outcomes because of a thing called utility, which I'll talk about in a little bit more detail, but essentially, utility is looking at the preferences, consumer preferences, for being in a particular health state.

Cost-utility analysis allows us to capture the timing and duration of disease and disability. Therefore, if you wanted to look at two health interventions, one that affected an infectious disease and one that included a chronic disease, you could easily make that comparison because we're looking at length of life and quality of life. And the final note on cost-utility analysis is instead of providing you a single estimate like cost-benefit analysis does, it provides you with

a ratio, where you have costs in the enumerator and the common health metric in the denominator.

Compare that to cost-effectiveness analysis, whereby your common health metric is no longer -- you no longer have a common health metric. Instead, you have a common natural unit. I have here on the slide that it's a natural health unit, but that's only particular to public health. It's really just a natural unit. So an example would be cases prevented or lives saved. And you use cost-effectiveness analysis when you're comparing results to interventions that affect the same health outcome.

So, for example, in varicella, you would compare intervention A to intervention B to prevent cases of varicella. Your health outcome is the -- your outcome, your natural unit, is the same, preventing cases of varicella.

And as with cost-utility analysis, cost-effectiveness analysis provides you a summary measure as a ratio where you have dollars in the numerator and now you have your natural units -- cases prevented, lives saved -- as your denominator.

There are five main components to an economic evaluation that I wanted to go through with you today. The first is framing the study; second, quantifying costs; third, quantifying outcomes; sensitivity analysis; and interpreting results.

Framing the study. Framing the study is important in conducting any type of study. The reason why I wanted to highlight it today is because for those of you who are looking at economic evaluation, evaluating economic evaluations for setting health policy, it's important to know whether the author framed the study appropriately.

In framing the study there are five main components: the study problem, audience, perspective, time frame, and analytic horizon. Let's talk about study problem first.

Study problem refers to what is the health outcome of interest, and why. So, again, this brings in the basic science. What is the incidence and prevalence of disease. How does incidence and prevalence of disease vary across your population. What is the burden of disease associated with this health outcome. What is

the economic burden of disease. What is the cost of illness associated with this health outcome of interest.

So let's take an example here, and that is influenza, and let's say you're interested in a vaccination policy for healthy working adults, for that population. So that's your study problem. We can talk about the reasons why the burden of disease is great for influenza, and the cost of illness associated with influenza in healthy working adults is large, as well.

So the next question you ask yourself is, who is the audience. This refers to who is going to be the users of the economic evaluation, what are their information needs, and how are they going to be using the data.

So, in my example, of vaccinating healthy working adults against influenza, you can imagine that there are many audiences who would be interested in this data, two of which are, one, you all and CDC, people who are setting national health policy would be interested in these results; and also the employer, because the employer may be interested in having influenza vaccination be a covered benefit for their employees.

So then, audience drives the perspective of the analysis, and perspective refers to who bears the costs and benefits associated with the intervention. So in my employer perspective, the costs that would be included in the analysis would be things like what is the cost of an employee clinic vaccination program, what are the productivity losses associated with a worker staying home because they're ill with influenza.

A larger perspective and one that we recommend for setting national health policy is the societal perspective. This is the most inclusive of all perspectives and includes all costs and benefits, regardless of who incurs them or who bears -- who bears the costs. So back to my influenza example, from an employer perspective, it's quite limiting in the costs that are collected, because you can imagine if an intervention program is set at the employer setting that many people will get their reminder notice, let's say, to go get a vaccine. But instead of going to the employer clinic or the health clinic on-site, they'll go outside of that clinic and either go to their own

private physician or to a public health clinic. Well, those represent real costs associated with the program, and the only way those would be included is if your perspective is broad enough to include all the costs and benefits, and that would be using the societal perspective.

The final two points in framing a study are time frame and analytic horizon. Time frame refers to the period in time during which the intervention occurs. So in your influenza example, you may have a two- to four-week intervention period where you have your clinic open to for people to come in and get their influenza vaccine.

The analytic horizon is beyond the time frame of the intervention and it includes the period during which all costs and benefits stemming from that intervention occur. So in the influenza example, while you may get your vaccination on the last day of the influenza program, the benefits of that vaccination are going to last throughout the vaccination season. So your analytic horizon is typically longer than your time horizon.

These are all components that are very important to define explicitly up front in an economic evaluation. And when you're evaluating economic evaluations for setting health policy, if your researchers do not state these components up front, you need to be very hesitant in assessing the quality.

