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 8:30 a.m. on Wednesday, February 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

(By Group, in Alphabetical Order)

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National Immunization Council and Child Health Program
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P R O C E E D I N G S

8:30 a.m.

DR. MODLIN: Good morning. I would like to welcome everyone to the February meeting of the Advisory Committee on Immunization Practices. We will get started by turning things over to Dr. Dixie Snider, who is Executive Secretary of the Committee. Dixie?

DR. SNIDER: Thank you, John. Good morning to everyone and welcome to the Advisory Committee on Immunization Practices. If that's not the meeting you intended to attend, you might want to look at the signs outside the doors down the hall.

We're pleased to welcome three new members to the Committee: Dr. Jaime Deseda-Tous, Associate Professor in Pediatrics at the San Jorge Children's Hospital in San Juan, Puerto Rico; Mr. Myron Levin, Chief, Pediatric Infectious Diseases at the University of Colorado School of Medicine in Denver, Colorado; and Dr. Natalie Smith, Chief, Immunization Branch, California Department of Health Services in Berkeley, California.

Also new to the Committee is the ex officio from the Department of Defense, Colonel Benedict Diniega. Joining the ACIP as liaison representative is Dr. Kathy Neuzil for the American College of Physicians and Dr. David Salisbury for the London Department of Health. Unfortunately, Dr. Salisbury is unable to be with us today.

Dr. Jose Ignacio Santos is not with us today. However, Dr. Margarita Nava will be serving as the liaison from the National Immunization Council and the Child Health Program in Mexico.

On December the 14th of 2000, Dr. Copeland signed an amendment to the ACIP Charter adding three additional members to the Committee. Actually, John, Walt, and several of us had talked about the workload on the Committee and decided that we needed additional people to keep up with the activities. Because of the time involved in processing the nominees, the new members are not yet appointed. However, because of the increased members to the Committee, the quorum for ACIP is now at eight. Therefore, it's important that the 12

appointed members present today return from lunch and break in a timely manner to assure that a quorum is present at all times.

Also, be aware that the meeting will go to 3:45 tomorrow, and I'm requesting that members not leave the meeting early.

I believe, by now, everyone is aware of the ACIP e-mail address. It's very simple: acip@cdc.gov. Please continue to use this address for all e-mail correspondence related to ACIP. In addition, ACIP now has a home page. The ACIP home page is located at www.cdc.gov/nip/acip. You'll find the address on a bright pink paper in your books and at the back of the room. The home page contains the Charter, the members, dates, and locations of the scheduled meetings, and when an agenda is formulated, it will be posted on the home page and updated regularly as changes occur.

There also is a direct link to the ACIP recommendations and the VFC resolutions from the ACIP home page.

The ACIP Policies and Procedures document will be added to the home page when it's completed. We've been

working on that in conjunction with the Office of General Counsel and the Office of Government Ethics in D.C. The document is undergoing revisions that we -- as we consider internal issues. An issue that is taking considerable discussion time is the process of determining future candidates for nominations to ACIP. Approaches we are considering including -- we're considering including are not nominating individuals who have certain relationships unless those relationships are severed or alternatively not providing waivers for certain relationships. Examples would include: stock ownership, direct stock ownership in vaccine companies; membership on a vaccine manufacturer's advisory board when the scope of advice goes beyond technical to business advice, is what we're trying to get at; and serving as an expert witness on behalf of a vaccine manufacturer. Again, I'm talking about during the tenure on ACIP, not before or after service on the ACIP. So I just wanted to give you a flavor of some of the things we're thinking about. If any of you have some comments, we can talk about it

individually at breaks.

The next ACIP meeting is June 20th-21st, 2001. It's scheduled to be held here at the Marriott Century Center. The following meeting is October 17th and 18th. Committee members will find the dates on yellow paper in their book. These dates are also available on the handout table.

The dates for the 2002 meetings will be set at the next meeting. We'll have those available for you.

We've met here so much, I think most people know that the rest rooms are located down the hall to my right.

You'll find the restaurant in the lobby of the hotel.

The Adult Working Group will meet at the hotel restaurant during lunch. There will be an area set aside in the back of the restaurant and the attendant can direct you to where that working group is going to be meeting.

Dinner this evening is at the 57th Fighter Group on Clairmont Road. There's a set menu with six entrees from which to choose. Dinner will be 26 dollars, which includes tax and gratuity, and dining is casual. A

cash bar is available.
There is a pink sheet available to you. If you'll just indicate your choice of entree on the menu in your notebook and return it with the cost of the dinner to Gloria or Latarsha by noon. If you need a menu, please see Latarsha or Gloria. We'll leave from the lobby of the hotel at 7:15.
For those of you driving, if you go out of the hotel parking lot and turn left and go down to Clairmont and take a right and drive straight on down Clairmont, you'll come right to the restaurant. It's about two miles.
The ACIP Charter gives me, the Executive Secretary, the authority to temporarily designate the ex officio members as voting members. This does not take place unless there are less than 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 necessary. The ACIP has always held open discussion and reserved meeting time for official public comment, but we have restricted time in

which to conduct business. Therefore, in some limited circumstances, we've scheduled a formal comment period during the deliberation of an agenda item. Casual comments are received during open discussion depending upon the amount of time available, and these comments need to be restricted in time in order to keep within our allotted agenda.

Those members of the public who wish to address the Committee today or tomorrow should sign up with Gloria or Latarsha so that we can arrange time for you to make your comments.

For those of you not familiar again with the logistics of the Committee, the appointed Committee members and the CDC support folks are located at this inner table. The ex officios and liaison representatives are seated at the outer table.

Because it is important for us to hear all comments, we've set a microphone at each end of the Committee tables for members of the audience to use when they address the Committee, and I would appreciate that anyone who wishes to comment step up to the microphone.

This not only enables us to hear your questions and comments, but we are taping this session and it would allow for your commentaries to be recorded clearly. And also, I would ask, when you come to the microphone or when you begin speaking, if the Chair hasn't recognized you by name, please identify yourself.

I think that's all the housekeeping I have, John.

DR. MODLIN: Terrific. Thanks, Dixie.

Let me add my personal welcome to Dr. Deseda-Tous, to Dr. Levin, and Dr. Smith as new members of the Committee. I also would like to add my personal welcome to Dr. Diniega and Dr. Neuzil, who will be joining as liaisons and ex officio members, and I also welcome Dr. Nava from Mexico.

I also want to personally congratulate Melinda Wharton, who is our new Director of the Division of Epidemiology and Surveillance. We welcome Melinda to the table formally.

You will find in the back of your books the Childhood Immunization Schedule for the current year, the Joint Statement on thimerosal in Vaccines, and also the

recently-published anthrax recommendation that we completed at the last Committee meeting. There are also a number of information pieces and updates from the MMWR that have been published since last October and they're in the back of your books as well. You will find that these and a few related articles are in the accordion folder in the back of the book.

Dixie has already mentioned the dates of the next meeting, which, again, will be June 20th and 21st here at the Marriott Century Center, and Dixie has also announced dinner plans for tonight, but I would remind everyone -- those of you who are planning on attending the dinner to fill out the pink sheet and give it to Gloria or Latarsha prior to the lunch break.

It's critically important for everyone to be able to hear, that all of the Committee members who are seated at the tables and those of you in the audience who are participating, speak directly into the microphones and we would certainly appreciate those of you in the audience who have comments identifying yourself prior to making your comment.

At this time, I'm going to ask each of the voting members of the Committee to introduce themselves and, at the same time, to disclose whatever financial conflicts of interest they may have. I want to remind everyone that ACIP members who may have a potential conflict of interest should make it known at this time. All members, regardless of a conflict, may participate in discussions of all issues, provided their full disclosure of potential conflicts of interest has occurred. However, the person or persons with a direct conflict of interest may not vote on any issue related to the conflict. Only members need to disclose. The ex officio and liaison members are not required to disclose their conflicts, although I think we clearly would hope that if you do have conflicts of interest, you would make it known.

Members with financial conflicts of interest must abstain from voting on the 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 of a VFC resolution. ACIP's policy

prohibits a member with financial conflicts of interest from introducing or seconding an ACIP vote or VFC resolution.

So why don't we start -- We'll go around counterclockwise this time, beginning with Dr. Brooks.

DR. BROOKS: Yes. I'm Dr. Brooks from Johns Hopkins School of Medicine. I have no conflicts of interest.

DR. CLOVER: I'm Richard Clover, University of Louisville, and Professor and Chair of the Department of Family and Community Medicine. I or my department have received funding from Wyeth, Merck, SmithKline, Bayer, and Astra Seneca [phonetic].

DR. WORD: My name is Bonnie Word. I'm a pediatrician from New Jersey, and I participated recently at an Advisory Committee meeting for Merck.

DR. HELMS: I'm Charles Helms. I'm a professor at the University of Iowa and Chief of Staff at University of Iowa Hospitals and Clinics. I have no financial conflict of interest, but I did participate as a consultant at the Merck Vaccine Division's National Immediately Advisory Board in November. I took no

honorarium for that.

DR. TOMPKINS: I'm Lucy Tompkins, a Professor of Medicine from Stanford University, and I have no conflicts of interest.

DR. RENNELS: Margaret Rennels, University of Maryland, Center for Vaccine Development. I am doing vaccine trials for Wyeth-Lederle, Aventis Pasteur, Glaxo SmithKline, and Merck, and I chair a safety monitoring board for Aventis Pasteur.

DR. OFFIT: I'm Paul Offit from the Children's Hospital, Philadelphia, and the University of Pennsylvania School of Medicine. I am the co-holder of the patent on a bovine human resort rotavirus vaccine and serve as an unpaid consultant to Merck on the development of that vaccine.

DR. SMITH: I'm Natalie Smith from the California Department of Health Services. I have no conflicts of interest.

DR. LEVIN: Myron Levin, University of Colorado Health Sciences Center. I have -- I do clinical research with Merck, SmithKline, Glaxo, and Medimmune, and I have

stock in Glaxo SmithKline and Baxter.

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

DR. DESEDA: I'm Jaime Deseda from University of Puerto Rico School of Medicine, and I have no conflicts of interest.

DR. MODLIN: John Modlin from Dartmouth Medical School, and I have no conflicts of interest.

Why don't we introduce each of the CDC representatives, beginning with Alison.

DR. MAWLE: I'm Alison Mawle. I'm the Vaccine Coordinator for the National Centers for Infectious Diseases at CDC.

DR. WHARTON: Melinda Wharton, Epidemiology and Surveillance Division, National Immunization Program.

DR. ORENSTEIN: Walt Orenstein, National Immunization Program.

DR. MASTRO: Tim Mastro, HIV Vaccine Section [inaudible] for HIV, STD, and TB prevention.

DR. MODLIN: Thank you. I expect that there are

probably very few people in this room that know that Dr. Helms is going to be making his solo vocalist debut as a vocal soloist. Is it in the first week in June, Chuck?

(LAUGHTER)

DR. MODLIN: I just wanted to pass that on to the Committee -- the Committee wishes you all the best.

DR. HELMS: I don't know who your lines of communication are, but they're good.

(LAUGHTER)

DR. MODLIN: Let's go on and ask the liaison members to introduce themselves, if you would, please, and then the ex officios, beginning with Dr. Howe.

DR. HOWE: Good morning. Dr. Barbara Howe from Glaxo SmithKline, liaison member for Pharmaceutical Manufacturers Research.

DR. PETER: Georges Peter from the Department of Pediatrics, Brown Medical School, and I'm the liaison representative and Chair of the National Vaccine Advisory Committee.

DR. PICKERING: Larry Pickering, Director of the Center

for Pediatric Research in Norfolk, editor of the Red Book of the American Academy of Pediatrics.

DR. ABRAMSON: Jon Abramson, Chair of Department of Pediatrics at Wake Forest School of Medicine and Chair of the Committee on Infectious Diseases for the American Academy of Pediatrics.

DR. MAHONEY: Good morning. Martin Mahoney, liaison from the American Academy of Family Physicians.

DR. ZIMMERMAN: Rick Zimmerman, University of Pittsburgh, liaison from the American Academy of Family Physicians.

DR. WILSON: David Wilson from the University of North Dakota, liaison for the American Medical Association.

DR. SCHAFFNER: Bill Schaffner from the Department of Preventive Medicine at Vanderbilt in Nashville. I'm liaison from the American Hospital Association.

DR. NEUZIL: Kathy Neuzil from the University of Washington. I'm the liaison from the American College of Physicians, and I do receive research grants from Glaxo Welcome and Aventis Pasteur.

DR. McKINNEY: I'm Paul McKinney, Professor of

Medicine, University of Louisville, liaison for the Association of Teachers of Preventive Medicine.

DR. SIEGEL: Jane Siegel, Department of Pediatrics, University of Texas Southwestern Medicine Center and the liaison from Healthcare Infection Control Practices Advisory Committee, or HICPAC.

DR. KATZ: Samuel Katz, pediatrician, professor at Duke University, representing the Infectious Diseases Society of America. The only grant I currently have is from the Gates Foundation and I don't think Microsoft makes vaccines.

DR. MODLIN: Not yet.

DR. FRANCE: I'm Eric France from Kaiser, Colorado, liaison representative from the American Association of Health Plans.

DR. JACKSON: Rudolph Jackson, Department of Pediatrics and International Health, Morehouse School of Medicine, liaison member representing the National Medical Association.

DR. NAVA: Margarita Nava from Mexico City. I represent Dr. Jose Ignacio Santos from the National

Immunization Council from Mexico.

DR. MARCHESSAULT: Victor Marchessault, Infectious Disease from the University of Ottawa, Chairman of the Committee of the National Advisory Committee of Immunization.

DR. MYERS: Martin Myers, National Vaccine Program Office.

DR. DINIEGA: Ben Diniega, Department of Defense, Health Affairs.

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

DR. CHEEK: Jim Cheek, Indian Health Service.

DR. HEILMAN: Carole Heilman, NIH.

DR. MIDTHUN: Karen Midthun, FDA.

DR. EVANS: Geoffrey Evans, National Vaccine Injury Compensation Program, HRSA.

DR. MODLIN: I'd like to, before beginning the official agenda, make a note that we will be forming two new advisory committees very shortly, actually with this -- I'm sorry, working groups, pardon, working groups, thank you, Dixie -- to begin with this meeting. One

will be a working group to examine the data on rhesus rotavirus vaccine and intussusception and other rotavirus vaccines, although principally the RotaShield product. I think, as everyone knows, there are studies that are being conducted and have been conducted, some of which are complete and some of which are not, some of which are being conducted by the CDC, some under the auspices of NIH. Hopefully, most of this information will be available in a complete form over the next few months, and we would like for the working group to have an opportunity to examine these data in detail and ultimately bring this information back to the Committee, probably in October, for a full discussion at that time.

Those of you who volunteered to serve on the working group will probably need to commit to attend a meeting on -- specifically on this topic that will be held under the auspices of the NVPO. That meeting will probably be in September. Marty, do we have any dates yet?

DR. MYERS: September 5th, 6th, and 7th.

DR. MODLIN: September 5th, 6th, and 7th. Let me ask who would be --

DR. MYERS: And those dates are locked in. So . . .

DR. MODLIN: September 5th, 6th, and 7th for a two-and-a-half-day meeting?

DR. MYERS: Two-and-a-half-day meeting to examine the -- all of the science related to rotavirus vaccine and intussusception.

DR. MODLIN: Thanks, Marty.

Could I ask who would be interested in serving on this working group? First of all, voting members of the Committee.

(SHOW OF HANDS)

DR. MODLIN: Okay. Dr. Deseda, Dr. Levin, Dr. Offit, Dr. Rennels. Then liaisons: Dr. Peter, Dr. Pickering, Dr. Katz, Dr. France, and Dr. Evans, and Dr. Jackson. Thank you.

The second working group will be a working group to focus on the development of the Harmonized Schedule. I think, as everyone knows, the Harmonized Scheduled is published by the ACIP, the American Academy of

Pediatrics, and the American Academy of Family Physicians as a collaborative exercise. It's a process. The last few years has normally been that we put together a small group at the last minute, just before the October meeting, to discuss the Harmonized Schedule, try to hammer it through at the October meeting, and then it's published in -- early in the year on an annual basis. I think we recognized that the process probably could stand some improvement. So we would like to have a working group that will not only focus on the process of developing a Harmonized Schedule, but also serve to work together to actually develop the Harmonized Schedule for this next year. I think several different options are under consideration. One would be publishing the Harmonized Schedule in different formats; certainly the option of publishing it in an electronic form perhaps so it could be updated on a continuous basis, rather than once a year, would be an advantage to many of us. Obviously, this is an issue that affects each of the three organizations that would have input, so that this would

be a broad working group at least organized here at the ACIP.

Maybe I could ask for, first of all, voting members who would be interested in serving on this group. Dr. Smith, Dr. Brooks, terrific, and Dr. Clover. How about liaison members? Dr. Peter --

DR. ABRAMSON: Can I nominate someone from my committee? Is that okay?

DR. MODLIN: Absolutely.

DR. ABRAMSON: Then I would nominate Dr. Charles Prober, who is an associate editor of the Red Book and on the --

DR. MODLIN: So Dr. Charles Prober would represent the Academy for the AAP.

Dr. Zimmerman, Dr. Siegel. That's about the right size. Terrific. We will get both of these working groups up and running shortly after this meeting.

The third group is not actually a working group, but I think that with a reasonable degree of assurance, I can state that we hope to and probably will have a hepatitis B statement, a draft for the Committee to

finally sign off on in June. In order to get there, I would like to ask one or two members, voting members of the Committee, to work with Hal Margolis to bring this to completion. We think we're almost there, but if there's anyone who is interested in working on the hep B statement between now and June, if you would let me know. It doesn't need to be now, but sometime during the meeting.

With that, we'll go on to the first item on the agenda, and we're going to be spending the morning talking about influenza and influenza vaccine, and this will be introduced by --

DR. SNIDER: I just wanted to welcome Dr. David Fleming, the Deputy Director for Science and Public Health at CDC, who has just joined us at the table.

DR. MODLIN: Welcome, Dave.

DR. FLEMING: It's nice to be here.

DR. MODLIN: Keiji?

DR. FUKUDA: Thanks, John. I think that over the next couple of hours, we have several items to discuss about influenza. Just to note that there are a couple of

speaker changes on the agenda.
In the place of Dr. Cox, Ms. Lynette Graham will be giving the update on what the influenza season has been like this year and will inform the Committee about what the new vaccine strains will be for the coming season. And I believe in the second session having to do with the vaccine supply situation, Dr. Norman Baylor will be speaking instead of Dr. Karen Midthun for FDA. I think that Mr. Dean Mason will be speaking in the place of Dr. Lance Rodewald.
Anyway, so without much further ado, what we'll first do is go over what the season has been like this year, what the vaccine strain selection has been, both at the FDA and WHO meetings, and then we'll go into the discussion for the 2001 -- 2001-2002 recommendations.
DR. GRAHAM: Good morning. As Keiji said, I would like to start the influenza session this morning with a brief summary of this season's influenza activity and an update of vaccine strain selection process for the 2001-2002 northern hemisphere influenza season.
This first slide shows influenza virus detections

reported to CDC this season by WHO and National Respiratory and Enteric Virus Surveillance System Collaborating Laboratories. The bars -- In the bars, the green portion represents influenza B viruses; the yellow is influenza A viruses that have not been subtyped; influenza A(H3N2) viruses are represented in red; and influenza A(H1N1) viruses are shown in blue. The black line is the percent of respiratory virus specimens tested by these labs that are positive for influenza. You can see from this chart that the majority of viruses reported this year, approximately 68 percent, are influenza type A viruses, and of those influenza A viruses that have been subtyped, the majority of those viruses have been A(H1N1).

You can also see from this chart that, by looking at the percent positive, it appears that influenza activity in the U.S. peaked this year during week four and is now beginning to decline.

This season has been a relatively mild influenza season and I think you can see this in this comparison. This shows the percentage of respiratory specimens testing

positive this year, shown in red, versus last year which is shown in blue. You can see here that the percent at the peak of the season is lower this year than it was last year. I believe that's about 25 percent versus 31 percent; and the peak also occurred later this year, four weeks later than last year.

This is a look at our Sentinel Physician Data. The red line shows the percentage of patient visits for influenza-like illness to Sentinel Physicians for this year and the blue line is the data from last year. And you can see a similar picture to the virologic data, we have a lower peak this year, and the peak was also four weeks later this year than it was last year.

To sort of round out this picture of a milder season, this is mortality data from the 122 cities Mortality Reporting System. The bottom smooth line is the baseline level of activity that we would expect to see and the upper smooth line is the epidemic threshold. The jagged line is the actual percentage of death certificates that list pneumonia or influenza on the death certificate anywhere. And you can see, so far

this year, we have not seen any -- have not seen excess mortality associated with this season.

The WHO collaborating labs in the U.S. submit a subset of the viruses that they isolate to CDC Strain Surveillance Laboratory for antigenic characterization. And this year, the majority of the H1N1 viruses that have been characterized in our lab are similar to A/New Caledonia/20/99, which is contained in this year's vaccine. A smaller number of viruses are similar to the older vaccine strain A/Bayern/07/95, but antibodies produced against A/New Caledonia produce high titers that cross-react with the A/Bayern-like strains.

We've seen very few influenza A(H3N2) viruses in the U.S. this year, but all of those that we have seen are similar to A/Moscow/10/99 and A/Panama/2007/99, which is contained in this year's vaccine.

The influenza B viruses that have been seen in the U.S. so far this year, the majority of those viruses are now similar to a virus called B/Sichvan/379/99. This virus is a drift variant of the B/Beijing/184/93-like viruses which are contained in the vaccine. While these

viruses are antigenically distinguishable, they do cross-react, so we would expect that there would be cross-protection with the vaccine strain for this virus this year.

The picture internationally has been very similar to what we've seen here in the U.S. In the northern hemisphere influenza A(H1N1) viruses have predominated overall, although there has been a -- quite a bit of influenza B activity also identified. Influenza B viruses have actually predominated in several countries, including Canada and Portugal, and as of this time, so far there have been no countries reporting widespread influenza A(H3N2) activity this season.

FDA's Vaccine and Related Biological Products Advisory Committee meet this year on January 30th and WHO held their vaccine strain selection meeting on February 12th through the 13th this year. Both of these meetings -- it was determined that the A/New Caledonia (H1N1) virus and the A/Moscow-like (H3N2) virus should be retained for the northern hemisphere vaccine for the 2001-2002

season. Both committees also decided that because the majority of viruses worldwide are beginning to look more like the Sichvan virus than the Beijing-like viruses, that the influenza B component should be updated to include the B/Sichvan-like virus.

FDA's advisory committee will meet again on March 9th, and at that time they'll finalize the selection of the actual strains that will be used in the U.S. vaccine.

At this point, I would be happy to take any questions.

DR. MODLIN: Questions for Dr. Graham?

(NO RESPONSE)

DR. GRAHAM: Okay, thank you.

DR. MODLIN: Thank you.

DR. FUKUDA: Dr. Carolyn Bridges will be walking the Committee through the proposed changes to the 2001 recommendations.

DR. BRIDGES: Good morning. We have substantially fewer changes this year than last, and we anticipate that next year possibly, if there is licensure of the live-attenuated influenza vaccine that we will have a fairly major re-write at that time. So for this year,

we tried not to do a major re-write because we know that it may be coming in the near future.

I'll try and walk these through fairly quickly. Lynette has already talked to you about the vaccine strains for next year. These will be updated in the recs that you see once we have the final decision by FDA next month. There are a number of references that have been updated. I've also received a lot of comments about additional references that people would like to be included. In particular, we'll try and change out many of the abstracts that are included with peer-reviewed articles that have now been published. So there will be additional references incorporated, in addition to the ones that you currently see in your draft.

The first thing on page 8 of the recs, you'll notice that the introduction has been shortened. The information is still there, but we've now tried to eliminate some of the redundancies in the draft, and some of the information that was in the introduction has now been moved back to the vaccine effectiveness

section and sections on groups recommended for -- targeted for influenza vaccine.

One of the things that you'll notice in the introduction is that the number of -- the way that the high-risk groups or target groups are described has now been broken down into three groups, as opposed to two groups that we had last year. One of the reasons for doing this was because of some of the confusion that was generated as a result of the vaccine delivery delays last year and some of the ACIP recommendations that came out in the MMWR, which were supplements, which indicated that healthy 50-to-64-year-olds were somewhat lower priority or should be vaccinated later in the season last year as opposed to persons who were 65 years of age and older.

We do not have good information yet, but we're working on that, to get better impact information on the 50-to-64-year-old age group, and we hope to be able to include that information in hopefully next year's draft. But for this draft, now the target groups vaccination are separated into people who are 65 years

of age and older, plus people less than 65 years of age who have a high-risk condition. The second group are people who have -- or groups of people that have a high prevalence of chronic medical conditions, and those are the 50-to-64-year-old persons. Then the third group then are contacts of high-risk people. So, formerly, in last year's draft, we had included 50 and older into the high-risk group and we had put contacts in the second group. Now they are split into three groups to try and clarify what the rationale was for adding the 50-to-64-year-old age group. A suggestion has been made that we include more information about what the health benefits are for 50- to 64-year-old people. That was included in last year's draft. We had moved that more to the vaccine effectiveness section, but we can move that back into the rationale section for the 50-to-64.

Could I have the next overhead? And this is the suggested language that was proposed to add persons in this age group without high-risk conditions also receive benefits in the forum of decreased rates of

illness, work absenteeism, and medical visits, and taking medications.

Is there discussion on that particular section?

(NO RESPONSE)

DR. MODLIN: I guess not, Carolyn. Why don't we go on.

DR. BRIDGES: You can skip those, Lynette.

The next set of changes then is on the burden of disease section on page 10. A suggestion has been made that we include a table that lists the burden of hospitalization and death by age group, and we can easily do this. The suggestion was made because the text tends to be a little bit long and difficult to get through. So we can put a table to list the burden in hospitalization and death by age group rather than just have it listed in the text.

Then on page 12, in the effectiveness of influenza vaccine, there was a suggestion that we add information on the number of weeks that it takes for people develop antibody response after vaccination, and we can certainly do that.

Are there other suggestions in these sections?

DR. ZIMMERMAN: I question -- I notice here there was a discussion about whether the whole virion product was still going to be produced or not. Do we have an update on that?

DR. BRIDGES: We were going to be checking with the vaccine manufacturers. I don't know if any of them would like to comment on that.

DR. MODLIN: Why don't we put that off for just a second. I think we'll come to that when we may ask for some comments from the manufacturers. We can bring it up at that time.

UNIDENTIFIED SPEAKER: When we talk about the health benefits, it's a very general statement and I guess -- I think it would be helpful to say something specifically about the decreased use of the antibiotics in those who receive the vaccine.

DR. SNIDER: Let me just people again, be sure and identify yourselves since this is being transcribed.

DR. MODLIN: Jon?

DR. ABRAMSON: Yeah, Jon Abramson.

I think we need to get out there this issue of

influenza-associated encephalopathy. I don't know if this is the right vehicle. It could go under burden of disease, but there is a lot of discussion going on about whether we're seeing kids with that, whether we're not seeing kids with that, and what do we know about it. I do think we need to get something out there, whether it's a separate document or part of this document. I do think that.

DR. BRIDGES: I think there have been other cases of myocarditis and -- with influenza and we could outline more rare complications of influenza infection and the burden if that would be helpful.

DR. MODLIN: Jon, I think we all understand and recognize, certainly as clinicians, that there's a number of different non-respiratory complications of influenza. I think the difficulty is getting our arms around it or getting a handle on what the rates -- the risks are. So maybe trying to articulate that in the statement without being too precise in the absence of really good data I think is going to be -- would be appropriate but maybe kind of -- may not be easy to do.

I'm sure Carolyn and Keiji are up to it.

Other comments on these changes?

(NO RESPONSE)

DR. BRIDGES: All right. A suggestion was made that we include a separate cost-effectiveness section. Formerly what we had done was refer to some economics of influenza very generally within the effectiveness section. So for this draft, there is a separate cost-effectiveness section which is on page 12 and 13 in your copy. So this more directly addresses economics of influenza. A suggestion was made that we try and emphasize more the cost-effectiveness and cost-utility analyses rather than the cost-benefit analyses. This would allow for more comparison of vaccination with other preventive services, and the concern is that emphasis on cost-benefit analyses implies that one must have cost-saving for a vaccine to be cost-effective. And it also perhaps puts vaccinations on a different plane or it has them have some other kind of threshold economic value to reach as opposed to other preventive services. So more emphasis on cost-utility would allow

vaccines to be compared with other preventive services such as treatment of hypertension to prevent stroke, for instance. So that's the way that the -- what we had in mind when this section was written.

I've received some suggestions that additional references should be added. There was some concern about not having more information on cost-saving. I had a couple of e-mails from Dr. Nichol, and her concern was mostly for the healthy adult group, that in some of the cost-effectiveness and cost-utility analysis, there was very little information on productivity losses and that this was a major contributor for vaccine cost-saving in healthy adults. And for that particular population, cost-benefit analyses may be the most appropriate type of analysis. So I would really like some direction from the group as to how people think about this issue or if they feel that this is enough information currently in the draft about the cost-effectiveness.

DR. MODLIN: Why don't we take that up now if members of the Committee or others have comments, particularly

about this section. It appears to be a major addition to the statement. Kristin Nichol is not with us today? Okay. Any comments, pro or con? David?

DR. JOHNSON: I was listening to your comments about the difference between cost-savings and cost-utility, and I'm not sure, as I read through this the other day, whether that came across to me, making that distinction and making arguments for use of the vaccine or in favor of vaccine use in the absence of cost-savings. So, perhaps, that could be a bit more explicitly stated in there.

DR. BRIDGES: Some type of statement that although the vaccine may not be cost-saving, it is cost-effective in terms of producing illness and complications?

DR. JOHNSON: And then go on to add the things that Dr. Nichols mentioned to you about the productivity -- worker productivity, particularly for healthy adult recipients of the vaccine.

DR. BRIDGES: Okay. We do have some of that in the second line, "Studies of adults less than 65 years have shown that vaccination can reduce both direct medical

costs and direct costs from work absenteeism." Would you want us to be more -- have additional information than that, or is that sufficient?

DR. JOHNSON: For me, I think that's one of the stronger arguments for broader use of the vaccine in healthy adults. So perhaps if that could be expanded a little bit.

DR. SNIDER: Carolyn, Dixie Snider. I just wanted to pick up on a comment you made because I don't see it written down.

You stated that one reason to put the information in there about cost-effectiveness to be able to compare it to other interventions, and you have the data here about the estimates in the 18- to 64-year-olds, but it seems to me that it would be logical to say something about how that compares, because it does compare very favorably with many other preventive interventions that are routinely provided.

So I wondered if you feel comfortable adding a statement to that effect?

DR. BRIDGES: I think some of the difficulty in making a lot of comparisons among these different economic studies is they include very -- their methods are actually quite different and it is very difficult to compare these without putting in a considerable amount of text about the nuance difference between the studies, some of which can -- assumptions that are made can actually make a quite of bit of difference.

If we wanted to actually -- Folks in the Epidemiology Program Office here at CDC, along with other people in NIP and NCID, are working on a cost-utility analysis for high-risk people, and I think may give us a little bit better data because the cost-utility analysis data -- currently it's not very strong for influenza. We do have the Office of Technology Assessment report and we could certainly add that in there and that would give us information over age groups. We could possibly compare it with some of the pneumococcal vaccine information.

DR. MODLIN: Carolyn, reading over this last night, maybe I can -- I'm thinking out loud here, but maybe I

can kind of summarize perhaps what several -- a couple of the members of the Committee are articulating. It seems to me that the statement already has an awful lot of information and a lot of data, and the statements that are in there go about as far as the data will allow. But it may be that there is a way to highlight some of these data regarding cost issues, perhaps by putting them in a table of some -- for people who read a statement may gravitate quickly to a table that summarizes this information rather than -- I shouldn't use the word "burying" it in the text, but keeping it in a text of a fairly lengthy statement. I would maybe just encourage you to think about that and look and see if that might be a feasible way of getting at the same issue.

Other comments?

(NO RESPONSE)

DR. MODLIN: Why don't we go on and finish with the changes and then I -- maybe we could hold the rest of the comments until we finish the -- all the changes to the statement.

DR. BRIDGES: We've added information. We had formerly stated that there are racial disparities in terms of vaccine coverage, and now we have included the percentages that were differences in vaccine coverage by race and ethnicity supplied by NIP. So that is now part -- And everything that we've mentioned now in the vaccine coverage levels is for the last two years where there is data. Vaccination rates for people 65 and older appears to have plateaued. Obviously, we need the third year to say much, but that's something to bring to your attention.

The other thing that we did was add a paragraph on vaccine supply, mostly to acknowledge that this occurred last year, though we really don't -- can't make predictions about the future, but more as an acknowledgement that this happened. I'll just say that there was a typo on page 19 where we had not updated the information that Tamivir being approved for prophylaxis, and that will be corrected.

But in particular, I would like to get comments about the paragraph on vaccine supply.

DR. MODLIN: Maybe this would be an appropriate time actually to ask the representatives of the manufacturers to comment, if they would, about what they can tell us about next year's vaccine supply since it is an issue and since it is -- We have obviously added some new language to the statement that addresses this issue.

Maybe I could ask representatives of at least two of the major manufacturers, maybe starting with Wyeth. Is Dr. Paradiso -- if you would be willing to show your hand.

DR. PARADISO: Thank you, John. Peter Paradiso from Wyeth.

We have begun production of FluShield and have begun making the bulk concentrates for this next season. So manufacturing is ongoing. Obviously, we're waiting on finalized strain selection and you can no longer -- or it's no longer safe to predict what will happen as time goes on, but the current projections are that manufacturing this year and supply will be similar to the volumes of last season. And we don't, at this

point, anticipate any issues.

DR. MODLIN: Peter, do you want to say anything further about timing of the -- of availability of supply vis-a-vis the problems that we've had this past season?

DR. PARADISO: As I said, the two strains we know, the two A strains, and so we have experience with and feel comfortable with those. There's going to be a new strain. So at this point, we don't anticipate any coming issues, but we'll know more in the next couple of months, obviously.

DR. MODLIN: Thank you. Phil Hosbach?

DR. HOSBACH: Aventis is going to going to tip their hand a little bit and turn over a few more cards. I just wanted to let you know that our plans for this year are producing 38 million doses. However, we can produce an additional 17 million doses contingent upon three very important factors: one, to ensure that we're going to have that early strain identification on March 9th, which gives us about four weeks additional production time; also ensuring that we have a influenza season, that is, an immunization season that extends

minimally through the end of November, and I would strongly encourage this Committee to adopt such language; and then lastly, we also are working very closely with the FDA and it will take some work to expand our capacity, and that includes adding additional incubators. If all those three things come together in a timely fashion, we'll be able to produce upwards of 55 million doses and get it out to the market by the end of November.

DR. MODLIN: Thanks, Phil. Maybe this -- I should ask. I don't believe there are any representatives from Medeva here, but I should, for the sake of completeness, ask if anyone is representing Medeva, if they would like to make a comment.

DR. FUKUDA: John, I spoke with the company yesterday, and they said they would feel comfortable letting the Committee know that they plan on making -- they project on making a little bit less than they made last year, to around the same amount, again predicated on how the strains grow and process and, again, predicated on how long they expect to sell vaccine for the season and

what the demand is for this coming season.

DR. MODLIN: Thanks, Keiji. I probably should, at this point, ask if members of the Committee or others have comments or questions for either Dr. Paradiso or Dr. Hosbach. Bonnie?

DR. WORD: Actually, my question is addressed to both of them, in that -- you know, last season we didn't anticipate having difficulties -- didn't have anticipate having difficulties with production, and I don't know if you -- from a realistic perspective, are we going to go back? Is there any way that you can foresee trying to prevent the situation that happened this previous year? I mean, right now, is anyone having any difficulties growing or culturing anything right now in terms of production that you foresee that you could avoid so that we don't end up in that type of crisis mode situation as we did last year?

DR. MODLIN: Dr. Rubin?

DR. RUBIN: I'm Fred Rubin, Aventis Pasteur.

I think we're fortunate this year in that the -- that the selection of strains has been as announced,

and that puts everybody at a much more favorable position to producing vaccine. The B's -- There have been some strains provided to the manufacturers that might reflect what the final selection will be. So we only have one variable, one real challenge this year, and that's with the B. The problems that we're faced with, the new A strain last year, have been dealt with. So I think it looks a lot better for this year.

DR. MODLIN: Dr. Smith?

DR. SMITH: I guess we don't know from Wyeth yet the volume of doses that will be produced, but I'm just wondering if there's a sense of the overall supply this year.

DR. PARADISO: Last year our manufacturing supply was around 24 million doses. So our target this year will be in that same range. I agree completely with the last speaker. The ability to identify strains early, having experience with the two A strains already, reduces the risk considerably.

DR. MODLIN: Thanks, Peter. Dr. France?

DR. FRANCE: I think that also above and beyond the issue of slow growth, there was an issue of good manufacturing practices, I think, with some slow release from certain lots. I think that was specifically with Wyeth. So I'm curious just to see if those issues have been resolved from the viewpoint of --

DR. MODLIN: Eric, we may actually -- after the break, we have a session scheduled to discuss the delay in a little bit more detail. So maybe this will be an appropriate to bring that up.

Chuck?

DR. HELMS: The structure of the paragraph says we had a problem, we elected to do some priority changing. It seems to me, if it were possible and we were capable of giving a general statement about the efficacy of that intervention, not necessarily in the -- we will not know the incidence of flu, but we will be able to say how many people got the vaccine? Are we in a position of adding a general statement about our ability to respond?

DR. BRIDGES: We just received last week some data from the FoodNet survey, which is run by NCID. It's conducted monthly, and that data is from September through December. So we just got it and we're just starting to look at that to see what the distribution of vaccine was and by age group. We may have a little bit of data to put in there. Some of the other surveys that are done may take a little bit longer, but I think they're going to discuss that some more in the afternoon. If we have some data to show how that recommendation was followed, then we may be able to add it. The publication date for this ACIP is -- sorry, April 20th. So we're on a fairly short time frame.

DR. MODLIN: Other questions or comments? Rick?

DR. ZIMMERMAN: Rick Zimmerman.

There been had the question raised in the document about what was the different ways the different types of vaccine -- the purified surface antigen versus the split virion versus the whole, and it's just that this would be a good time to ask that question.

DR. BRIDGES: And if the manufacturers would want to

answer split versus whole versus what's going to be produced.

DR. MODLIN: I believe Aventis is the only manufacturer of whole virus, is that right?

DR. HOSBACH: Yeah. We were the only manufacturer making whole virus, and last year we took the decision to discontinue manufacturing that product, specifically to provide more doses. It really chews up a lot of our capacity to make whole virion, and we don't have that many people purchasing it anymore. So we elected to go fully to the split.

DR. PARADISO: We make only split cell.

DR. MODLIN: All right. Other questions? Yes, Marty?

DR. MYERS: I would wonder if it would be advantageous to have a sentence in here that encourages provider groups to consider planning for administration of vaccine later in the season. We'll see later this morning, there's an issue of late-in-the-season administration, but that doesn't appear to occur.

DR. MODLIN: I think there is such a statement in there, if I'm not -- from reading over it last night,

Marty.

DR. MYERS: But I meant under the supply, because I think the vulnerability is, again, delay in vaccine when it -- when it occurs. So there isn't, at this point, obviously an effective means of distributing vaccine later in the season then we're accustomed to.

DR. MODLIN: Perhaps not in this section, but is there not in the statement a -- some guidance as to what to do in case there is a bit of delay in terms of planning for mass immunization clinics and so on?