Quantifying costs is the second component in an economic evaluation. There are four types of costs that I'd like to talk about. The first are direct medical costs. Direct medical costs refer to things like diagnostic tests and procedures, drugs and medical supplies. In the vaccination world, you might consider the cost of the vaccine, things -- minor things like swabs and alcohol which, if calculated across a large population, can mean great costs, the cost for the physician office visit, the physician time to administer the vaccine.

Direct non-medical costs include the cost for program administration, physical space, utilities, that sort of thing. Indirect costs in the economic evaluation world refer to costs associated with productivity losses, so these are costs borne by the employer because

the employee had to stay home, either from an adverse reaction from the vaccine or because they didn't get vaccine and they got influenza instead.

Intangible costs are things like fear and anxiety about getting a vaccine, the pain and suffering associated with getting a vaccine. Now, while these are very real costs, you can imagine that intangible costs are extremely hard to quantify. And so they are typically not included in an economic evaluation, but at least mentioned in the discussion section.

Now, depending upon what type of economic evaluation you do drives the costs that are included in the analysis. In cost-benefit analysis, as I've mentioned previously, the theory says that you should be including all costs and benefits. And that includes intangible costs, if you are able to quantify them in some reasonable fashion. In a cost-utility analysis, if you remember, that's where your denominator is some common health metric that looks at utilities, preferences for being in that health state, we do not typically see indirect costs included because it is assumed that productivity losses are captured in

your utility for being in a particular health state. Whereas, with cost-effectiveness analysis, where our denominator is simply natural units, like cases prevented, indirect costs should be incorporated in the enumerator.

Quantifying outcomes. With cost-benefit analysis, we've said that outcomes are converted into dollars. Cost-utility analysis it's converted into some common health metric. In cost-effectiveness analysis it's converted into a natural unit, such as cases prevented.

So let's talk about cost benefit analysis. How do we go about converting outcomes into costs. There are two -- there are at least two ways to think about this, the first being the human capital, or cost of illness approach.

This approach uses lifetime earnings as a proxy for productivity losses due to either morbidity or premature mortality. Now, you can imagine that this is a conservative estimate because many of us would think that we -- our value in society should be greater than what our salaries indicate, especially for those of you who work for the Federal government. So we do

make some -- we do try to make some adjustments for this conservative approach by adding things in like the value of your housekeeping services, as well.

The second approach I'd like to focus on a little bit more because we're seeing willingness to pay studies used more and more in the public health arena and in particularly in the vaccination world -- I'm going to focus on the third -- the third piece here which is contingent valuation studies -- surveys. These are surveys where respondents are asked to -- are presented with a series of questions in order to elicit their marginal willingness to pay to rid themselves of a particular health condition.

So a very real example here -- this was a study conducted last year from the National Immunization Program where we asked parents how much they were willing to pay to reduce the risk of intussusception associated with the rotavirus vaccine. So we're asking for the marginal willingness to pay. We know that parents were willing at that time to pay a certain amount to have their children vaccinated with rotavirus, and that was assuming that there was a

minimal risk of intussusception associated with that vaccine. So that to get at what is the value of that intussusception to that parent, what is the value of reducing that risk, we then asked the question, okay, how much are you willing to pay in additional costs for a vaccine that reduces that intussusception risk down to zero? And from those numbers, we are able to calculate the value of the morbidity and mortality associated with intussusception. We're able to calculate the value of a statistical life which can then be used in a cost-benefit analysis.

Quantifying outcomes in a cost-utility analysis, this refers to using utilities. I've already briefly described that utilities are a quantitative approach for describing consumer preferences for being in a particular health state, or consumer preferences for a reduction in morbidity or mortality associated with the intervention. Utilities are typically based on a zero-to-one scale where zero represents the worst possible state that you can imagine and one represents the best possible state -- health state that you can imagine.

There are both direct and indirect methods of eliciting individual utilities. I'm going to talk about direct measurement techniques briefly.

The first step is describing the health state to the individual, and this health, as you can imagine, is defined by many components -- physical, mental, functional. All these components are used to describe the health state. And then we -- then the individuals are taken through a sophisticated process whereby we try to elicit their utilities using these particular measures. The four that I'm going to talk about are rating scales, time-tradeoffs, standard gambles, and person-tradeoffs.

Rating scales is the simplistic -- the most simplistic of all four types. It is simply a feeling thermometer where worst health state is on the bottom, best health state is at the top, and then the health state that you are interested in eliciting the utility for is placed, you know, in the hands of the individual and the individual then has to place it on the feeling thermometer to elicit a utility. You can imagine the biases involved in a rating scale. So, fortunately,

there are more sophisticated techniques that have been developed.