DR. BRIDGES: The statement currently, as we had modified it last year, recommends that mass campaigns planned for mid-October or later. Actually, Lynette, if you could go to this -- changes for -- There's also been a suggestion by Dr. Orenstein to add additional information. This was published in the October MMWR about the vaccine supply, to add information that, in fact, the influenza season often does not start until January or later, as another means to encourage people to continue vaccinating after October and November.

DR. SMITH: Yeah, I agree with that statement, because

we have endless calls about providers even not wanting to give it in November because somehow they thought that was too late. So I think adding that statement that it's fine to continue vaccinating would be very helpful.

DR. MODLIN: Dr. Rubin?

DR. RUBIN: On page 19 -- Fred Rubin, Aventis Pasteur. On page 19, about optimal timing for vaccination, I think the first sentence reads optimal time to vaccinate through mid-November. I just wonder if you couldn't make it easier and say "through November." I don't know why mid-November -- It seems to me that gives people an opportunity to stop vaccinating in the middle of November. Whereas, if you say through the month of November, I don't think you penalize anybody and I think you make it hard for people to wiggle out of giving shots through the month.

DR. BRIDGES: I think that the mid-November was used so that -- because there are occasional years where we'll see a lot of influenza activity starting at the

beginning of December. So that will give people the two weeks to develop antibody before the beginning of December. But as, you know, this statement indicates, the majority of time you're going to see most of the influenza activity in mid or late December or later.

DR. MODLIN: Larry?

DR. PICKERING: Yes. Larry Pickering.

Two points. One is, this is an extremely important teaching point, and I would suggest that it be put into a format of a table so that it, as Dr. Modlin said, isn't lost in the text.

The second point we have is that, in pediatrics, we're limited to two vaccines since the Medeva product is not approved or recommended for children less than four. Do we know if that is going to change with the upcoming season? Will data be presented to see if it can be utilized in the younger age group?

DR. MODLIN: Maybe we should ask Karen if she has any new information on that.

DR. MIDTHUN: I can't comment on that.

DR. MODLIN: Guess not. Turn on Dr. Midthun's mic.

There we go.

DR. MIDTHUN: I can't comment on that.

DR. MODLIN: There's your answer.

DR. BRIDGES: Actually, if you go to the next one on that, we did add that information to this year's recommendation. So it explicitly talks about the approved age group for the different manufacturers of influenza vaccine. So now it's in the rec. So it states it very clearly.

The other thing, if we're done with that part of the discussion, is we added information from Greg Poland's article in JAMA about needle length, about the fact that if you use a needle length of less than one inch in adults or older adolescents, that you may not reach muscle tissue. So that was just added there to clarify.

DR. MODLIN: Myron?

DR. LEVIN: Levin. I gather you've gone beyond page 17. Could I make some comments about pregnancy?

DR. BRIDGES: Sure.

DR. LEVIN: First is that we don't have any data on

coverage during pregnancy, or none is mentioned. I don't know if it's available, but I think it's an area where they can fall through the cracks. It would be nice if we could somehow indicate that obstetricians may take some responsibility for this during the appropriate time of year.

You might mention that the neonatal infection rate, which you pointed out is very high, might be affected by immunizing the mother. And maybe we could ask Dr. Glezen to give us some information on that.

Finally, occasionally, the issue of thimerosal comes up. I've heard it come up here in the past, and maybe you want to make a comment with respect to that, when you talk about pregnancy and immunization.

DR. MODLIN: Natalie?

DR. SMITH: Just a quick comment.

Back on page 19 under "General Population," there's a sentence that starts: "Physicians should administer influenza vaccine to any person who wishes to reduce likelihood of becoming ill with influenza." Given this past season, I would be more comfortable if there was a

little caveat or phrase in there that said "depending on vaccine availability" or something along -- besides -- It's just that word "should" I'm a little bit concerned about. "If vaccine is available" or something along those lines. Because, ideally, I think physicians would like to do that, given this last season.

DR. MODLIN: Carolyn, just in terms of being helpful, going back to the a couple of the comments that Dr. Levin just made, we -- there was a separate statement on thimerosal in influenza vaccine that was an update in the MMWR last summer, I believe, and there's no reason why that -- It was a very brief paragraph, and there's no reason why that couldn't be incorporated into the statement under the safety issues.

With respect to the issue of passive protection of newborns, we did discuss that here with -- when Paul Glezen was present, and my recollection of the summary of that discussion was that we just didn't have enough information to say anything with any degree of specificity. It was Paul's feeling that if there is

some protection, it's likely to be of relatively short duration in the first couple of months of life, but even that information was probably not sufficient to include in the statement.

DR. LEVIN: That is the highest risk period, as you point out.

DR. MODLIN: Beg your pardon?

DR. LEVIN: That is the highest risk period, as you point out. Yeah, I know it's not definitive, but it's just that it is a viable idea and might be worth mentioning.

DR. MODLIN: Walt?

DR. ORENSTEIN: If I could go back to this supply issue and the timing issue.

The concern I have is even with supply as it would normally be given, the adding of the 50-to-64-year-old recommendation, we still could run short. I'm intrigued with the Aventis Pasteur concern about adding 17 million doses, and I'm wondering if we can -- I know Carolyn was a little concerned about moving that mid-November date, but I'm wondering if we take Larry's

suggestion and put that table in and then add some wording that this would meet with concerns Aventis has raised, however, vaccination is still likely to be beneficial if vaccine campaigns are conducted into late November and beyond but to really try and focus on that issue, because I think 17 million more doses, I think, could be very, very helpful, especially given the new recommendations.

DR. MODLIN: Did you get that, Carolyn?

DR. BRIDGES: Uh-huh (affirmative).

DR. MODLIN: Okay. Rick?

DR. ZIMMERMAN: Additional support for that idea -- Rick Zimmerman -- could come from -- There is a study we're conducting. In about three-quarters of the elderly adults who are vaccinated, they're vaccinated at their primary care physicians offices. This is going to vary by region and by study, but it was a sizable percentage. Yet, adults -- elderly adults often only make three or four visits to their primary care provider in a year. So we have a six-week window and trying to get three-quarters of your vaccinees --

your potential vaccinees in your office in six weeks is a pragmatic challenge. If you even give another week or two, that gives you more time.

DR. BRIDGES: The recommendation also states that if high-risk people are seen in September for a regular visit, you can go ahead and start vaccinating then as well. So September, October, and mid-November.

DR. MODLIN: Rick?

DR. ZIMMERMAN: I also want to comment on page 15. The language about -- It's the very bottom of page 15: "Although healthy workers are at low risk for illness, adults" -- and then it goes on to describe the rationale that was used and it's crossed out for adults 50 to 64. I realize it's covered in the cost-effectiveness section, but if you're discussing the rationale and you're cutting out the issue of cross-effectiveness, decreased absenteeism, decreased office visits, that is part of the rationale. And I realize you mention it one place, but I think it still deserves to be summarized in this section because it's a substantial portion of the rationale, at least it was

for the AAFP in our decisions.

DR. BRIDGES: We did plan on including that, based on other comments as well -- similar language.

DR. MODLIN: Carolyn, why don't we move on? Do we have some more changes that you wanted to go over?

DR. BRIDGES: I'm sorry?

DR. MODLIN: Do you have some more changes that you wanted to go over?

DR. BRIDGES: Very quickly while I'm standing here. Just to let everybody know, the antiviral medication section has been updated. Also Oseltamivir is now approved for prophylaxis for persons 13 years of age and older and for treatment in persons one year of age and older. Zanamivir is now approved for treatment of persons age seven years and older. Again, the references will be updated in this section.

The last thing I wanted to point out were the differences in Table 1. The primary difference is now that we -- Parkedale Pharmaceuticals, as you all probably know, is not going to produce this year. So we're now down to three manufacturers. If you could

just put up Table 2, the next table, this has just been updated, again to reflect the new indications in terms of ages for use of the different antivirals and use for prophylaxis.

And that's it.

DR. MODLIN: Any further comments, particularly about the section on antivirals or any comments regarding the entire statement? Eric France?

DR. FRANCE: This is Dr. France.

You described a new table on page 10, which is putting all your hospitalization rates for different age groups, and I notice on page 22, you have a paragraph that's referring to what the risks are for hospitalization again with relation to Guillain-Barre risk. And you may -- instead of having that sort of wordy big paragraph on hospitalization rates for different groups, you might just reference back to that new table you've put in on page 10.

DR. MODLIN: Myron?

DR. LEVIN: Levin. We're doing general comments now?

DR. MODLIN: Go ahead, please.

DR. LEVIN: On page 18 where you talk about HIV-infected people, you talk about the effects on CD4 and viral load, and several comments.

First of all, there is quite a bit of information from other vaccines as well that don't affect CD4 and viral load with those vaccines, and it would -- it might people more comfortable giving influenza vaccine if we mentioned -- you could do that in one or two sentences.

Secondly, it should be mentioned that there are two situations where you should be careful when you give the flu vaccine to HIV-infected people. If you are starting a new medication and you want to see the effect on viral load, you may not see that if you give the vaccine at the time you're measuring -- you're making your measurements or shortly before you make your measurements. So people have to be warned of that.

With respect to the Guillain-Barre Syndrome that you mentioned on 22 and 23, I found that a little -- I mean, you're trying to be careful and not tell people exactly what to do, but the way it's worded, it would

very hard for anybody to give influenza vaccine to someone who has had Guillain-Barre Syndrome following influenza vaccine or prior Guillain-Barre Syndrome. So I think we ought to just say it's -- well, we ought to talk about what we should say, but it doesn't help the reader, I think, in this particular paragraph.

DR. MODLIN: Myron, you're raising an issue that we probably spent an hour on when we were in a Committee discussion about a year ago, and I'm sure that the text and the language reflects just that. I guess the question is, how strongly do you feel about opening up a potential can of worms here again, or do you feel like --

DR. LEVIN: Well, I don't have any personal experience or strong feelings about it. I mean, I have personal feelings, but I don't have any data. Maybe -- I don't know if you need to talk about it at this open session or is there some way of just making the language a little --

DR. MODLIN: We did discuss the Guillain-Barre section and the language at some length at last February's

meeting, and this language seemed to be that that represented the best consensus and best compromise.

DR. LEVIN: I can offer one help.

DR. MODLIN: Yes.

DR. LEVIN: Elsewhere you say, in similar situations, that there are alternate ways of dealing with this and you mentioned the drugs. You don't mention that here, and you could.

DR. MODLIN: That's a good point.

DR. LEVIN: So, you know, during influenza season, if you didn't want to give vaccine to these high-risk people, you could manage it prophylactically.

DR. MODLIN: Well, that's an excellent suggestion. Are there other comments -- Yeah, it is an excellent suggestion? Jon?

DR. ABRAMSON: Jon Abramson.

I think we need to at least let you be aware that we will consider, to be more encouraging, whether there is cold-adapted influenza vaccine or just trivalent inactivated vaccine for children for the vaccine and ask you to consider that, whether you also want to be

more encouraging. That is different, again, than a recommendation, saying everybody under three or under five should get it. But I think from the sense of the Committee that I have -- and Peggy perhaps can chime in on this, I think at the very least, we all have got to be more encouraging. It's hard to stomach the data or hospitalizations and then recommending it for 50 to 64 and not at least do that, regardless of where we are with cold-adapted.

DR. MODLIN: Jon, are you encouraging us to actually change the language in the current statement now to be a bit more encouraging for use in children?

DR. ABRAMSON: Right.

DR. MODLIN: Could you maybe work with Carolyn and Keiji to suggest some language to that effect? I'm not certain whether the Committee is going to -- Could I -- How do others feel about this at this point? Obviously, we have plans over the next six to 18 months to examine the issue of influenza immunization in the pediatric age group in great detail. I don't think we had planned to make major changes in the statement this

year with this statement but clearly will be examining -- I guess a quick question, how others feel about moving forward now.

Dr. Neuzil?

DR. NEUZIL: Kathy Neuzil.

Just a comment, I think that this is a big issue and I know there are -- there's a working group looking into it, but I do think if we put hospitalization rates into a table, it will become quite obvious that the hospitalization rates in young children are as high in these other groups, groups for whom we do recommend vaccine. So switching our format, in and of itself, I think is likely to highlight that discrepancy.

DR. MODLIN: That's a good point. How do others feel about this? Maybe if that's the case -- Dr. Fetson?

DR. FETSON: David Fetson, Aventis Pasteur.

I think it would probably be a good idea for the Committee to sort of stick its camel's nose under the edge of the tent on this childhood immunization issue because in about two months or less, the *New England Journal of Medicine* will publish a paper by Thomas

Rickert and colleagues that will show that the Japanese program for vaccinating school children over a period of 20 years prevented something on the order of 37,000 to 49,000 deaths each year, and that when they stopped this program, the seasonal mortality in the wintertime returned.

So this is going to change, I think, in a major way our conception about the community-wide impact of influenza vaccination of children, and it really is a verification using six billion person years of observation of what Arnold Monto [phonetic] showed 30 years ago in Tecumsah, Michigan, that you can reduce adult influenza by vaccinating school children.

DR. MODLIN: Keiji, did you want to comment on this issue?

DR. FUKUDA: Actually, not. I had a question. This is gigantic issue.

I think that the rationale for vaccinating children, again is something that the Committee and the working group has discussed for a couple of years, and I think that, again, the -- the general philosophy of ACIP

guidelines has been to reduce mortality in that group of people who has been vaccinated. There has been a lot of discussion of whether there are sufficient data to indicate that if you vaccinate, say, kids that you will induce some sort of herd immunity, and Dr. Rickert's analysis has been anticipated. We know that it is coming out and stuff, so it will be good to see that analysis in print. But I think that is a very big paradigm shift. That's a very big change in thinking about vaccine. In part, that's why Paul Glezen has been doing that study in Texas, to try to test that hypothesis. I think that before the Committee really tries to make any major changes in that area, I would suggest that a lot of these data should be presented and looked at in depth. But that's my comment for that.

The question that I had for the Committee was just going back to some of the previous discussion. I'm a little bit unclear about where the Committee stands on the idea of expanding the season or changing the language. Again, the way that this has been presented,

I think, in the past is that there is a relatively optimal time to vaccinate high-risk people. And then after that period, that for those high-risk people who remain vaccinated, it makes all the sense in the world to continue to get vaccinated. The epidemiologic data, the risk data for individuals all indicate that that's a good thing to do.

The question of whether to shift the recommended vaccine season by another couple of weeks is, again, a little bit of a change in that. And I'm a little bit unclear of how the Committee is leaning on this issue.

DR. MODLIN: Keiji, if I understand, it was Rick Zimmerman who had made the suggestion and it was a logistical, practical issue of having a practitioner who deals with a large number of elderly, actually being able to get those individuals into his or her office and to immunize them in time.

I guess I would throw the question back to Rick. Do you think that having a recommendation for an optimum time for immunization with the -- obviously, throughout the entire statement, we encourage immunization well

past November for those who are -- who are at high risk and remain unimmunized? Rick, how do you -- with the stated rationale that it's -- we may do a slightly better job of protecting those individuals if we immunize them by the middle of November, assuming that influenza season can begin as early as the first of December.

DR. ZIMMERMAN: Rick Zimmerman.

I think the question about when the influenza seasons begin -- I think there have been some data -- there are a number of years that they've peaked in December. And I guess the question is, when is that peak in December? My guess, just looking at the Thanksgiving vacation, it's probably -- won't be much vaccination occurring that -- you know, after that time, and are we -- is it really that the peak is occurring mid-December, late December, or early December? Because that would make a difference. You know, if there was a number of seasons that the peak was the first week of December, then I think your optimal time -- I mean, that's pretty obvious -- would

be through mid-November. If the peak is usually occurring mid to late December, that changes things. So I guess the question -- the science question is, what's the epidemiology of those seasons that occur in December? When do they peak? So that would be my first question.

Secondly, I think you can use different wording to -- I think the wording currently in here doesn't give enough strength to expanding. I think that it could be expanded and you can use "optimal" and "still possible." You could use other ways of wording to get around the wording issue to encourage expanded use. I come back to, what's the basic epidemiology?

DR. BRIDGES: I think say even though the peak influenza activity may not occur until late December often, you know, we build up to that peak. And in some communities, there may be substantial influenza activity early in December. So even though the national peak may not be till late December, there are some communities who may be hit with quite a bit of influenza in early December.

DR. MODLIN: Just taking a look at the curves that Dr. Graham showed us at the very beginning, there certainly was a substantial amount of activity in November and December so that I'm sure there are a number of high-risk people that are being infected that early.

So I would encourage us to continue with the current language, but there may be ways -- if you have suggestions -- Rick, if you think it might be modified to suit things along the line as you suggested, why don't you speak with Keiji and Carolyn about it, if that's okay?

Are there any other questions about this specific issue, about the seasonality? We've got the unresolved issue of encouraging more use in the pediatric age group, recognizing that this is going to be a major focus for our working group going forward. I think in order to move things along, I'm going to suggest that, again, you might work with Keiji and Carolyn to suggest some language that would nudge us in that direction, but I think all of us would be, for reasons already stated, reluctant to make a major -- we're just not in

the position now to make a major shift. So the -- I think we can do that and still achieve what we all want to achieve.

Any other questions, comments about the statement? Myron?

DR. LEVIN: Yeah. Myron Levin.

On page 25, you talk about RSV confusing the -- some of the epidemiology that you're trying to derive for influenza. I think it might be worth mentioning that RSV actually may logistically make the disease worse and that when you see the two together, it not only complicates the interpretation of the numbers but also might make the disease worse. At least I believe that's the case.

DR. BRIDGES: I'm sorry. So you're talking about co-infection?

DR. LEVIN: Co-infection. You say it's hard sometimes to figure out which disease we're dealing with.

DR. MODLIN: I think the problem here is an epidemiological one in terms of trying to assess the impact of influenza during -- when RSV season overlaps

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DR. LEVIN: I understand. I'm just saying, where the two come together, it actually may be worse than when they don't.

Secondly, page 26 and 27, the laboratory diagnosis section, I think it might be worth putting more words in there to use it as a chance to teach people some things. For example, I think we should say somewhere that the specificity and sensitivity vary greatly by laboratory and by the test, you intimate by the test. But actually, I believe that in any region that the health care providers ought to have some idea as to how good their laboratory is with the test they're using at the time, because I see it very -- a great deal. Let me just find that page.

DR. BRIDGES: There was a suggestion made that -- by someone else also that we include what the sensitivity and specificity is of these rapid-antigen tests compared to culture. Would that be --

DR. LEVIN: That would be. Although the point I was trying to make is that even though there are published

on them, they do vary a great deal from year to year. You know, somebody publishes something three years before and a test goes on line, but then you find that when the virus changes, the sensitivity isn't as great. I see that all the time. Even though it's supposed to be 80 percent sensitive, it's only 60 percent sensitive.

It's also worth mentioning that some of the tests don't use -- are not licensed for all specimens that come in. Some are for swabs only. Some use nasal wash in children, but some do not. If you do create a table, it may be worth adding that to the table. Some tests actually are, frankly, bad. I don't know if you want to mention that. That is formatting of certain ones.

DR. MODLIN: I think these are excellent suggestions.

DR. BRIDGES: Okay. Does everyone else agree? I hear you mention table. You're suggesting we do a table of the different kinds of laboratory diagnosis of influenza? Is that what I was --

DR. LEVIN: Yeah. I think a table designed properly would help.

On page 35, your first paragraph talking about Zanamivir, and it mentions the problems that it may have in some people who have bronchospastic diseases. I found that -- again, a situation where we kind of told people all the problems and then say, if you want to go ahead -- It seemed to me like we were on both sides of the --

DR. BRIDGES: First of all, we don't have any rate information. I don't know if there's any -- Karen, I don't know if you have any other information about that.

DR. MIDTHUN: I'm sorry. That's under the purview of Center for Drugs. I'm sorry, but I really can't comment materially on that.

DR. BRIDGES: So the problem is we really have no rate information, you know, what is the risk, and that's why it's written the way it is. We can't be a lot more specific about rates.

DR. LEVIN: Okay. You mention the drug interactions of some of these drugs with -- with other vaccine, some of these drugs with other drugs. Is there any information

on interaction of any of them with the Peak 450 system in the liver? Because that's what is of interest HIV treating people -- people who treat HIV.

DR. BRIDGES: I think it's in the package inserts and we do have a section on -- among persons with liver disease, and if you think that would be helpful, we could use that.

DR. LEVIN: It's not just liver disease. If this up-regulated or down-regulated certain of the enzymes, then you would -- it would affect how you treat HIV, and the information may not be available, but if it were available, I think it would be worth adding there. And finally, in the table where you give -- which table -- it gives the formulations, I think Tamiflu now is in a suspension formulation, and that isn't mentioned. I can find the table. It's on page 53.

DR. MODLIN: Lucy?

DR. TOMPKINS: Lucy Tompkins.

I just wanted to affirm a statement Dr. Levin mentioned, which is I think a statement in there about laboratory diagnosis, that the clinician being aware of

what the predicted value of the test that's being used in the laboratory where they are having that test done is very important. You need to know how your own laboratory performs, and as you said, these published studies really don't tell you that.

DR. MODLIN: The point they're both making also needs to be underscored because this document is used as an educational document. People use this extensively to find out more information. So I think since we're going the route of having more information about antivirals, more information about the tests makes an awful lot of sense in this setting.

Jon?

DR. ABRAMSON: Jon Abramson.

I think there's one other point, and that is, there is at least one and, I think, now two tests that are available for use in the physician's office that do not have to be under clear regulations. So they have been approved for their use and there's no feeling that you get from there about whether the Committee thinks that's good, bad, recommends its use. I mean, you can

see the potential advantage of doing it in your office. You would be able to start antiviral therapy if you felt like that was appropriate.

DR. MODLIN: Phil?

DR. HOSBACH: I hate to re-raise the issue again, but just about the immunization season, just to give you a little bit about our experience as a manufacturer. Essentially, we get about 3,000 phone calls per day during the second half of September and throughout October. With the November 15th end of the optimal season, we actually get a shutdown in our phone calls by November 1st. So, really, to provide us with incentive to continue to manufacture, we just see orders stop and phone calls stop in a normal season when there's not a delay or a shortage of some sort. It just ends November 1st. And I think by taking this out to the end of November, perhaps you are going to be able to immunize people throughout mid-November. So that's just a comment from our experience.

DR. MODLIN: Thanks, Bill. Any other comments? Well, we do need to bring some closure to this.

Unfortunately, the flu statement is -- must be published in April so that we don't have the luxury of being able to see yet another draft that includes all of the comments and suggestions that we've made, and I think we have to take it as a bit of an article of faith, that the Flu Branch will accurately and thoroughly revise this statement to reflect the suggestions and the comments of the Committee. I think the only perhaps, kind of sticky issues remaining might be the wording with respect to pediatric use and perhaps some change in emphasis regarding seasonality. Is the Committee comfortable that Keiji and Carolyn can work these things out with perhaps some input from Dr. Pickering and Dr. Abramson and others regarding the pediatric wording? Dr. Neuzil may participate as well, if you might, in helping out with some suggestions regarding the pediatric wording.

If that's the case, I will entertain a motion that the Committee approve the Influenza Statement as presented and as amended, according to directions.

DR. DESEDA: I would like to make a brief comment. It

may not be the proper timing, but I think one very important issue that I see coming every year in my patients is that if any other respiratory illness affects anybody after the flu shot, that person is very unlikely to get it next year because they feel that it's a vaccine failure. And as physicians, we are the ones that perhaps contribute most to this because we call everything flu. I think if we're going to improve our ability to make the proper diagnosis, that will change, but it's going to take some time. And I didn't see anything in the statement mentioning that people should remember that not everything is flu and there's plenty of other respiratory illnesses around.

DR. MODLIN: That's a good point.

UNIDENTIFIED SPEAKER: So moved.

DR. MODLIN: Okay. It has been moved and --

DR. HELMS: Seconded.

DR. MODLIN: -- seconded that the ACIP approve the Influenza Statement for the influenza season 2001-2002. Those who have conflicts with Wyeth and with Aventis, or potentially with Medeva, are not eligible to vote.

So those in favor of the motion, if they would raise their hands.

(SHOW OF HANDS)

DR. MODLIN: Those in favor: Dr. Deseda, Dr. Johnson, Dr. Levin, Dr. Smith, Dr. Offit, Dr. Tompkins, Dr. Helms, Dr. Word, Dr. Modlin, and Dr. Brooks. Those opposed?

(NO RESPONSE)

DR. MODLIN: None. Those abstaining?

(SHOW OF HANDS)

DR. MODLIN: Those abstaining: Dr. Rennels, Dr. Clover. The motion passes.

DR. BRIDGES: Thank you.

DR. MODLIN: Thank you. We'll take a break and start back up at 10:30 promptly. Thank you.

(RECESS FROM 10:08 A.M. TO 10:32 A.M.)

DR. MODLIN: Can I ask everyone to please take their seats so we can get started with the remainder of the morning session. We will be ready to start in just about one minute.

Let me again urge anyone who has further comments

regarding the Flu Statement to please get them to Dr. Fukuda or Dr. Bridges as soon as possible, during or after the meeting.

The next item on the agenda will be a session and discussion on the influenza vaccine supply and the delay that we've experienced this past season. We have a number of presenters, but I understand that the presentation will be led by Dr. Marty Myers. Marty?

DR. MYERS: Thank you. I think we have the technology organized here.

Well, the national immunization programs, I think, are the greatest achievements of the 20th Century, but one of the issues about them are the vulnerabilities and the number of vulnerabilities to the immunization programs. We've talked about a number of these over the years. One is the loss of disease visibility. We don't see children with paralytic polio or measles encephalitis anymore. And as a consequence, there's a lessened parental and patient motivation. We have a lot of challenges to safety credibility. There are disparities in coverage and what we're going to discuss

today, which is the whole issue about vaccine supply vulnerabilities to the immunization programs. This was in the *Atlanta Journal-Constitution* and I would suspect in a few other newspapers a couple of weeks ago, which is "I'm sick, the world has ended, call for help." And then Cathy asks, "Is there a shot to protect me from a whiny flu patient?" Huge demand, we ran out early this year. I just had to put it in. At the NVAC last week, we considered as a generic topic the whole issue of vaccine supply vulnerability, and we used influenza from this last year and the tetanus-toxoids-containing vaccines that we're going to consider later at this meeting as examples of vulnerabilities to the immunization programs and to vaccine supply. We also mentioned the issue about meningococcal vaccine, which is utilized episodically, the need for an oral polio stockpile, and so on. But basically, we concentrated on the influenza experience of the last season as a -- and the toxoids issues as an example of the vulnerabilities of the vaccine supply. And we established a working group to consider defining

those vulnerabilities to specifically look at where the places are that vaccine supply is vulnerable and then to consider the challenges that occur in addressing the issues of distribution and re-distribution of vaccine under circumstances of vaccine in short supply. So now you know why we picked influenza as the example to -- last season as an example to consider the whole issue of vulnerabilities to supply and then the consequences of dealing with trying to distribute and re-distribute vaccine in short supply.

There are a whole lot of aspects of vulnerabilities of vaccine supply and quite a number of them are given by the influenza experience last year. First of all, there are changes and sometimes unpredictable changes in vaccine supply -- in vaccine demand. So this morning's -- early this morning, we spent a lot of time talking about pediatric -- more permissible pediatric recommendations, the more permissive recommendations for the 50-to-64-year age group and so on and increasing demand for this vaccine.

There are a limited number of manufacturers and we'll

address obviously in a few moments, but for all of the vaccines there are limited number of vaccines. There's the whole issue of high development costs, the often limited profit motivation, particularly one of the issues we deal with with influenza and then the whole issue about public skepticism about safety. Some of these vaccines are produced in the United States and some of them are produced offshore. There are a whole series of regulatory imperatives so that we have issues relating to good manufacturing processes and the impact that that can have on vaccine supply. Influenza is probably one of the most complex production cycles for vaccine development, and when a new strain fails to grow at high productivity, it represents a vulnerability to the vaccine supply. Then, of course, there's the whole issue about dependence on other industries. In this case, for example, the egg supply is one of the other industries that drives or impacts the whole issue of influenza vaccine supply, and we saw many of these aspects this last year with influenza. Now, when a couple of people reviewed my slides

yesterday, they said this slide doesn't have a title, it doesn't a legend, and they're right. That's because I borrowed this slide by cut-and-paste from Norm Baylor, and he's going to show this slide in just a few minutes and he's going to give you the -- show the example, but it's 1998, 1999, and 2000. But what I would like you to do is instead of thinking of it that way, think of it a different way. Think about it as three manufacturers producing vaccine in a given season and one of the vaccine manufacturers, or more than one of the manufacturers, coming on line later than the other manufacturers so that there is a discrepancy between the rate of production of vaccine. Now think about the vulnerabilities that this makes to the vaccine supply, because this is clearly what happened this last year. This isn't manufacturer A, B, and C, but it gives graphically the issue that happened last year with a delay in the production, causing a functional shortage of vaccine during the primary immunization months. And then raises the whole issue of maldistribution of vaccine in short supply so that

if you were the red manufacturer here, then -- or rather, if you had licensed or contracted with the red or the green manufacturer to provide your vaccine, you would get it at very different times and it would show up in different parts of the distribution process at different times and impact -- So if you were a grocery chain and you had your vaccine from the green supplier and you were a nursing home and you had it from the red supplier, you have a lot of the types of problems that we experienced last year.

So some of the issues that relate to the distribution and re-distribution of vaccine in short supply are some of the things that we experienced last year. First of all, trying to determine how many doses are available and where they are, which would seem like a fairly important thing to know, is proprietary information.

So tracking vaccine in the pipeline. Clearly, the manufacturers provided a great deal of information, but it's very difficult to get this information and provided. There exists pre-existing contracts the manufacturers had to the various distributors and the

distributors have to different providers. There are issues about managing stockpiles we talked about and we will probably talk about later when we talk about the toxoids.

And then there's the whole issue of the private and the public distribution systems as being remarkedly different. Of course, with influenza vaccine, as Mr. Mason will show us, the vast majority of influenza vaccine is in the private distribution system.

Then there's the whole issue of infrastructure, the differences between adult infrastructure and pediatric infrastructure for the delivery of vaccines, and we'll say a little bit more about that later. Then the whole issue of -- We heard a lot of anecdotes about supply and demand, cost gouging that occurred this past season.

So that's sort of an overview of the issues that we're going to talk about. We're going to concentrate on issues of influenza, and Norm Baylor, from the FDA, is going to talk about this first from the FDA's perspective, and then Mr. Dean Mason from NIP, and then

I'll come back and make a couple of little summaries. So, Norm is next.

DR. BAYLOR: As Marty said, I'm going to give you a brief overview of the FDA's perspective on the influenza vaccine supply and delays this past season. As most of you know, the flu vaccine is a good example of how vulnerable this system -- the vaccine system really is. In fact, we know that the vaccine strain changes, the potential is to change those strains every year. The target of the vaccine is to produce antibodies against the hemagglutinin and neuraminidase, and what we try -- and the goal is to try to match -- get an antigenic match of the HA and the NA with the new strains, and that's how we predict the vaccine effectiveness. Then, of course, the influenza viruses are constantly evolving to escape the immune system. So this is a yearly process that we go through of having to try to make determinations on what the strain should be for from year to year.

In this slide, this is the slide that Marty just showed

you and now with the figures. And this is an example of the trivalent vaccine submitted for release, and basically, we're looking at 1998, 1999, and 2000. We all know that there's -- as I said before, that there was a delay in the vaccine distribution this last season, but the amount of vaccine produced in the year 2000 was actually similar to the amount produced in 1999. However, in this slide, you see -- if you look at 1998 in the green, we had -- about 50 percent of the total vaccine was available around August. That's here in the green. Whereas, this year, it took us about until October to get to the 50 percent of total vaccine for release and we were out until November and December before we got up to -- close to 100 percent of the vaccine distributed. Whereas, in past years, that's -- that vaccine was available in October.

Now, the causes of the delay, there were a couple of causes of delay in the vaccine production. One was there was a production delay at three of the four manufacturers licensed to produce influenza vaccine in

2000, and we had really never been in the position where we had three out of the four manufacturers experiencing problems. Usually, you get one, sometimes two, but last year was -- we had three out of the four. Then there were also corrections of deviations from good manufacturing practices that were noticed last year. Then we have the low yield of the A/Panama strain. One of the manufacturers had difficulties growing this particular strain. So with the combination of all these factors, we had a delay last year.

Now, this slide depicts the vaccine production cycle, and as you can see from this slide, this is a year -- this is every -- all throughout the year, something is going on, I mean, from January to January. And we start up here with vaccine use. Generally, the vaccine use is -- vaccine is used between September and January as -- from this morning's discussion, in October, November in past years, we've been seeing most of the vaccine used up, but it stretches -- it may stretch from September to January. Of course, then the

distribution starts about July. We get -- The FDA gets the submissions reviewed and approved and you start distribution. Of course, you can't have -- it's obvious that you can't have distribution until you make the vaccine and the trivalent formulations, starting May, June, and the monovalents, this is going on all year and especially as we make the recommendations -- as the recommendations for the strains come out in that January VRPAC meeting, the manufacturers are able to get started about this time when -- if we are able to give them at least one or two of the strains that are going to be in that season's -- that flu season's vaccine. And then the new seed viruses, that's going on all the time as far as trying to develop seed viruses that have good yields. Of course, the recommendations, again, January through March, January VRPAC, February is WHO, March VRPAC to wrap up all -- to get all three strains selected. Surveillance is a year -- through the year, and then, of course, new reference and reagents, these are occurring as well throughout the year.

This slide is a little bit busy, but I'll walk you through it, but it's basically the time of distribution of strains and reagents. And what we're doing here is showing you the timing by the month of the year of distribution of strains of the last five new strains recommended since 1998. The blue is the reference virus's potency and the red is the potency reagents. As you can see for last year, the A/Panama, we had reference virus ready at about December, January. Potency reagents were available in May. Looking at New Caledonia, reference viruses were made rather early and, again, the potency reagents were available around March. The yellow here, this is a constant. This is the time of the recommendations as I showed you on the last slide, January through March.

Then the B strain, the Yamanashi, again, the reference virus is available February, June for the potency reagents. But the key here is that these strains -- Last year we talked about delays, but these -- the reference viruses for the strains going into last year's vaccine were available at or -- either at the

same time as years past or somewhat earlier, such as the case with the New Caledonia strain. So this -- the time of distribution of these strains and reagents last year was not a reason for delays.

In this slide, it's just briefly to show you the seed viruses submitted for release. And in this slide, red represents A/Panama, blue New Caledonia, and green Yamanashi. And you can notice that if you look at the Panama seed virus, this was completed earlier and over a shorter time period than for other strains. So we're looking at the red here, April throughout -- April, May, the bulk of this seed virus was submitted for release. Whereas, you see the New Caledonia went out as late as September before all of it was released and the same thing with Yamanashi. So even though there were some problems getting the Panama going for one of the manufacturers, still the seed virus submitted for release was pretty much on target.

This slide shows the trivalent lots submitted for release over the past decade. And what you'll notice here is that between 1990 and the year 2000, there's

been about a twofold increase in the amount of vaccine available. We went from about 40 million doses in 1990 to around 80 million doses in the year 2000.

So, in summary, the distribution or delay for shortages, they can be expected if production is delayed at multiple manufacturing facilities. And this is something we really can't predict, as the manufacturers begin growing the strains. We really don't know if there are going to be manufacturing issues early on. So this is hard to predict.

The production of the vaccine was delayed by temporary difficulties with the new vaccine strain and by need to correct manufacturing practices. Hopefully, we won't experience much of this working with the manufacturers, making sure the facilities are up to good manufacturing practices, and hopefully we can get -- in dialoguing with the manufacturers, we can minimize this.

Of course, as you all are aware, Parkedale did not complete the corrections and they withdrew from production in the last flu season. Besides one of the strains growing slow, that was corrected, and the GMP

problems, the year 2000 was not that atypical from previous years. I mean, as far as getting the reagents available, that was on target. As far as getting the strains selected, that was on target. There were just -- There are some factors that are not completely within our control.

So I'll stop there and take any questions.

DR. MODLIN: Thanks, Norm. Mr. Mason, Dean Mason from NIP?

MR. MASON: Thank you very much. I'm Dean Mason with the National Immunization Program. My purpose for being here, unless you ask my mother, is to present to you information on the impact of flu vaccine supply on program operations. What I hope to accomplish is to provide a brief view of CDC's flu vaccine contracting history -- I thought you might be interested in this because it gives you some insight as to who some of the past players have been in the flu market in the United States -- and also to address the differences in supply this year compared to recent years; describe the problem, the public health response and some of the

lessons we've learned; and highlight some of the key steps necessary for on-time production and supply for the coming season. Norm has focused -- much of his focus was on the front end and my focus will be on the result of this flu supply situation this year.

CDC's contracting history for influenza vaccines actually began in 1976 with the Swine Flu campaign. The legends characterize the different companies in the initial year, '76. We contracted with four companies. The yellow, Merrell-National; Connaught, now Aventis Pasteur -- They clearly lead in mergers -- the maroon; Evans Medical, the light blue; ER Squibb; you'll notice Merck, an original, the initial three years was a producer of flu vaccine for the U.S. market. So 1976, indeed, with the production volume and so forth, was the year in which we had the most producers of flu vaccine.

CDC contracted intermittently between 1976 and 1995, not every year, primarily because the focus of our funding and 317 grant program was to place priority emphasis on pediatric vaccines. Contracting has been

consecutive for the six years, or since 1995. CDC has had contracts for 14 of the past 25 years. Flu contracts have typically been stimulated by special initiatives or dedicated funding. For example, we worked collaboratively HCFA beginning in '86 through 1991 on a pilot program in which we contracted each year to evaluate cost-effectiveness and to evaluate if Medicare would pay for influenza vaccinations.

Aventis Pasteur, who we show twice in this bar graph because we had two contracts with them in year 2000, the regular contract and a contract of 9 million doses -- Aventis Pasteur has contracted with CDC 11 of these 25 years, including two contracts for this year. Of the seven companies, only three have given indication they will produce flu vaccine for the U.S. market for 2001-2002. The 2000 bar represents the two contracts. I think I mentioned that.

The figures on this table are provisional and are subject to change. This was the year when vaccine supply was sufficient but quite late. For 1999, looking at the -- and this does not include the 9-

million-dose CDC contract, but the 1999, or green bars, shows the typical distribution, not production, but actual distribution of product in the U.S. market. For 1999, 98 percent of the flu vaccine had been distributed by October 31st. Contrast that for 2000, only 36 percent of the vaccine had been distributed by October 31st. Distribution of vaccine through the 9-million-dose contract did not begin until December 18th. So we can see that distribution was completed last year by October and the bulk was still to take place this year in that experience.

We thought we would try to reflect who the customers are, where is the vaccine going to. Again, this data is provisional and not completely accurate, because one of our reporting sources could not truly tell us how much vaccine they distributed to nursing homes. But in terms of percents, and this is obviously conservative, at least three percent of the vaccine with the figures given to us went directly to nursing homes. 14 percent of the vaccine was bought by the Government. This would include DOD, CDC, U.S. Public Health Service,

Veteran's Administration, et cetera. 35 percent of the vaccine went to distributors, that is, resellers of product, and 47 percent of the vaccine went directly to private providers. If Schein/GIV is counted as a distributors and not as a manufacturer, and for the purpose of this slide we counted them as a manufacturer -- if you clump them in, cluster them in with the manufacturers, then distributors for the nation would be responsible for up to 54 percent of all the flu vaccine supplied in the United States.