The time-tradeoff technique asks individuals to go through a process whereby they trade a certain length of life in a bad health state, let's say being blind in both eyes, for a shorter duration of life in perfect health. So then by doing some math calculations, we can see the difference between those durations, we'll be able to elicit utilities.

With standard gamble we take them through a process where they are said that they have a certainty of being in a particular health state, being blind in both eyes, and then compared to a gamble where they would have perfect health, a probability of perfect health or death, and it's that probability that gets at the utility, how low does the probability of death have to be for you to be indifferent between those two options.

And then person-tradeoffs takes it beyond the individual utility elicitation to a population level utility level, and this is used for disability-adjusted life years. So an example would be, imagine that you could extend the life of 1,000

healthy individuals by one year. How many blind people -- that's the health state I'm interested in. How many blind people -- people's lives would you have to extend by one year in order for those two -- those two things to be equivalent in your mind. Okay? So you're comparing populations, but the health of those populations differ, and from that we are able to elicit utilities.

So once you get these utilities, then you can combine quality of life on a zero-to-one scale with length of life. So you can see from this very crude diagram here that we've got a person who is experiencing relatively perfect quality of life for most of their life, most of the duration of their life, until, let's say, middle age, and then something happens and their quality of life starts to decline. Now, with an intervention we -- you can see an increase in quality of life, not to where it was prior to the health outcome occurring, but at least it remains a steady state for a while and then the utility or quality of life declines until they die.

So the key here is to get at quality-adjusted life years

gained from the intervention, you look at the area between those two lines of where there's an intervention that occurred and an intervention that did not occur.

Now, if you were only looking at survival duration or life years saved as your denominator, then you would only have the difference between death on the X axis and you would be ignoring the quality of life that's associated with the intervention.

Quantifying outcomes in cost-effectiveness analysis, the key point here is that there's a difference between intermediate and final outcomes, and it's important for your researcher to state these differences up front and why they collected one or the other. Intermediate outcomes are things like persons immunized, cases prevented, or disease averted. But a final outcome measure -- let's say you only have data available on persons immunized. Well, it would sure be nice if you could get some information on how persons immunized translates into life years saved or lives saved. But oftentimes that data is not available and so we'll see economic evaluations that use intermediate outcomes.

And as long as they explicitly state this, you know, as a negative of the study or a potential flaw with the study, then it's appropriate.

Sensitivity analysis I'm not going to go into in great detail because this is another whole field in and of itself, except to mention that sensitivity analysis should always be conducted when you're doing an economic evaluation. We strongly stress that providing one point -- point estimate for cost-effectiveness analysis or cost-benefit analysis isn't appropriate, because as we'll show you in a few examples, your point estimate can really vary depending upon your population, depending upon the incidence, depending upon the model parameters in general. So we strongly encourage sensitivity analysis to always be performed.

Now, interpreting economic evaluation. There are three myths that I would like to address. The first is only implement programs with a positive net present value or a positive net benefit. The second myth: Only implement programs that have less than a $50,000 per quality saved -- per quality-adjusted life year

saved. Many of you may heard of this as a threshold level used. The third myth: Cost savings equals cost effective.

Myth number one, interpreting results in a cost-benefit analysis. As I mentioned earlier, there are two summary measures used in cost-benefit analysis. The first is net present value or net benefits. This is benefits minus cost. The second is the benefit-cost ratio, which is benefits divided by costs. In a net present value greater than zero, there definitely is a strong argument for investing in a program where the net present value or net benefits are positive, because it means that your benefits from the program outweigh your costs, and so there's a strong economic argument.

However, if you have a negative net benefit, it's simply saying that the economics are not there, but recall that we have three other tiers or three other pillars upon which setting health policy are based, including biological feasibility, technical feasibility, and political economic feasibility. So a negative net present value or negative net benefit simply implies

that you need to come up with some other justifications for why you're recommending the policy.

Now, a benefit-cost ratio was used very often ten years ago, but we no longer recommend it, and let me explain why. The benefit-cost ratio are benefits divided by costs. If it's greater than one, again we have a very strong argument for investment. But the interpretation here can be somewhat misleading. I've included a slide here -- that is not in your new packet but was in the first packet that I sent out prior to the meeting -- to illustrate the difference between using a net present value and a benefit-cost ratio. If you look at program A, we have costs of $1, benefits of $10, net present value is positive, $9, strong argument for investment, and you have a positive benefit-cost ratio, 10. Strong argument for investment.