I won't spend a lot of time on this slide. Suffice it to say, some of the key issues this year were the yield strain that's already been covered, the fact that Parkedale had intended to produce roughly 12 or 14 million doses, did not come through in that production, and that there were good manufacturing practice issues with two companies. And finally, 100 percent of all of the vaccine was not distributed through the regular channels until December 27th by the vaccine manufacturers.

What was the public health response to the supply

problems this year? This list is by no means exhaustive and it's slanted toward actions taken by CDC, with which I'm obviously most familiar. CDC learned about the GMP issues and the strain yield issues in March of 2000. We had weekly contacts with FDA for updates after that. The FDA still, under regulation, had some constrains as to what they could and could not tell us. So part of our planning problems truly relate to -- by law, there are only certain things that can be revealed to CDC and, thus, we can pass along in a public forum to the states and to our partners. So, certainly, government communication, by law, is limited in some of these areas and you don't know the extent of the true problem or the degree of production or supply. Oftentimes, or at least this year -- not oftentimes, but this year's experience was that that information came even into June and July of the year and, certainly, Parkedale's withdraw from the market was -- I can't say totally unexpected, but we did not have any inside information as to that occurring.

We first alerted the states in April of this year of the potential problem. We gave recommendations very early on to the states about postponing mass clinics. The basic counsel was obtain your vaccine before you plan clinics. Don't plan clinics and obtain your vaccine.

CDC contracted for 9 million doses in September to roughly bring the total amount of vaccine that would be available in the market this year to the same level as it was in 1999 and 2000. We also established a flu vaccine availability web site on October 2nd. This web site had a lot of hits, but we didn't have a lot of information about where you could obtain vaccine until December. And Aventis Pasteur began delivering on the 9-million-dose contract at the conclusion of their regular distribution. The original vaccine that we contracted for, that began December 18th.

Regarding the 9-million-dose contract that we undertook, this was a precedent for CDC to contract directly or with a manufacturer. We do contract each year for vaccine, but we typically contract on behalf

of the states. This year, with the 9-million-dose contract, which was accomplished on August 30th, the sales price was almost three dollars a dose in the public sector, five dollars a dose in the private sector. 7.7 million doses were packaged. We decided not to have prepared 1.3 million doses because the demand was low. Ordering began November 6th. Vaccine shipments began in December and 67 percent of the 2,700 orders wound up being canceled.

I don't want to spend a lot of time on this slide because it's somewhat misleading, though this slide will show you that the persons most frequently canceling were resellers of product. In point of fact, 1.8 million doses were canceled by one reseller. So that inflated the proportions that truly were being purchased by resellers. Of course, you can speculate as to reason for the cancellations as people obtained their vaccine ordered, they canceled the back-up order that they placed with us and Aventis because, obviously, they had received their supply or they were speculating in terms of vaccine, anticipating there

might be a market demand later on. When they determined that there wasn't a market demand, then they canceled the contract -- the purchase orders with Aventis Pasteur.

However, it is important or clear that we could point out that the most reliable of the orders was the public sector with the fewest number of doses -- orders canceled. The actual number of purchases in proportion, the private sector purchased half of the vaccine and the four percent actually wound up being purchased by resellers, 46 percent by the public sector.

I want to spend a little bit of time on this slide. I think it's an important slide because it reflects the influence that the public health sector or CDC has on the market. The yellow bars are what we contract for with flu vaccine each year. You can see that our contracts are limited, not by what we would like to order, but the manufacturers basically, up and until -- we hope this won't be true this year, but they've limited us to between 1.5 and 2.5 million doses. For

this year, Wyeth limited us to a million doses and Aventis Pasteur limited CDC to a million doses. Again, these are the doses that the states actually -- we pass the state orders through on the CDC contract and then the orders go directly to the states.

The blue bar represents -- or let me stay with the total flu vaccine. The red bar represents the total flu vaccine that is distributed. This is provisional reporting, it's voluntary reporting, and it's under-reported because not every year did manufacturer report their total volume. But the point is that the public health proportion of vaccine, 1.5 million doses out of 58.2 million doses, is a very small portion of the market. So our influence is very limited. Even this year, when we contracted for an extra nine million, bringing our total up to 11 million, it was 11 million of 78 million. I believe that's 77.9, if I'm reading that correct. Yes.

So in a -- I mean, we've never come this close before of having anywhere near seven or eight percent of the market. Very typically, it's less than five percent of

the market.

Now, the green bar -- to contrast this, this green bar represents the total pediatric vaccines purchased and the blue bar represents the total pediatric vaccines purchased through CDC's contracts. So in every year, you can see that the majority proportionate purchase of pediatric vaccines is through the public health sector, and this allows you to understand a little better perhaps the degree of influence that we exercise in the public sector and, by extension, the ACIP exercises directly by its recommendations, the influence being much greater in pediatric vaccines than it is in flu vaccine.

So what did we learn this year? Perhaps some of you could have predicted these things in advance of our actually experiencing it. We learned that there's a potential supply problem every year. The point that the manufacturers have long made, that FDA makes, is that flu vaccine, unlike MMR, unlike pneumococcal conjugate, is basically a new vaccine every year, a new production, a new formulation, and there are risks

involved in that in terms of reliability.
Private contracts for the purchase of vaccine often precedes the ACIP recommendations so that when the ACIP decides to target certain groups, certain peoples in the middle of the year, you may or may not be aware that the manufacturers are already beholding to a number of contracts that they have signed with resellers for the supply of vaccine to the reseller without regard to the ACIP recommendations. This is merely the timing and the way that the business cycle has to proceed. The ACIP recommendations may have only limited impact. And of course, this was something I know the ACIP deliberated about last year, but the motivation for a large employer to get all of their employees vaccinated may be a different motivation, to reduce the absenteeism, for work productivity, et cetera -- may be a different motivation than our trying to target the vaccine first to those who we've judged to be at greatest risk.
Distributors play a major role in vaccine supply. The market demand ends in November. We simply did not have

demand for the additional vaccine in December, certainly not January. And there's a wide variance in state operations in infrastructure related to influenza vaccine in particular and adult vaccines in general. We run the gamut from A to Z in terms of state interest in flu vaccine, from those states that want a very central focalized distribution system and influence some policy statewide to those states who basically say, we have no role in public health in flu vaccine, it's strictly local initiatives.

Finally, key steps for flu vaccine supply for 2001 and 2002, I think Dr. Myers and Dr. Baylor have covered much of this: certainly, the ACIP recommendations will have an impact on demand; the identification of the viral strains; the CDC vaccine contracts we anticipate will be awarded about April 16th, if all goes smoothly. And in August, vaccine distribution begins, if all goes smoothly.

That concludes this. Thank you.

DR. MODLIN: Dean, thank you. Marty, are you going to wrap up?

DR. MYERS: I'm just going to summarize. Dean already said it. I think that this is an extraordinarily complex process that we all take for granted, and the remarkable thing is that the manufacturers manage to produce between 70 and 80 million doses of vaccine year-in and year-out. It's rather surprising that we haven't had this kind of a problem previously, but I think, as Dean said, the vulnerabilities are there that this could -- this could certainly happen again. Influenza vaccine is distributed mostly in the private sector, which limits the available responses in periods of vaccine in short supply. I think one of the other things that Dean pointed out particularly well is that there isn't an infrastructure surrounding adult immunizations similar to that which we have for routine childhood vaccines. And then it's difficult to address the re-distribution of influenza vaccine in short supply because of each of those reasons, which sort of gets us to the bottom line, John, the issues of assuring supply, consideration of distribution and re-distribution of vaccine in short supply, and the whole

issue of adult immunization infrastructure.

DR. MODLIN: Marty, thanks. I think we obviously owe a debt of gratitude to Marty and the National Vaccine Program Office, NVAC, for taking on this issue and beginning to address a very important problem that I'm sure we'll be addressing for years to come.

We do have a little bit of time to open this up for discussion. It's obviously a very important broad topic. We don't have a lot of time, but let's take comments and discussion first.

Why don't we begin with Georges, and then Jon.

DR. PETER: Well, the National Vaccine Advisory Committee discussed this issue in equal detail last week, including other shortages. And as a result, we have formed a work group to study the broader issues with two specific points that Marty mentioned. One is the vulnerabilities and the second is challenges. We are not in a position yet to make recommendations to such -- for such a complex problem. I think the National Vaccine Advisory Committee, in its role, would be well-served by an ACIP representative, John. So we

very much would welcome a participant. And we expect that the working group will have a conference call in the relatively near future in order to get us started on this issue. Dr. Klein is the Chair of this committee and we have, I think, seven members, Marty and several designated -- seven members and several DFO's, and an ACIP member would be very helpful.

DR. MODLIN: We'll take care of it. Jon?

DR. ABRAMSON: Jon Abramson.

The *New York Times* has reported that there was a gray market that aggravated this maldistribution of vaccine. I'm wondering what we know about that, and to what extent it did contribute to the problem, and is there truly an investigation going on.

DR. MODLIN: Marty, are you prepared to address that?

DR. MYERS: I think there are a lot of anecdotes, including those in the *New York Times*. We certainly -- everybody -- each of the different agencies received a lot of calls and commentary about that. It's very hard to get concrete data on that.

DR. MODLIN: Walt?

DR. ORENSTEIN: I was going to say that the General Accounting Office is conducting an investigation in what happened this past flu season.

DR. MODLIN: Lucy?

DR. TOMPKINS: John, first of all, I'd like to volunteer to join Georges' committee, bearing in mind, Georges, that I have no expertise, nor understanding, nor was I actually aware of how little influence the CDC and the ACIP has on adult immunization. And my question to you pediatricians over there is just, is it -- why is there so much more influence on pediatric vaccines? What's the history of that? What organization -- Is it the AAP, you know, what is it, that's really made the big difference?

DR. PETER: Well, Lucy, that's a very, very important question. I think the Academy has played a very major role in the sense of -- that the pediatricians are the ones who deliver vaccines, together with family physicians. And I think their involvement helps greatly because pediatricians get their information

from the Red Book Committee, not necessarily from ACIP. So the collaboration is very important, but mostly importantly is we have a public health infrastructure that is focused on childhood vaccines, and I think that dates back to the history of vaccines, with the major problems of polio and measles, et cetera, et cetera. But I think your involvement would be very helpful because, first of all, you're an internist and, secondly, is you're very much involved with the major organization of Infectious Disease Physicians, the IDSA. So I think you might very well bring a perspective that would help us, too, but I'll leave the decision to John.

DR. MODLIN: Thank you, Lucy. You have your representative.

Are there other comments or questions? Dr. Marchessault?

DR. MARCHESSAULT: I think the Canadian experience has been -- might be something to look at. Of course, influenza vaccination has been under the responsibility of public health in Canada. They have a general

purchasing, and really, they control the flow of influenza vaccine in Canada. So if ever there was a delay or a shortage, they would be able to provide the necessary individual who needed the vaccine and not provide the others. It's a very effective model and it controls the price also.

DR. MODLIN: All right. Walt, do you or Dean want to say anything more about the contract this past year, the extra contract, with Aventis, and with respect to any assessment of how ultimately successful it was in terms of vaccine reaching those at high risk? I know that that data probably is difficult, if not impossible, to come by, but I'm sure it's an interest to everyone.

DR. ORENSTEIN: There will be attempts to evaluate what happened. Obviously, only 1.5 million doses of the 9 million that were contracted for actually got purchased. How many of them were actually used, I don't know. I don't know if any of the states have any information, but we will be trying to make some evaluation of what went on.

DR. MODLIN: Certainly, it, I think at one point in time, provided a certain degree of -- it was a small insurance policy that was -- I think was -- at least in my opinion, was very well thought through.

Natalie?

DR. SMITH: Yeah, just a couple of comments from a state prospective.

Dean mentioned that the market demand ended in November, which is true. Part of the issue that we had and other states had was that it was actually a lighter flu season than general. So I think if there had been a heavier flu season, more of that vaccine would have been used up.

Then, secondly, I --

DR. MODLIN: Natalie, could I press you on that?

DR. SMITH: Yes.

DR. MODLIN: Even though we saw some data that showed that it was a lighter flu season, it also looked like it peaked later this year by about a month.

DR. SMITH: Yes.

DR. MODLIN: So we're still on the very early part of

the down slope. You think that truly did affect vaccine acceptance and uptake even this late in the year?

DR. SMITH: It certainly did in our state because multiple media reports went out that the flu season seem to have peaked around the end of the year. And judging from conversations I've had with other states, or at least some of the other states, it did seem to have an effect.

DR. MODLIN: Okay. Rick?

DR. ZIMMERMAN: I think Lucy's question was very insightful, and there have been a number of factors, clearly the Red Book, the VFC --recommendations from this Committee. I think a third thing would be the Harmonized Schedule has had an impact in pediatric vaccine recommendations. And that leads me to the next question. There's been some discussion here about the idea of a Harmonized Adult Schedule, and is -- are we going to proceed in that direction? Is that part of the charge to the childhood harmonized group, is that part of the adult group, or are we going to create a

harmonized adult group? But I think that's a question that is actually a fairly important question.

DR. MODLIN: It is an important question, and we have began to discuss it a bit. We've discussed it with -- Rick, do you want to -- do you have anything to say, other than the fact that this issue has been put before the adult group, which would be the appropriate place to start.

DR. CLOVER: It is an issue that has been addressed in our working group and we'll begin discussion on that today at noon in the group.

DR. SNIDER: I guess maybe others might mention it, but I want to be sure that the school immunization requirements are on the table as another incentive for childhood immunization, which has clearly made a big difference. Also, I did want to mention that influenza vaccine coverage has just recently been included in HEDIS. So, hopefully, in future years and trying to think about incentives for adult immunization, that kind of -- a carrot, if you will, or stick, depending on how you look you look at it, will be available and

other tools will be available to improve coverage.

DR. MODLIN: That's an important message. And at the same time that we are beginning to experience stresses in the supply, we've also seen marked increases, particularly in some of the high-risk groups in terms of vaccine acceptance, and those two are not unrelated. I think as we go forward, that's an important message to carry.

Lucy?

DR. TOMPKINS: Just one other comment. Peggy Rennels just reminded me that a large proportion of the adult coverage is coming through Medicare. And of course, that would get the very highest risk group. It doesn't help with the 50-to-64-year-olds, but -- so what is our relationship with health care financing and our recommendations and how are those impacting on -- I mean, if Medicare is simply an individual responsibility, you've got your influenza vaccine paid for if you're Medicare-eligible. But what's our coordination with that?

DR. MODLIN: Dixie, Walt? Randy?

DR. GRAYDON: One thing I want to say is that we are in a project now with CDC in ten states where we're promoting standing orders by using our pros. And in addition, we sent an "All State Medicaid Directors" letter out this year encouraging all states to send letters to their -- all their nursing homes asking them to use standing orders. We, of course, pay for it. We allow them to bill in manners that make it easy for them to bill. They can bill on a ledger billing, that is, that the whole -- everybody in one nursing home be put on one bill. So we do everything we can to make it as easy for them to uptake the vaccine as possible.

DR. MODLIN: Thanks. Bonnie?

DR. WORD: Just to go back to Lucy's comment and even in one sense, I think one of the major differences as a pediatrician is that the concept of routine childhood immunizations -- I mean, that's a concept that's accepted and most parent understands that. The average individual knows that. And I think one of the things that may be is a marketing issue or whatever, but that concept of routine adult immunizations does not exist.

And until that concept is accepted amongst adults, then you're not going to get that big buy-in with all the other parties. I know that the National Medical Association was beginning to work on a project and they were calling it a "Family Affair," to try to push it as this is something that we can do as a family, to try to bring the adults in, not just to have it. So it may just be the way that it's approached to adults. There's no such -- The concept is nonexistent as routine.

DR. MODLIN: Sam?

DR. KATZ: I would just like to add -- This is Sam Katz. I'd add to Bonnie and to Lucy, that you're not old enough. Having sat through these meetings for a good number of years, there were only three people who ever spoke on behalf of adults: Bill Schaffner, David Fetson, and Pierce Gardner. They tried to develop a Green Book for the internists that would mimic the Red Book and generate interest. It's the physicians who've never been interested and who've never generated the enthusiasm that pediatricians have for immunization.

Over and over and over again, they've dropped the ball as far as making immunization an important part of primary care medicine for adults. Here he is.

(LAUGHTER)

DR. MODLIN: Dave?

DR. FETSON: David Fetson, Aventis Pasteur. Of course, Sam is right, but not completely so. I mean, I think that people here ought to recognize that 63 percent of people have -- who are over the age of 65 get influenza vaccine. That is a very credible performance, particularly since it's increased so much in the last five years or so. The major factor of that, of course, is the Medicare reimbursement which came into effect for paying for the administration, not just for the cost of the vaccine, but it's administration in May of 1993 that had been previously not allowed under the rules of Medicare, and that's had an enormous affect in this country. And our pneumococcal polysaccharide vaccine use in adults is probably now close to 50 percent. The United States leads all developed countries in the world in its use

of both influenza and pneumococcal vaccines, and those are vaccines for older adults. So I don't think that the story is all that bad, but it can get a lot better. Victor Marchessault described very briefly, in few words, what goes on in Canada and, unfortunately, very few people I think really responded to the truth of what he was saying. In Canada, about 95 percent of the influenza vaccine is distributed by provincial health departments to physicians who give it in their private offices. A problem that occurred in the United States this year would never occur in Canada, and I think we've got to remember that. It would never occur in Canada. It takes a morning's activity on the phone to determine how much vaccine is going to be required by the provincial health departments. That's all -- one morning. And they decide exactly what their national use of vaccine is going to be and they get on with their business. I think there is some lesson to be learned in that, certainly for adult immunization in the United States.

DR. MODLIN: I don't know if Lance Rodewald is still

here, but -- Sorry about that. Lance, do you want to bring us up-to-date on the movement towards new HEDIS standards for the vaccine?

DR. RODEWALD: Right. Two weeks ago, the NCQA, the National Committee for Quality Assurance, voted to accept, at a fairly narrow vote, the HEDIS measure for flu vaccination 60 to 64 years of age. They've had one for elderly adults for sometime now. This is out for public comment and public comment will be accepted until, I think, the third week of March or so. And the vote was fairly close unlike the childhood. They had another change in the childhood measure, which was to reduce the length of participation in a plan before a child is counted, but this will bring the flu measure for 50-to-64-year-olds -- it will bring millions and millions of adults under measurement in here, and I think it has the potential to have a huge impact of the uptake of flu vaccination.

So one of the things to do is to, I think, support recommendation. I think it was a very good one, but it's not done yet.

DR. MODLIN: Thanks, Lance. I'm going to take the initiative to draw the discussion to a close, just in interest of time, but obviously, this is a topic that we will continue to put before the Committee, probably on a regular basis from meeting to meeting.

The next item on the agenda is an update on the live-attenuated influenza vaccine and I understand that that will be led by Dr. Fukuda. Keiji?

DR. FUKUDA: Thanks, John. What I'm going to just do in the next few minutes is update the Committee on, I think, where we are and sort of give you a sense of the dynamics and what the time table is, because I think that it is getting close to the time when the Committee is going to have to begin making some decisions.

So, basically, in terms of flu vaccine recommendations, there are two main issues. The first one is whether healthy and young children should be routinely vaccinated against influenza. This is an issue Jon brought up a little while ago, but it's been in front of us for a while. And the second issue is if a live-attenuated flu vaccine -- if it's approved by FDA, how

would ACIP recommend its use.
Now, to a certain extent, the live-attenuated issues and the pediatric issues have been kind of muddled and sort of lumped together, and there's a couple of reasons why these issues appear to be intertwined.
The first one is that it's really been very clear that the potential approval of a live-attenuated influenza vaccine has spent a lot to focus attention on children and on the question of whether children should be routinely vaccinated against flu.
A second reason is that there have recently been some live-attenuated influenza vaccine efficacy and effectiveness studies, again really focused in children, and these reports have been generally -- generally quite favorable. Again, this has sort of engendered a lot of discussion about potential benefits of using live-attenuated vaccine in kids, for example, the fact that you can administer them without needles.
In addition, there have been some other recent studies, some conducted by Kathy Neuzil, some by Hector Desureata [phonetic] and people at CDC affirming that

influenza has a serious impact in young children. And here I want to emphasis young children, and by that, we're really talking about the group of kids who are, say, less than four or less than three.