But if you compare it to program B that has a significant return on investment compared to program A, if you were to only look at the benefit-cost ratio, that ratio in its single value of 5, is somewhat misleading because it's lower than 10 for the first

program. So it would suggest to you that the benefit-cost ratio for program A is higher and, therefore, we should be putting our resources into program A. Whereas, the net present value give you a true sense of what's going on with benefits and costs in that the net present value is higher and therefore that -- the return on investment is greater in program B.

Here's an example that's been published recently by Kristin Nichol in Archives of Internal Medicine. I wanted to highlight this example because it is a very well-done study, not only in the way that the study was conducted, but also in how it was reported, which is important for evaluating economic evaluation. She looked at the cost of a vaccination and she broke this down by direct and indirect costs, which are the costs, and then for the benefits she looked at costs averted, again breaking it down into direct and indirect costs. Her summary measure, because this is a cost-benefit analysis, is net benefits, or net present value, $13.66. It's positive, which suggests that there is a strong argument -- economic argument for investing

in this program.

Now, she did a sensitivity analysis, as we recommended, and she did a worst case and best case scenario. In the worst case scenario, she found that there was a cost to society of $21, and in the best case scenario there was a savings of $174. So this stresses the importance of doing a range around your point estimate to show that, depending upon the parameters that go into the model, depending upon the effectiveness of the vaccine that year, for example, really will determine your bottom line.

My second myth was that you should only invest in programs that are less than $50,000 per quality-adjusted life year saved. This is a hypothetical number that has no empirical or theoretical basis whatsoever. This number came out of the literature about 15 or 20 years ago, and the number is the dollar values have never been inflated to current-day dollars. So the number really is fictitional, so please ignore it.

So what do you do? If you have a cost per quality-adjusted life year saved of $20,000 or $2,000

or $10,000, how do you assess the quality of that ratio. Well, one thing you might consider is to compare it to other interventions, other prevention interventions that we currently -- that society currently deems acceptable and that we are promoting. And in this case that I'm showing you here, this is comparing immunization vaccinations in general. This is a summary of economic evaluations that have been published about immunizations and vaccinations, comparing it to other clinical preventive services. So you can see that compared to screening tests, the immunizations/vaccinations does much better, and it -- this table also provides a minimum and maximum value.

The third myth I wanted to talk about was that cost-effective equals cost-savings. This is particularly of interest to the vaccination world because 10, 15, 20 years ago it was not unheard of that vaccinations were cost-savings, meaning that overall there was no -- there were no costs associated with a vaccination program. Now, however, we are seeing that while vaccination programs may not be cost-savings, they are still cost-effective, meaning there are still

costs associated with the program but the cost-effectiveness relative to other clinical preventive services that we're conducting, these vaccination programs are still extremely cost-effective. So this example here I think is a very good one for the vaccination field.

This looks at percent of people vaccinated on the X axis. So it goes from about 20 percent people vaccinated to 100 percent vaccinated. On the Y axis, we have cost per case prevented, so this is a cost-effectiveness analysis. You can see that when the percent of people vaccinated is below 65, 70 percent, there's a cost savings associated with vaccination. However, when the vaccine -- the percent of people vaccinated increases up to 100 percent, there's a cost-per-case-prevented associated with the program. Now it's still relatively cost-effective if you think that cost effectiveness less than $20,000 per case prevented is a good value based on other services that you already promote.

The point being here is that if you only provide a point estimate for a given population level of people being

vaccinated, there's -- you're being deceptive because it may be cost-savings for one level of people being vaccinated, but it's cost-effective in another level.

So, to reiterate, the basic elements of setting health policy rely on four components: economic feasibility, which we've talked about here today; the biologic feasibility and technical feasibility, which I imagine you talk about on a regular basis at this meeting; and then there's the social and political feasibility, which we can't ignore given the power of the statements that come out of the ACIP.

So I have two conclusions. The first one is that economic evaluation is valuable to the decision-making process and should always be included when setting health policy. And the second conclusion is that interpreting these results is often complex. So where do we go from here?

I only had an hour to present today and I've stayed within 45 minutes, but these are very important concepts that we teach in a two-day course, training course here at CDC, intensive on the mechanics of cost-benefit, cost-utility, and cost effectiveness

analysis. So training is one option.

The second is technical assistance. We run a post-doctoral fellowship program in my office, which is a two-year program where we bring in economists who sit at various places at CDC, including the National Immunization Program, to help our CDC researchers conduct economic evaluations and evaluate economic evaluations. We also have an economics contract with the Research Triangle Institute whereby CDC program offices can commission for an economic evaluation to be conducted to fill the gaps where economic evaluation doesn't exist in the literature. And finally, our office is in the process of developing standardization of methodology. The key here is if you want to compare one cost utility analysis to another, it's important that they're using the same methodology. So we are working rigorously to promote that and we sent you our prevention effectiveness book you should have received prior to the meeting, which is our first attempt at standardizing the methodology, and we're working currently on the second edition. Thank you.

**DR. MODLIN:** Dr. Corso, thank you. You certainly

clarified a few things for me.

It is late in the day, but if there are questions for Dr. Corso -- Yes, Eric?

**DR. FRANCE:** Very nicely done. I'm Eric France from Kaiser Colorado with American Association of Health Plans.

It sounds then like, as I was listening to your talk, our group then would always be interested in both the cost-utility analysis when we're thinking about the general policy issue of some new project and might be wanting to compare it to other standardized accepted prevention programs that are used, but then also the second tier of cost-effectiveness analysis when we might be trying to decide whether we should be vaccinating all children under three versus all children under five, and looking at the different impacts of those two things. So it seems like both of those would occur as we're reviewing some new policy. Would you agree with that?

**DR. CORSO:** I totally agree with that. The only problem when you're looking at more than one type of economic evaluation is, you know, in the long run you

would like to be able to compare all of your economic evaluation in one basket, and it makes it a little bit difficult when you're looking at the cost-effectiveness side alone. So I agree that setting broader health policy at a national level, cost-utility analysis is appropriate, and at the micro level, cost-effective analysis is. But also in comparing to economic analyses that have already been conducted, you may want to follow the same methodology so you can compare in that way. For example, the Nichol study that I presented is a cost-benefit analysis. I think one of the reasons why she chose cost-benefit analysis is because she had done previous work -- she had done a previous analysis on cost-benefit and I think she wanted to be able to make some comparisons across populations.

**DR. MODLIN:** Other comments, questions? Eric?

**DR. FRANCE:** Just one more. Is there an easy place to go to try and make comparisons of -- as we're considering the cost utility of something? I mean, does your office give us ideas? I know some of the things we might look at might be millions of dollars

per quality saved and others might be quite cheap, and we all kind of scratch our head and saying, when is this too much.

**DR. CORSO:** The slide that I showed that compared to other clinical preventive services is probably the closest we're getting to that. Those are called lead tables, and we're seeing more and more lead tables published in different peer review journals. So that may be a place to start. You can contact our office and we can help you in that search, as well.

**DR. FRANCE:** Thanks.

**DR. MODLIN:** Other questions or comments? I think in part -- I think the clarity of your presentation has been such that the questions have been unnecessary. Thank you again.

**DR. CORSO:** Thanks.

**DR. MODLIN:** We've entered the period for public comment. I have no one signed up to give public comment today. I don't see anybody rising very quickly. So I'll take the opportunity to draw this meeting to a conclusion. See you in October.

(Whereupon, the meeting was adjourned at

approximately 3:44 p.m.)

# C E R T I F I C A T E

STATE OF GEORGIA

COUNTY OF FULTON

I, PAMELA T. LENNARD, BEING A CERTIFIED COURT REPORTER AND NOTARY PUBLIC IN AND FOR THE STATE OF GEORGIA AT LARGE, HEREBY CERTIFY THAT THE FOREGOING IS A TRUE AND COMPLETE TRANSCRIPTION OF SAID PROCEEDINGS; AND THAT I AM NEITHER A RELATIVE, EMPLOYEE, ATTORNEY, OR COUNSEL OF ANY OF THE PARTIES, NOR A RELATIVE OR EMPLOYEE OF SUCH ATTORNEY OR COUNSEL; NOR FINANCIALLY INTERESTED IN THE ACTION.

WITNESS MY HAND AND OFFICIAL SEAL, THIS, THE 14TH DAY OF JULY, 2001, IN ALPHARETTA, FULTON COUNTY, GEORGIA.

PAMELA T. LENNARD, CCR, CVR

NANCY LEE & ASSOCIATES

CERTIFICATE NUMBER B-1797
(CCR SEAL - NOTARY SEAL)

NANCY LEE & ASSOCIATES