Then, finally, it's clear from the submission by Aviron that the company is planning to market live-attenuated influenza vaccine for children.

However, there are some points that I want to take some pains to point out and try to separate.

The first one, and the most important one and one I'm going to repeat a couple of times, is that the issue of whether to recommend influenza vaccination of kids is a separate issue from how ACIP might recommend the use of a live-attenuated vaccine, and we have to take pains, I think, throughout the summer and the whole process to keep those issues separate. They are different issues.

The second thing is that I want to point out that there already is an inactivated influenza vaccine, a vaccine which we use in the country, and this vaccine is recommended already for children six months and greater. And perhaps -- almost the most important

point is that ACIP already recommends vaccination of kids older than six months if they have a high-risk condition, and to point out that, again, this has been a relatively unsuccessful effort. Some of the data that we've heard about in the past couple of years indicates, for example, that vaccination groups in kids, for example, with asthma, are as low as about nine or ten percent. So we have recommendations out there and we haven't really been able to implement them, even though there is a licensed vaccine. Now, in terms of what's coming up this year and into next year, here are some of the important dates. On October 31, a biologics license application was submitted by Aviron for a live-attenuated vaccine. The BLA was accepted by FDA at the end of December. And it's probable, again not known, but it's probable that sometime during the summer or fall of this year, there will be a review of the product by FDA's VRPAC. Now, what's uncertain is that after that review what the FDA -- the timing of the FDA decision will be related to the live-attenuated vaccine.

So after we get past the summer and fall period, it's really unclear what's going to happen, but one of the possibilities is that in time for the October ACIP meeting the Committee will be faced with having a licensed live-attenuated vaccine and could need to make decisions at that time. It's also quite possible that there will be no decision at that time, but one could be made in the winter so we could have the possibility that ACIP would have to make a decision in February or perhaps later. So it becomes unclear.

Now, sort of taking those things into account and sort of, I don't know, working out the process for the last couple of years, a timetable has evolved for the summer and for the coming year, I think. The first thing is that we're at this meeting in February. In May, the working group, the Influenza Working Group, which I think you all know is chaired by Bonnie Word, is planning to hold a meeting in Atlanta and there are going to be several different topics discussed in a fair amount of depth over two days. The first one will be the safety and effectiveness of inactivated

influenza vaccine in children, a review of that and a subgroup discussion. The second thing will be that there will be a review of the development and published studies on the effectiveness of live-attenuated influenza vaccines, not just the current product, but going back for the past 30 or 40 years. Then there will be some subgroups which will be presenting their take, their sort of review of certain topics, and one of the topics will be what's the potential for reversion of live-attenuated influenza strains back to some more virulent type of strain; what's the potential for the recombination of live-attenuated strains and wild-type viruses; and then there will be a lecture or review by a couple of people on what the impact of influenza is on children. I think at that time we'll be able to look both at morbidity and mortality data. Another subgroup is going to be reviewing the potential for repeat influenza vaccinations to have adverse immunologic effects on children and then another subgroup is going to be reviewing the potential biologic issues relating to the co-administration of

flu vaccine with other childhood vaccines. And I think that at that meeting, we'll begin the process of drafting what some of the ACIP options may be in the fall or winter.

So then we envision that after that meeting that the Full Committee will apprised of the working group discussions. Now, I think that, again, a lot of this whole process is really predicated on what happens at FDA and with VRPAC. Again, we don't know the timing, but possibly in July, August, or later in the year, there will be a VRPAC review of the Aviron product. And basically, the purpose of the VRPAC review is to look at the existing efficacy and safety data. So once the VRPAC goes through its process, at some point FDA will digest that information and basically the FDA will come to a point where it's ready to either approve the product, reject the product, or to request more data. Again, we can't -- we can't predict -- we don't know how that process is going to evolve, but based on the fact that the May meeting is only going to cover some of the important topics, we're envisioning that there's

going to need to be at least a second working group meeting, possibly in September or October. This is certainly not decided but under discussion. But some of the issues that also need to be discussed at that point would be: what are the feasibility of carrying out pediatric recommendations if they are made; what are the economic considerations of such a recommendation if it was made; and then what would be the impact of pediatric recommendations on existing childhood vaccine schedules and programs.

Also, at the second meeting, if VRPAC and the FDA have completed their review of the Aviron submission, what we're envisioning is that the working group will also want to look at the -- some of the data on whether there is an increase in adverse symptoms in live-attenuated vaccine recipients. We also envision that the work group and Committee is going to want to look at whether exposure of live-attenuated vaccine to certain high-risk groups, such as people with chronic lung disease or people who are immunosuppress, poses a risk to them. Then I think also at that second

meeting, we will continue to draft the potential options for ACIP.

So I think what this is driving at is that it is possible that in October of this year, the Committee will be faced with the possibility of making pediatric recommendations, really aiming for the 2002 season. And I think that in October -- by the summer, we should be clear whether it's the right time for the Committee to either make a decision or whether that decision should be deferred.

In terms of the live-attenuated vaccine, I think this really depends on how the process goes with VRPAC and FDA. If the LAIV is approved by FDA prior to the October ACIP meeting, I think that it's quite possible that the Committee will need to decide whether it wants to make recommendations on its use or whether it wants to defer that decision until later. If the Committee goes ahead to make recommendations in October for the 2001 season, for this coming season, these recommendations would have to come out in a supplement publication.

If the LAIV approval process is not completed at FDA and there is no approved product, then the possibilities are a little bit easier, and then basically they would just defer any recommendations until later.

So, in conclusion, I just want to point out again that the pediatric and the live-attenuated issues overlap, clearly. But I think that we need to work very hard to keep them separate. When you think about the two issues, the really fundamental issue is whether to recommend vaccination of young children. If there are pediatric recommendations that are made, this is going to have a broad impact and it's going to impact both on children and parents, it's going to have an impact on pediatric practice, it's going to have an impact on existing childhood programs and schedules, and it potentially could have an impact on supply situations.

Now, the second issue is that if there is a licensed live-attenuated vaccine, ACIP will eventually make some recommendations on its use but, again, when you look at the big picture, a licensed live-attenuated vaccine is

really going to provide another option for carrying out existing recommendations. So the final point I want to make is that, again, the ACIP has to be prepared to act potentially in October of this year, possibly in February of next year. Again, it becomes difficult to tell you exactly when votes are going to be coming up, but that's the potential time frame.

DR. MODLIN: Keiji, thanks. Keiji has very nicely laid out a road map for us and outlined the task at hand. He also has pointed out that -- I think that pediatricians may be subject to a bit of a mere culpa in this respect in the sense that acknowledging that our adult colleagues are doing a better job at immunizing our high-risk individuals -- patients than we are. Of course, it's an important issue. This is not the time to be discussing specifically the pediatric recommendation or LAIV, but if there are comments with respect to the process that Keiji has laid out -- Maybe we should start by asking Jon what the Academy is planning on doing in the parallel.

DR. ABRAMSON: Yeah. I think Keiji and we are in total

agreement that the issues are, you know, intertwined but separate, and what we are likely to do in our spring COID meeting at the end of March is decide whether we are going to liberalize to the extent of using words like encourage, economically and logistically possible, the use of the vaccine for the young group. So I just thought it was only fair to make the ACIP aware of that movement in that direction.

DR. MODLIN: Would you care to predict where you're going with this, Jon?

DR. ABRAMSON: I think that the three of us here think we're going to move in that direction. So when I say the three of us, for those who don't know, Peggy is also on the Committee of Infectious Diseases.

DR. MODLIN: Thanks. Bonnie, did you have anything else that you wanted to add?

DR. WORD: I think Keiji -- I think one of the things that we kept emphasizing was it is intertwined, but to really look at it as two distinct issues, because whether or not -- I guess I'm saying that I think he made the point, and I think that's what we really

wanted to emphasize, you know, you expand the recommendations and then, if so, we have options of two different things, but keep them separate.

DR. MODLIN: Yes, Dixie?

DR. SNIDER: Dixie Snider. I have a comment about the process.

I just wanted to make everyone aware of the fact that we obviously are working closely with the FDA on this issue. We do not want to get in a position where ACIP is making a recommendation before their vaccine is licensed. On the other hand, we don't want to be in a position of -- particularly since a lot of public sector activity depends upon the actions ACIP takes, we don't want to be in a position of having a two-tiered system whereby the private sector starts using a product and the public sector is unable to use it because ACIP hasn't made its recommendation. So it's a difficult balancing act.

We've had some discussions around ability to share information with Committee members, work group members, and the possibilities of utilizing appointment as a

special government employee to be able to share information that would be proprietary, of course, with the pledge of maintaining confidentiality. And we're still working on that issue with the legal folks at FDA, and I don't think we've come to a final conclusion on it, but from the program standpoint, I think we're in agreement that we would like to be able to share as much data as possible with ACIP work groups, including the Influenza Work Group on this particular issue.

DR. MODLIN: Thanks, Dixie. Yes, Dr. Neuzil?

DR. NEUZIL: Kathy Neuzil. I just have a question. You mentioned the two separate areas of the live-attenuated vaccine and the pediatric issue. I'm curious if the FDA indication is -- if they went in for a FDA indication for both children and adults, how that's tied together and if this Committee will also have to address the third issue is, what do we do with live-attenuated influenza vaccine in our adult population.

DR. FUKUDA: Well, I think that once the FDA -- I think that once the FDA process is completed, if there is a

licensed vaccine, then we'll have indication from FDA for what age groups the vaccine has been recommended for. And then I think that, you know, the group here will have to decide whether it will simply say in the recommendations that vaccine is recommended for high-risk people or it's recommended for these groups, and then there are two options. One if inactivated vaccine and one is live-attenuated vaccine. But I think that once we have the approved product, then this group here will have those discussions.

DR. SNIDER: I just might add -- This is Dixie Snider again -- that we've had some discussions with FDA around these issues, because what we're talking about is off-label use. And we don't want to be in a position, the ACIP, of not making recommendations for off-label use for -- in situations where we don't have the data, we're unlikely to get the data, and yet our clinical judgment indicates some action needs to be taken. The other side of the coin is that we don't want to be in a position of giving -- opening the door to indications that really should be studied by the

manufacturer, and so we have to be careful about the situations under which we make recommendations that are off-label and make sure that we're making off-label recommendations with a justification and not in situations where data could be obtained to justify doing the studies that are necessary. I think this is -- I say this for the education of some of the new members particularly, because I think we went through this similar issue around hepatitis B not too long ago. So many of you understand from that experience what we're talking about.

DR. MODLIN: Dr. Mendleman?

DR. MENDLEMAN: Hi. Paul Mendleman from Aviron. I think I can shed some light on the data in the biologics license application, having been involved in it intimately.

The indications that have been submitted and the data that are robust in the files support healthy children and healthy adults, healthy children beginning at one year of age and above. So there are no data in the application that would support six-to-twelve-month-

olds.
We have data that's been generated that is in the application, as well as ongoing, in certain subpopulations that are considered high-risk, but although those are in the file, those data are limited in terms of number. So there was a study conducted in adult HIV-infected subjects with mild or A cell dermatic disease that has been published by Jim King and JID that shows the vaccine was, in that subset of about 50 individuals, generally safe and well tolerated. There's also a similar study conducted by the NIH by Jim King and others that's been submitted as an abstract SPR this spring, and the data have been unblinded. And again, it's in mildly-symptomatic or asymptomatic children but not in AIDS children or in the adult subset in adults with AIDS.
We've also studied asthmatic children with moderate to severe asthma based on the NHBI guidelines published in 1997, and that's in the application, but it's also in a number of children, 48 children. 24 received placebo and 24 received Flumist. Again, in that population it

was generally safe and well tolerated. In a larger subset of asthmatics that have been tested, on exposure in Dr. Glezen's trial in Temple, Texas, in children 18 months to 18 years of age with a history of wheezing illness and asthma, it reacted well with disease. But I think the Committee should understand that it's really up to the FDA to decide on the data that's there for these higher risk populations and that our -- the robustness of our study population is healthy children and healthy adults and that's the indication they requested.

DR. MODLIN: Thanks, Paul. Other comments?

(NO RESPONSE)

DR. MODLIN: Keiji, thanks very much. Obviously, this is an issue that will be before us and on which we will be spending a lot of time and focus in the next two, perhaps three meetings or longer.

Chuck, Dr. Helms, and his working group are towards the end of the task of updating the smallpox recommendation. We examined the draft in some detail at the October meeting, and I believe the purpose today

is to go over whatever minor changes may have been added since then and to approve the document.

DR. HELMS: For those of you that haven't been around since the designation of the Bioterrorism Working Group, we came into being over a year ago now with the purpose of looking at those vaccines which are going to be important in regards to the civilian use of vaccines for prophylaxis and treatment of diseases that are of highest concern for bioterrorism. The two vaccines that we were assigned to work on were anthrax vaccine and also vaccinia vaccine.

You're aware from our last visit that the anthrax vaccine recommendations were approved and have now been published, and I guess they're in your handouts today. Today we're bringing before you what we hope is the final draft of the vaccinia recommendations as well. We've been very fortunate in the working group -- in having a working group of some experts which has been historically interesting to have so many -- I guess the term advisedly old-timers on the group who have actually seen a case of small pox and to have some

younger people that wouldn't even have the slightest idea about it. And this may well be one of the last times in history when have such a spectrum of activity. At any rate, Lisa Rotz is here to present the changes that have come about since the last draft that you saw and would be open for discussion on that, of course after that presentation. Thanks.

DR. ROTZ: I apologize for the slight delay. I had to make a quick change on a slide here. I would be one of the younger people that he was talking about that would have no idea.

As Dr. Helms said, we've been working on this since June or July of last year. It seems like it's even been longer than that, but -- I'll try to get through these fair quickly since it's lunchtime. I know that everybody is probably hungry.

As he said today, I'm going to present to you mostly the changes and additions from the 1991 recommendations that we included in the 2001 recommendations, and the draft you have still has 2000 on it because I've not quite caught up with the times, but it's been changed

on the presentation and will be changed on the next draft or the final working document that's presented for voting. So I'll present to you the major changes and engage in any discussion that you would like to have on those changes and then discuss whether or not you feel a draft is ready for a vote at this time.

This is just a quick outline of the different sections that are addressed in the draft that you see in front of you, and the ones that I'll be discussing in more detail are the ones that are underlined and highlighted in yellow. I've not put the subheadings that are listed on these just for space here.

So we'll move on, and what I want to do right now is just give a little bit of background information on the vaccine efficacy that we include in the current recommendations that support some of our later recommendations regarding re-vaccination intervals.

We have previous epidemiological data that suggests that vaccination contains a high level of protection against smallpox at least for about five years following initial or their very first primary

vaccination. And at that level of protection, even though it decreases up to 10 years following a primary vaccination, it does remain substantial during that time period. And we also know that antibody levels for people that have received more than one dose or that have received a booster dose of smallpox vaccine maintain high levels of neutralizing antibodies for periods of even longer than 10 years.

Now, though we don't know the exact level of antibody that's protective against smallpox or vaccinia infections, we do know that in studies by Cherry [phonetic] and others in 1977, that over 95 percent of persons that are successfully vaccinated for the first time and that's using a vaccine take or skin take as an indication of successful vaccination, that those people have a neutralizing antibody of greater than or equal to one to 10 and they seem to be highly protected for up to five years. And we also see that this high-neutralizing antibody titer lasts for up to 20 years in three-fourths of the people that receive a second vaccination and even up to 30 years in persons that

have received up to three vaccinations, and that study was done by Lublin and Tennenbaum in 1990 and El-Ad and others in 1990.

I would also like to present a little bit of information on certain recombinant vaccinia and other pox viruses because this information is used to change the previous recommendation for vaccination of laboratorians that worked with some of these strains. Now, currently, from 1991, we have more information on several of the pox viruses that are currently used for vaccine vectors and we also know that several of the strains currently used as vectors are not capable of treating clinical infections and have been reduced to BSL 1 or 2 levels. In addition, certain pox viruses that are used now as vectors are associated with different species, such as the ALVAC and TROVAC strains, and aren't affected by antibodies induced by vaccinia vaccine and therefore, really, in all actuality, vaccination provides no benefit.

So, currently, for our recommendations on non-emergency use or non-bioterrorism-related use of the vaccine --

just to talk about some specifics, I've laid it out here and I can show you this particular wording in the document. But currently, we recommend vaccination for laboratorians who handle cultures or animals contaminated or infected with the non-highly-attenuated vaccinia or other orthopoxvirus strains that infect humans, and I list the ones that we do not require vaccination for because of their highly -- high attenuation. We also offer vaccination but don't require it for health care workers whose contact with these non-highly-attenuated strains is limited to contaminated dressings, mainly because their risk of infection from this type of exposure is extremely low. And in the interval between '91 and now, we've not had any reports of health care workers being infected in this manner by vaccines in -- or in vaccinia recombinant vaccine trials. We also do not require, which is a new change from the vaccination requirements in 1991 -- we do not require vaccination for personnel working with only MVA, TROVAC, NYVAC, OR ALVAC strains of the pox virus, and that's because these are highly

attenuated strains that do not cause meaningful infections in humans. They do not replicate very well in mammalian cells and, therefore, do not cause meaningful clinical infections. These recommendations have been -- had already been somewhat adopted by NIH in their laboratorians in that they don't require vaccination for laboratorians that working with MVA or NYVAC or the other two currently in their laboratory protocols.

Now, according to our available data on the persistence of neutralizing antibody and our epidemiologic data that I quoted earlier that we know from the previous smallpox era, persons working with non-highly-attenuated vaccinia viruses, recombinant viruses developed from these non-highly-attenuated viruses or other non-variola orthopoxviruses that infect humans, should be revaccinated at least every 10 years. And that's not changed from 1991. The interval was still 10 years in 1991. The only thing that's changed is that we're specifying the types of viruses that we're working with, that they should be vaccinated for. And

in order to assure a higher level of protection against more virulent, non-variola orthopoxviruses, such as monkeypox, vaccination every three years may be considered. And that was actually a new recommendation brought forth by several folks that have had experience with laboratories that manipulate monkeypox, and at the previous -- the previous protocols that they followed recommended vaccination every three years, and for some reason that was changed in '91 and nobody could recall exactly why that interval was changed for the specific laboratorians. So we gave them the option to vaccinate more frequently if they feel that they need a high level of protection because they're working with virulent strains of orthopoxviruses in those laboratories.

Now I'm going to move on to the list of the precautions and contraindications for routine or non-emergency use of the vaccine. This is essentially the same as those listed in the 1991 recommendations.

We have included some additional information on immunosuppressive conditions to -- that we've added to

the altered immunocompetence subsection, and that includes specific information on the dose of high-dose steroids that we could consider to present an immunosuppressive condition, as well as the addition of transplant recipients in the listing of immunosuppressive conditions that we would recommend avoiding vaccination in. And we also added a statement that vaccination of infants and children is not indicated for routine non-emergency uses since we specifically address the group when we talk about emergency use or bioterrorism-type use on the vaccine, and that's just so we can contrast and compare the two groups.

In addition, we added a table that outlines the vaccination contraindications during the routine non-emergency use and the contraindications during smallpox emergency use for easier reference for people that are referring to the document to compare and contrast when they would or would not vaccinate under certain conditions. And as you can see here, the things that are highlighted there, if those conditions are present

either in the vaccine recipient or a household contact, that would be for routine non-emergency use of the vaccine or contraindication to vaccinating that person, and that's not changed from 1991.

Moving onto treatment of complications that are -- vaccinia immune globulin on page 8, these also are essentially the same as the 1991 statement. However, we did add a statement about the currently limited VIG supply and that its use should be reserved for treatment of complications with severe clinical manifestations. And this has sort of come up as we've talked with the drug service personnel who handle these calls from the clinicians because the majority of times when they call in with a complication from a vaccination, it's not necessarily severe enough to require VIG. And a lot of times, consultation and watching of the patient is done. So this just gives them a little bit more leeway to evaluate that when the call does come in, on whether or not VIG would be indicated and let's the clinician know that it's not necessarily always indicated for some of the conditions

that are talked about in a section.
We also added the table for easier reference in this section that lists vaccination, adverse reactions, and whether or not VIG is indicated or helpful or not, because sometimes that gets lost in the text of the document. We also added the statement that VIG is contraindicated in vaccinial keratitis because it may increase corneal scarring, and that's based on rabies studies. That was not necessarily brought out well in the 1991 recommendations.
What's new to these recommendations? That should be 2001 recommendations, obviously. What's new to this is also a section that talks about any other treatment options for complications that may or may not be available. Currently, I'm going to skip to this and actually just go to the direct wording of this section. Currently, no antiviral compound has been FDA approved for use in treating vaccinia virus infections or other orthopoxvirus infections, including smallpox. Several antiviral compounds have been shown to have activity against vaccinia virus or other orthopoxviruses in

vitro in animal models. However, the safety and effectiveness of these compounds for treating vaccinia vaccination complications or other orthopoxvirus infections in humans is unknown. Questions remain regarding the effective dose and the timing and the length of administration of the antiviral compounds. There's insufficient information currently to allow the recommendation of any antiviral compound to treat post-vaccination complications or orthopoxvirus infections including smallpox. However, additional information may become available in the future and health care providers should consult CDC to obtain up-to-date information regarding treatment options for smallpox vaccination complications.

It was the thoughts of the working group that currently the studies that are out there and the information that we do have do not lend us to the ability to make specific useful recommendations to clinicians regarding the use of these antiviral compounds, but the Committee also understands -- the working group also understands that there's currently more active research in this

area and that additional information may become available in the future before recommendations are revised. And this encourages the clinician, if they have a concern or a question, to at least contact CDC to talk about whether or not there is additional information or any more specific recommendations could be given.

Moving onto the section on prevention of contact transmission, page 9. Most of these changes were based on inquiries received by the NCID Drug Services following the 1991 recommendations, inquiries from clinicians or research -- primary investigators that had to vaccinate their laboratorians on certain aspects after vaccination and care of the site.

Basically, this section gives guidance on care of the site, which emphasizes careful hand-washing as one of the most important things to prevent auto-inoculation from the site to another area of the body or to someone else. We did leave them -- give them the option to leave the vaccination site uncovered or to cover with a porous bandage, and that will bring -- we will bring

that out and emphasize more that if they leave it uncovered, they certainly need to maintain strict hand-washing control. And that was brought out mainly because in the past the site was never covered and some people have experienced more maceration when they've done the covering. And there was confusion about how to cover it, how long to cover it, and things like that. So we allow them the option of keeping that site uncovered with a bandage as long as they use very careful infection control measures of just hand-washing.

They are also told to keep the site dry in general with not putting any salves or ointments on the site, but they may bathe normally, and lots of questions came up on -- The previous recommendation said keep it dry, and lots of people called and said, "Well, can I take a bath?" So we kind of gave them a little more guidance with that.

Then we also have some guidance on how to dispose of contaminated materials, bandages, that are left on the site and care of clothing or cloth materials that come

into contact with the site. There were lots of questions regarding whether or not the shirt I was wearing, can it affect my wife if she's going to wash it, or how should we make sure that it doesn't contain any virus and infect anybody.

Then one thing that is different from previous recommendations, the previous recommendation did not have any restrictions on health care that were recently vaccinated on their care of patients or even care of immunosuppressed patients. And the working group felt that that actually should be addressed a little more closely with these recommendations, and that if it's possible, recently-vaccinated health care workers should avoid contact or working with unvaccinated patients to minimize the risk of nosocomial transmission, especially those patients with immunodeficiencies until the site is no longer infectious. But realizing that sometimes there may be not an option and a contact may be unavoidable, that they should wear a dressing and minimize the potential contact -- to minimize the potential contact

transmission to patients, and they might consider a more occlusive dressing that has been outlined in the recommendations that was also contained in the 1991 recommendations.

Added back to the 2001 recommendations are more specific information on site of vaccination, method of vaccination, and evaluation of the vaccine site. These were brought back from previous ACIP recommendations that were dropped in the most recent recommendations. This information was given in the recommendations previously when they were considering vaccination for protection against smallpox more so than what it is been considered in recent times. And the working group felt that this information would provide useful guidance in both non-emergency use situations, as well as emergency vaccine use situations. So we brought back some of that information. And you can see here where the information was obtained, and the majority of the time, the information was obtained from either WHO documents or previous ACIP recommendations as previously accepted techniques or evaluation of the

site.
Now, moving onto the section that is completely new in the 2001 recommendations is the smallpox vaccine for bioterrorism preparedness or the use of smallpox vaccine for bioterrorism preparedness. And in this overall section, we include an introductory statement on why these recommendations were developed and included in the current recommendations. And some sort of illusion to, you know, even though we know that the risk of smallpox is extremely low, there is concern. And then as being good stewards of public health, the ACIP has gone in to include some recommendations along these lines should this event ever occur. So this could be a useful guidance for clinicians.
We also put back in a surveillance section which was adapted from previous ACIP recommendations. We reintroduced this into the current document to provide guidance on reporting of suspected cases and initial measures for infection control for a quick reference for the clinician.
Now, moving into specific wording for pre-release

vaccine use recommendations, as you can see here, it's not currently recommended. Now, if things were to change with the higher risk groups or change with the actual risk of smallpox occurring, then pre-vaccination may be indicated for certain groups that would be at definite high risk during a release situation, and I'll talk about the specific wording in that section.

And it goes: At the present time, the likelihood of smallpox occurring as a result of a deliberate release by terrorists is considered to be very low and the population at risk for such an exposure cannot be determined. And that goes along with some of the similar recommendations in the anthrax vaccine recommendations.

Therefore, pre-exposure vaccination is currently not recommended for any groups other than laboratory or medical personnel working with non-highly-attenuated orthopoxviruses, and it refers you back to the section where those initial recommendations are made.

If the potential for an intentional release of smallpox virus increases at a later time, pre-exposure

vaccination may become indicated for selected groups, and it lists some of those groups, who would have an identified higher risk of exposure because of work-related contact with smallpox patients or infectious materials.

The working group felt that that was an important point to bring out, that currently the risk does not warrant vaccination, but in the future, if we have additional information or different things come to light that the risk versus benefits of pre-exposure vaccination may actually lean back towards the pre-vaccination recommended, whereas, currently they do not.

Moving onto the post-release vaccination recommendations on pages 12 through 13, currently the groups -- the working group actually approached this as saying, you know, there are probably lots of groups that would think they would want or need a vaccination in a post-release, and there probably are lots of other groups that this might be expanded to include.

However, realizing that it's much easier to expand your recommendations than to contract them, the working

group decided to focus on groups that they knew had a definite need for vaccination because of their high risk of infection due to exposure or potential exposure. And that's kind of where they approached these recommendations, realizing that public health officials or other officials may decide to expand that later on but, again, it's much easier to expand and then contract recommendations for groups -- for vaccination.

So working within those guidelines, if smallpox were to be released in an aerosol setting as one of the possibilities, persons that were exposed to that initial release would obviously be indicated for vaccination. People were face-to-face household or close-proximity contacts to smallpox cases, or probable cases, would have an indication for vaccination. Any personnel that's been designated to be involved in direct medical care, public health evaluation, or transportation of potential smallpox patients, if they haven't already come into contact and fallen into the second group, if they are designated for continued

activities, they should receive vaccination, as well as laboratory personnel that would be involved in collecting or handling specimens from potential cases. Then again, also, persons with a high likelihood of contact with contaminated materials, and within the recommendations, we go through and discuss in more detail who those might be and specifically talk about if a certain facility was designated to care for an evaluate smallpox patients, personnel that might be required to handle laundry or process things like that, that would have a high risk of infection from handling those materials would also require vaccination under these types of guidelines. And it's brought out within those recommendations that -- when we talk about pregnant women or children, any of those that fall into this category, pregnant women or children, if they fall into a category where they have a high risk or had a high-risk exposure to smallpox, vaccination would be indicated even though, in the previous routine non-emergency use, it was contraindicated in those groups, and specifically indicated because those people also

have a higher risk of having a very severe smallpox infection. Therefore, sort of everything goes out the window when you come face to face with smallpox and just about everybody would be an indication for vaccination if they had high-risk exposure.

One of the groups that the working group sort of struggled with for inclusion in this -- or some of the other folks that are very important or would be very important in the overall response are public health, medical emergency response to a smallpox emergency because you're going to have a lot of people that want to have -- or want to be vaccinated or ask to be vaccinated, and we also again have to sort of narrow that down to the people that we know would require it because of the potential high risk of coming face to face with the virus and contracting the virus because of their responsibilities during a response.

Therefore, we put the one other group in here, that "persons with contraindications whose unhindered function is essential to response activities," and we used, for example, law enforcement personnel that were

assigned certain duties, "who have a reasonable risk of contact with smallpox patients and infectious materials during non-patient care activities," and then a couple of other examples for that, "should also be offered vaccination."

The one caveat that we put on this, as well as the caveat that we put on selecting health care workers to perform these duties is that if you're dealing with somebody that's not had a contact yet, but you want to designate them to do duties, you need to select people that don't have contraindications to be voluntarily vaccinated for those duties and the other folks should be reassigned to duties that don't put them at risk for contact.

And then finally, public health officials need to evaluate the potential for aerosol spread in the hospital setting because there have been obviously a high level of transmission in hospital previously -- reported in previous hospital settings, smallpox outbreaks, and that potential vaccination of non-direct hospital contacts will have to be evaluated by public

health personnel.
Moving on to talking specifically about the contraindications to vaccination during a smallpox emergency, contrasting this with the non-emergency use contraindications, the working group felt and it's been stated in previous ACIP recommendations during smallpox, that there are absolutely no contraindications to vaccination of individuals with a definite high-risk exposure, and that's specifically because their risk of having a very severe infection of a smallpox is higher as well their potential risk for having an adverse reaction to the vaccine.
When the level of exposure is unclear, careful assessment of the potential risk versus benefits in vaccination must be done, and you have to weigh that when you're looking at somebody that might have a potential contraindication and you're not clear what their exposure risk was. You have to sit down and weigh that individual in between the clinician, the public health personnel, as well as the patient.
I'll go quickly through these because these are some

additional press release vaccination recommendations that the working group thought would be important to include to give some guidance to hospital and medical personnel, as well as public health personnel during a smallpox emergency, so to speak. I alluded to this earlier that we would ask people to utilize personnel without contraindications to vaccination for all activities that would put them at risk for contact with smallpox if they haven't already been that way. And if they do have contraindications, to put them in positions where they would not come into contact or be at risk for an exposure to the smallpox virus at that point and that, potentially, if you have them available, to select previously vaccinated personnel, people that have had childhood or other vaccinations -- smallpox vaccination for one reason or another, a previous laboratorian or whatever, for patient contact activities early in the outbreak. In other words, to vaccinate them and to utilize them early in the outbreak because they may potentially have a higher rise in their protective antibody titers than somebody

that's receiving their very first vaccination. And realizing that even though smallpox vaccine appears to be very effective in at least modifying the disease or potentially even preventing a disease given two to three days after exposure, realizing that potential, that it seems prudent to have personnel utilize other precautions, protective precautions, even after vaccine until they've had a demonstrated vaccine take, because not all personnel might have a vaccine take. And to continue their exposure without some sort of protection until you know that they've had a vaccine take might be -- might be a little bit remiss. So they should utilize other precautions until they know they are protected by vaccination. Even after that, they need to continue standard contact precautions to protect against exposure to other infectious agents that are still floating out there that we deal with on a day-to-day basis, and potentially to prevent transmission of the virus to someone else. In other words, they're going to wear protective clothing while they're in fomite contact with these patients, remove that

clothing, and go -- before they have contact with other non-immune, non-vaccinated individuals so they don't transmit the virus on contaminated clothing to other patients or other people that have not been vaccinated. We have one -- This sort of goes along with what we talked about with the VIG statement. This sort of approaches that the use of VIG in a prophylactic manner -- because it has been used as a prophylaxis when you've had to vaccinate people that have contraindications, and the working group felt that this was an important statement to put in there to help guide -- or to let people know how VIG will probably be utilized at the current levels of VIG during a smallpox outbreak. And that should vaccination with individuals with contraindications be required because of exposure to smallpox virus, current stores of VIG are not sufficient to allow for it prophylactic use as vaccination. Because of the limited stores of VIG, its use in such a scenario should be reserved for complications that are considered severe and life-threatening. If additional VIG becomes available in

the future in sufficient quantities to allow for its prophylactic use, VIG should be administered at a dose of .3 milligrams per kilogram, along with vaccinia vaccine in persons with contraindications who require vaccination. And that allows for if -- you know, if more VIG becomes available in the future, there are at least some dosing recommendations there for people and guidance on how they would use it. But knowing currently, it would not be used in that manner because there's not enough available to allow for that.

The last few additional infection control measures, we talk about the strict respiratory isolation or potential cases in the hospital unless the entire facility is designated to care for smallpox patients only, and everybody within the facility are going in and out of the facility have been vaccinated. There's some guidance on decontamination of reasonable bedding and clothing, which goes along with some of the guidance that was given in the care of the vaccine site section.

There is an option of non-hospital isolation out there

that should be made -- utilized with the public health input, if that is so chosen by public health, but that some guidance on what that isolation would require includes that it has to be to a sufficient degree to prevent the spread of smallpox to other people within the surrounding area and that would include not having people isolated in places that have shared ventilation or heating or air conditioning units, and that making sure that access to the place where they are isolated, it can be limited to vaccinated individuals so you don't have people going in and out that you can't keep track of or can't vaccinate.

Then, finally, surveillance and contacts with isolation is a must to -- surveillance of the contacts with isolation if you were to develop a incubation period is another thing to indicate to medical personnel, that these people have to be tracked, these people have to be notified and watched to a certain degree, or at least told what they need to watch for and who they need to report to.

The final aspect is the research agenda that we

approached, sitting down and thinking about some of the things that have to be sort of approached along these preparedness efforts, and that is, first and foremost, the development of a new vaccinia vaccine because we need additional quantities of vaccine to augment the current stores that we do have and replace any out-of-date vaccine that is currently there. The viruses will have to be approached in a FDA-approved cell culture substrate and that any new vaccine produced has to be evaluated for its safety and efficacy in animal models, serologic and cell immunity models, and evaluated on its cutaneous indicators of successful vaccinations since that's most likely going to be the thing that would be utilized in an emergency, is a visual clue that vaccine has taken and it's effective and that immunity has developed.

And we also, obviously, with the VIG shortage, have to look towards alternatives to VIG for adverse vaccine reaction treatment, and that includes looking at antivirals, which is currently ongoing for activity against vaccinia virus and utilizing animal models and

in vitro assays to evaluate this, as well as developing and evaluating monoclonal antibodies potentially against vaccinia virus and evaluating those on their effectiveness.

And that's it. I would like to thank the Bioterrorism Working Group members. I apologize for any omissions or misspellings because I can't spell or remember. So there you go.

I'll open this to any questions.

DR. MODLIN: I would like to thank Dr. Rotz, Dr. Helms, and the other members of the working group for obviously their very thorough and thoughtful review of an important document. I think that the fact that this is a document that may very well only be used or pulled out in an emergency situation, in any many cases, means that it needs to be thorough, educational, and useful. And I think, in my opinion, you've achieved this with this. Again, my congratulations.

We have discussed this in some detail at the October meeting and the plan was to try to achieve some closure, but we certainly do have some time for

comments and questions. Lucy?

DR. TOMPKINS: Lucy Tompkins.

I just mentioned to Chuck that I thought one thing that would be very helpful for some organization to do would be to provide photographs of lesions of smallpox to all emergency departments in the United States, because the point of first care is going to likely be the EDM -- virtually, none of us have ever seen a case of smallpox. So it was pointed out to me that it's not possible to include that in this document, but I do think we should support such an effort by whatever organization. Our own organization, Infectious Diseases Society of America could probably make all of this available to i.d. clinicians, but, of course, we're not going to be the first ones to see the lesion either.

DR. MODLIN: I wonder if this might be included in some sort of public -- or public information or in an emergency information campaign that deals not only with smallpox but, perhaps, media-style widening of anthrax and other issues --

DR. TOMPKINS: Yes, exactly.

DR. MODLIN: -- that are similar that would be important to --

DR. HELMS: It's interesting. CDC has a wonderful slide collection that's available on its bioterrorism web site, in some connection of emergency room with its availability with the wonderful quick way for an emergency room to get some information quickly or a slide or two.

DR. MODLIN: Paul?

DR. OFFIT: There was this fairly long period of time when the CDC was unable to provide to laboratory workers that worked with these non-highly-attenuated vaccinia virus recombinant vaccine. Has that situation been resolved, and if so, can we expect it will stay resolved?

DR. ROTZ: Yes. That situation was -- because of the questions regarding the current VIG supply and whether or not it could be used, because it had changed in color and it had to undergo some toxicity testing to make sure that the color change wasn't anything that

affected -- the made it toxic or affected how well it would work in a situation. So we couldn't release any vaccine until that was resolved. And currently, the VIG is under an investigational new drug type tag and could be potentially used if needed. If John Beecher is here, he can tell me for sure, but that was my last understanding.

DR. MODLIN: Dr. Siegel?

DR. SIEGEL: I just have a couple of comments. Since the Commission is requiring institutions to have a bioterrorism plan, this kind of document should be included in an institution's bioterrorism plan however they're doing that.

A couple of terminology things in the infection control section. I think (inaudible) respiratory isolation in airborne precautions. And with hand-washing, you need to address hand hygiene, if the hand hygiene products are incorporated to say that.

DR. ROTZ: Thank you.

DR. MODLIN: Rick Zimmerman?

DR. ZIMMERMAN: Hi. Rick Zimmerman. I agree this is an

excellent document and congratulations on it. One of the questions I had dealt with on page 6 that issue of looking -- paying special attention to a history of eczema. And I wondered if a little clarification might be helpful. Probably almost every one of us in this room who's, in part of their career, done surgical scrubs has gotten a little hand dermatitis or dyshidrotic eczema as a result or anybody who has done a number of dishes. And if one were to go to searching to that level of detail, I'm not sure there's hardly anybody that hasn't had a history of dyshidrotic eczema --

DR. ROTZ: Right.

DR. ZIMMERMAN: -- and therefore would not be a candidate if you want to push it to the limit. So I wondered if a little wording to clarify that so it's not over-interpreted.

DR. ROTZ: We actually sort of mulled this over in our working group, and it was difficult because we based some of these on the 1968 national and ten-state survey done by Michael Lane at CDC, looking at reporting of

adverse events. And obviously, the national survey was based on looking at places were VIG was requested, and that's how they sort of got their database for reporting. Whereas, the ten-state survey sent out questionnaires to clinicians in 10 states and asked them when giving vaccine, did you see x, x, or x, and rates were obviously reported higher in the ten-state survey. When they talk about vaccinia -- when they talked about, they actually had several instances where people did not, because that was obviously a contraindication back then also, where people had a history of it but didn't have active eczema but were given the vaccine and did develop that. So there was the question there. What we don't know is how severe their past history was and that's the problem that we came up against in saying, well, what degree do we call when we talk about history of eczema. Is it childhood where you haven't had it for 20 years, is it a mild case? I guess we'll just have to leave some of that up to the risk-versus-benefit clinician-patient evaluation, and we can try to clarify that a little bit

more. I don't just don't know that we'll get to something that will be very useful because the information is just not there.

DR. MODLIN: Dr. Deseda?

DR. DESEDA: Dr. Deseda from Puerto Rico. Maybe it was discussed in October, but I'm just curious if there's any possibility that the available vaccine may have some prior contamination because it's made from cow serum?

DR. ROTZ: I'm sorry?

DR. MODLIN: Pre-on contamination from bovine-derived --

DR. DESEDA: That's what I mean.

DR. MODLIN: That was a time-limited issue, as I recall, wasn't it, Karen, with respect to --

DR. ROTZ: That I don't know.

DR. MIDTHUN: I think that the main concern has been for product from 1980 and after.

DR. MODLIN: Yes, Dr. Diniega?

DR. DINIEGA: Dr. Rotz, Dr. Gravenstein [phonetic] was a member of the work group, I

think --

DR. ROTZ: Uh-huh (affirmative).

DR. DINIEGA: -- and we had -- he had forwarded some comments --

DR. ROTZ: Right. He forwarded them after I had already sent this to the working group. They will be incorporated before it goes to press.

DR. DINIEGA: And in the pre-release -- or the bioterrorism preparedness part of it, it has reference to the military. In the anthrax immunization -- anthrax statement, there's a very nice sentence in there for use of anthrax vaccine as a pre-release vaccination that included the military populations and other select populations based on calculable risks. That may be a good thing. I would like to recommend that we add that to the pre-release.

DR. ROTZ: We've had it in and we've had it out. It's been kind of -- We sort of mulled over that. We had it in initially, and then after several comments, we took it out and evaluated that, but I can talk to Dr. Gravenstein and we can come to some sort of conclusion

on what to add with that if the working group is in agreement that that military population should be taken out and mentioned specifically.

DR. MODLIN: Dr. Katz?

DR. KATZ: Lisa, on both page 7 and in table 4, under immunocompetence, altered immunocompetence, you use agammaglobulinemia as an example. That's incorrect. It's cellular immune deficiencies. It's not agammaglobulinemia that renders you more susceptible. So I would try to strike agammaglobulinemia and where you say altered immunocompetence, I would say altered cellular immunocompetence.

DR. ROTZ: I think -- I've seen it both ways as far as -- when you talk about vaccinia necrosum, there was a nice table in the Red Book that describes sort of the two different types of conditions that could lead to that, and one is actually VIG -- helped by VIG, where the other is not, and when it's purely cellular immunodeficiency problem, VIG does not help. But when it is a condition where the production of antibodies is hindered by some other overwhelming infection that

could be -- that could be fixed -- in other words, they do have some cellular immunity -- that VIG would actually be helpful. Now, whether or not you could ever make that distinction, I don't know, but I can certainly change that. I think that was just taken straight from the 1991 recommendations, but we can certainly change that.

DR. MODLIN: Sam, is that a satisfactory answer? It sounds like you may have been on slightly different wavelengths here.

DR. KATZ: Well, I think that part of it, of course, goes back to so much of this earlier work being done before people distinguished between humero and cellular deficiencies. I think the vaccinia necrose and gangrenosum patients were SKIDS patients or patients who one way or another had markedly depressed cellular immunity as with even the Armed Forces HIV patients. It's not an antibody. It's cellular response. But I don't want to quibble about it.

DR. MODLIN: Dr. Brenau [phonetic]?

DR. BRENAU: I'd like to offer another suggestion, and

that is, if you ever get into a situation where you need to vaccinate, that pictures of what the vaccination site is supposed to look like be sent out with the vaccine, because I'm sure most people who are going to be doing this have never seen a vaccine reaction.

DR. ROTZ: Right. We had wanted to include that but, obviously, the MMWR doesn't include pictures. We had explored all these options about including pictures of the vaccine site as well as some pictures of smallpox for the different stages, but we can't do that in this document. CDC is developing sort of a "how to vaccinate against smallpox" video that will include pictures at the end of it, what the vaccine site should look like and the progression of how it looks over two weeks.

DR. MODLIN: Would it be possible to refer to a web site address in the actual document that would contain nice photographs?

DR. ROTZ: I don't know that there's --

DR. MODLIN: That might be an appropriate way to deal

with that issue.

DR. ROTZ: I don't know if there's one that's been set up specifically yet, but we can look at maybe including that on our bioterrorism web site.

UNIDENTIFIED SPEAKER: There will be by the time this is published.

DR. MODLIN: I just had one other comment, and that's on the use of VIG on page 8. In the interest of this being an educational document, we don't have much information here that actually documents the data regarding the efficacy of VIG. We just say it's effective in these settings. And I wonder if, at the very least, be helpful to refer to whatever evidence there is that it is effective in those situations. That would be a nice addition to the statement.

Are there other comments?

(NO RESPONSE)

DR. MODLIN: Terrific. I will entertain a motion that the Committee accept the smallpox document that has been presented by the working group.

DR. TOMPKINS: So moved.

DR. MODLIN: It's been seconded by Dr. Brooks, and subsequently so moved by Dr. Tompkins. Dixie, I assume, since there's no one currently manufacturing smallpox vaccine, that we have no one that could conceivably be conflicted. Is that the case?

DR. SNIDER: Is there anybody planning to manufacture -- I would make the same assumption.

DR. MODLIN: Okay. Assuming that, those in favor of the motion, if they would raise their hands.

(SHOW OF HANDS)

DR. MODLIN: Dr. Deseda, Dr. Johnson, Dr. Levin, Dr. Smith, Dr. Offit, Dr. Rennels, Dr. Tompkins, Dr. Helms, Dr. Word, Dr. Clover, Dr. Brooks, and Dr. Modlin. There are none opposed and none abstained. So the motion passes again.

Congratulations and thanks for a job well done. We will meet up again at 2:00 sharp. Thank you.

(LUNCH RECESS FROM 12:44 P.M. TO 2:03 P.M.)

DR. MODLIN: Good afternoon. Just a couple of quick housekeeping announcements. This is the last chance for those of you who plan to go to the dinner tonight

to get your reservation and your dinner preferences in to either Gloria or Latarsha. We will -- There will be some minor adjustments to this afternoon's schedule. Perhaps most important will be that Dr. Brooks' presentation on dose optimization for H. flu will be put off until tomorrow morning, and we'll wait for a few minutes just to decide exactly what the best time would be.

Secondly, tomorrow morning I understand that the two topics after the break in the morning on review of the Hep B safety studies and the general recommendations are going to be reversed in order, in part because Dr. Margolis may not be able to be here at the earlier time slot.

With that in mind, we'll go ahead with this afternoon's agenda and we will start off with the very important topic of an update on the issues regarding tetanus diphtheria and DTaP vaccine supply. Melinda will be introducing the topic.

DR. WHARTON: Thank you. I just wanted to provide a brief overview of this afternoon's session on Td and

DTaP vaccine issues.
We're going to start with an overview of the supply situation by Dean Mason of the Immunization Services Division of the National Immunization Program. Then we have invited the manufacturers to make whatever comments they would like. There will then be some opportunity for questions from the Committee and others. Then Dr. Lynn Zanardi from the Epidemiology and Surveillance Division will review for you the recommendations on use of Td in the face of limited supply that were published in the MMWR in November. And Kris Bisgard will then go over some options for how to deal with a DTaP shortage should we find ourselves in that situation in the next few months. And we'll looking for some guidance from the Committee on that. So with that as an overview, the first speaker is Dean Mason.

MR. MASON: Good afternoon. I think I also said, good morning. I wanted to bring to you some information that hopefully you'll find relevant and interesting pertaining to the availability of DTaP vaccine and

other tetanus- and diphtheria-containing products. The purpose for this presentation is to update you on the present supply situation, provide some information on what has led to the present circumstances, and offer some predictions about supply for the remainder of the year.

This problem has actually been building since early 1999 for products other than DTaP. Two companies informed CDC of supply -- if you want to say production/supply -- but supply problems in June of 2000. Supply had been quite sporadic from one company and marketshare very low for the other company for most of the year 2000. In December, Wyeth-Lederle announced a corporate decision to withdraw from the DTaP, the Td, the tetanus toxoid, and the DT pediatric market entirely. Wyeth-Lederle is a major player, or has been a major player, in DTaP, even more so in Td and tetanus toxoid. In terms of the entire marketshare for 1999, Wyeth-Lederle had about 32 percent of the Td and tetanus toxoid products on the market, public and private and 19 percent of the entire market year 2000.

In terms of market trends or purchase trends through CDC's contracts, the two biggest players, in retrospect, have been Aventis Pasteur characterized in red, 5.6 million doses of DTaP bought through the CDC contract, 1997, for Aventis. They have held fairly steadily, their low point being 4 million doses calendar year 2000. This is not proprietary because it's public information of purchases through the CDC contract. It does not reflect the United States marketshare. That information the companies do hold rather closely for entire sales, but given the fact that we have at least the majority marketshare, our trends will be significant.

Glaxo SmithKline, 1997 began -- or at least its first year, analyzed at 1.6 million doses were purchased through our contract. You see this steady upward market gain by Glaxo SmithKline, resulting -- Indeed, for the first time in year 2000, they became the leading DTaP seller through CDC's contracts. I should mention, these are open and competitive contracts. The grantees have the choice of which products, which

manufacturers they will purchase. In some instances -- in most instances, the states grant the providers choice, but that's not true in all cases.

The trend for Wyeth-Lederle in the green has been fairly consistent, 2.5, 2.5, and then, of course, in 2000, with sporadic sales through our contracts due to lack of product availability, and there was a significant decline. And Baxter Hyland, formerly known as North American, has had, albeit a small but important share, because they obviously were starting to build base, and then decided in 2000 to withdraw, at least from the immediate future, from the United States market.

If you looked at this in a different way, in terms of marketshare, based on ordering history through CDC's contracts, the public health need for DTaP -- And I'm not referring to combination products here, only DTaP -- is between 8.3 -- is between 8.3 and 11.1 million doses annually. The loss of both Wyeth-Lederle and Baxter Hyland equates to a loss of about 2.9 million doses of DTaP vaccine per year or about 24 to 20

percent of the total CDC market. This does not consider private sector losses.

To give you an update on the current status of DTaP back orders through our system among the grantees, this is a fluid situation that changes on a daily basis. However, at the present time, through our ordering system -- Of course, all state orders come through the CDC system that are purchased through CDC contract -- we have 53,000 and 110,500 doses that are over 30 days back order. So 42 projects are awaiting 163,500 doses. Our contracts require that the manufacturers deliver within 15 days of order receipt from CDC. So these are all truly delinquent orders and reflect the fact that we are living hand-to-mouth on DTaP supply at the present time.

The under-14 -- excuse me, between 14 and 29 days, we have almost a half a million doses pending among 47 projects. Under 14 days, which is still within compliance of our contract, we have an additional grantees. Of course, 32 projects are counted with pending orders in more than one time frame, that is,

they have more than one order in; 11 projects have only one order pending; and at this time, 20 of our projects have no orders pending.

The bottom line right now is that we 1,030,000 doses on DTaP on back order.

This provides you with a glimpse of the inventory levels in state depots or within the commercial distributor within the state's contract. We have seven projects in red that are reporting, as of February the 6th -- Of course, this wouldn't be exactly true today, but it gives you an idea -- seven -- six projects reporting less than 7-day inventory of DTaP in their central depot. We have eight projects in blue that reported less than a 14-day inventory. We have 26 projects with less than a 30-day inventory. And we had 15 projects that had less than a 60-day inventory in green. And the purple are projects that are being selfish and hording DTaP vaccine. Not necessarily. Maybe they were just fortunate in getting their orders in. I'm sure they'll be willing to share with those states that have a less than 7-day inventory. Easy for

me to say.

I'll just skip this slide. This is the state-specific or grantee-specific table reflecting the status of current inventory as of February 6th.

The DTaP vaccine supply production estimates for 2001, what do we have to look forward to. The green bar characterizes the CDC contract purchases, 8.3 million. Calendar year 2000, we purchased 10.4 million doses. Please consider this provisional until we publish it. The private sales, 6.8 in '97, 6.2 -- Fairly consistent figures here between public and privates sales; fairly consistent total sales of DTaP. The range in total sales -- I had mentioned our range in the public need -- was about 8.3 to 11.1. The total need for the United States, including our grantee -- our projects, which, of course, include Puerto Rico, the Virgin Islands, the Pacific Trust -- 15.1 million doses to 20.4 million, based on history, not necessarily what the true need is, but based on what ordering takes place. Frankly, ordering exceeds the birth cohort and birth need, and this has to do with pipeline inventory, multi-dose

vials. You serve one child, you need 10 or 15 doses of product. So we always have more out there than equates to one-to-one.

And finally, the important question is, how much do we think that the two remaining companies are going to produce in DTaP for calendar year 2001. And we appreciate the companies giving us information that in the past they would have considered proprietary. We don't break out the companies, but, in total, Aventis and Glaxo are predicting a production of between 21 and 25 million doses of product. So you would say, what's the problem? If we're going to have this kind of supply, assuming all goes well, and this is our maximum need, is there an issue?

The problem, of course, is if this was a January to December scale, we are living up front rather dangerously. We may be caught up by the end of the year, but at the present time, we literally are waiting on FDA CBER lot releases. As soon as those releases are made, the companies are filling back orders. They're not getting ahead of the curve, in other words.

So this is the issue, is, can we continue to survive with it literally coming out of the factory line to the providers' offices at this time.

Of course, we can't just focus entirely on DTaP. The national distribution of all diphtheria and tetanus-containing products, except DTaP, needs to be analyzed. The steady decline in total supply from 24.7 million doses of other diphtheria and tetanus-containing products down to the present, calendar year 2000, distribution of 15.7 million products is explained in large part by the replacement of DTP and DTP-combination vaccines with the DTaP product. However, it does not explain the decline -- I'm sorry. This explains the decline in terms of DTP, which is in red, and is now, of course, nonexistent. It contained thimerosal, and of course, the DTaP product was judged a superior product.

In the DTP/hib -- Because of the DTP being replaced by the acellular, this has also enjoyed a steady decline in the green, but it doesn't explain this drop right here in the Td. 16.1 million doses in 1998 down to

12.7 million in 2000, and this reflects the increasing pressure that one manufacturer has had in supplying, becoming basically the sole source or almost the sole source for tetanus supply in the United States. The maroon box or purple box is DTP pediatric, which is not so much of an issue right now. Clearly, the Td and the tetanus toxoid are issues.

So what's the current status? Only two DTaP manufacturers remain: Aventis Pasteur and Glaxo SmithKline. Aventis Pasteur is the sole manufacturer/supplier of DTaP/hib, DT, and tetanus toxoid. The University of Massachusetts Medical School produces a small amount of Td, mostly for state residents. It's my understanding that they have some ambitions to expand their production line and increase the amount of Td that they'll make available, not just to Massachusetts, but that is not an immediate ability. The Td national shortage is significant. The DTaP vaccine through CDC contracts are back-ordered. We've only had a few instances of spot shortages being reported to us to date, that is, literally doctors

turning children away for pediatric vaccines. We have had more instances of complaints about people being entirely out of tetanus toxoid or Td.

The actions that are being taken. Aventis Pasteur is screening Td orders, prioritizing shipments to hospitals, trauma centers, limiting amounts shipped. I believe that their basic policy is to limit maximum orders to 50 doses per week. They have a 24-hour hot line. They are interested in calls from people who are in dire need. Obviously, those caring for people with trauma or wound injuries are going to receive a higher priority than those who are receiving Td boosters at age 15 years with no other issues.

CDC has recommended the following to all states: that the states notify their providers to limit vaccine toxoid inventory to a 30-day supply -- We need to ask providers who are receiving public vaccine not to stock their refrigerators with 45-, 60-, 90-day supplies of product; state depots limit their inventory to less than a 45-day supply in response to the needs of their customer base. We will continue to monitor state

orders for DTaP. We'll allocate vaccine, if that becomes necessary and, of course, provide program guidance based on any recommendations that the ACIP chooses to make on this problem.

The outlook, Td shortages for remain for the next 10 to 14 months at least. With timely production release of DTaP vaccine, there may be some delivery delays -- There already are -- but overall supply, we believe, should be sufficient, though we can't guarantee that. DTaP supply issues will remain through this calendar year but should improve in the latter part of the year. The ACIP, of course, will be reviewing this situation at this meeting and considering other recommendations. Thank you.

DR. MODLIN: Melinda, should we take questions for Dean while he's here, or what would be the --

DR. WHARTON: That's fine.

DR. MODLIN: Are there questions for Mr. Mason? Yes, Paul?

DR. OFFIT: Two quick questions.

Are the withdrawals of the Wyeth-Lederle and Baxter

Hyland vaccines permanent or do those companies have an interest in coming back into the market eventually? And the second part of this question is, with now fewer competitors in this market, does that mean that these vaccines are going to become more expensive in the short term?

MR. MASON: I think the first question -- I believe, Dr. Modlin, there's going to be some time set aside for each of the manufacturers to present on what their plans are for DTaP. So I won't speak to the ambitions of Baxter or Wyeth-Lederle.

Regarding pricing, we will begin a new contract April 1st, and we are in the process of negotiating that, what we call, consolidated contract at this time. The manufacturers -- We have a unique provision in our contract that manufacturers can adjust their price every four months so long as they don't go above the original price of that contract period. So if the original price they bid to us for the next contract is, say, 12 dollars a dose -- and they can't go up above what their present price is until April 1, so you've

got a window frame there. But let's say they bid 12 dollars a dose -- I'm just picking this out of my head -- they can -- on the next opportunity to change prices, they can go down to $9.50, they can go down to six dollars, they can give it away, but they can't go above 12 dollars a dose. In terms of -- The companies really evaluate their marketshare and probably their production abilities, and that guides them, at least in small part, on what their pricing with CDC will be. Of course, we expect a discount above the -- above the price offered in the private sector, but at this time, it's difficult for us to predict what pricing will be.

DR. MODLIN: Paul, we may give you a chance to recycle your question in a minute or two.

Natalie?

DR. SMITH: Yes. A question about distribution of DTaP in the private sector. Do you have any sense of if there will be prioritization or limiting orders so that some private entities aren't stockpiling it?

MR. MASON: This may be something the manufacturers, in terms of their policies as to who they get the product

out to, in a prioritization manner, they might want to address. Our sense is that they try to give proportionate amounts to the public and private sector and they try to be responsive to individual circumstances.

DR. MODLIN: Myron, did you have a question? Okay. Further questions?

(NO RESPONSE)

DR. MODLIN: Dean, thanks very much.

DR. WHARTON: We had invited representatives of the manufacturers to make any additional comments they might wish to make. Dr. Howe, would someone like to speak for Glaxo SmithKline?

DR. HOWE: That would be me.

Thanks, Melinda. Barb Howe from Glaxo SmithKline. In terms of the supply of our DTaP infant product, Infanrix, the situation is very much the same as when we had these discussions around thimerosal last year, and that is that although we cannot supply the entire U.S. market for all five doses, we are able to supply the entire U.S. market for the three-dose primary

series. In other words, we have enough to supply a little bit over half the market.

I want to take the opportunity to say that we are committed to a DTaP supply in the U.S. and that DTaP vaccine is actually the cornerstone of our future pediatric combinations, as I think many of you are aware. I presented data on our combination DTaP, Hep B, inactivated polio vaccine I think it was a year ago at this meeting, and I'm happy to say that actually that product will be the subject of discussion at an upcoming FDA advisory committee meeting on March 7th, which is only two weeks from now. I mention that mostly as a measure of our commitment to DTaP-based products in the future for the U.S.

In terms of adult-type DT products, I thought I would mention that we do have reduced-antigen Td products, as well as a reduced-antigen diphtheria tetanus pertussis product licensed and in use outside the U.S. Neither of these products is licensed within the U.S., but we do have an active development plan for the reduced-antigen DT pertussis-containing vaccine for adult use.

And it's actually -- the pa component is the same product as was studied in the NIH-sponsored efficacy trial, which you'll hear more about tomorrow afternoon during the adult working group session. Again, I mention that because if one foresees that such a product could be replacing product for adolescent Td in order to not only meet the unmet medical need for pertussis vaccination in such a population, it also might serve to help supply issues as well.

DR. WHARTON: Are there questions for Dr. Howe?

(NO RESPONSE)

DR. WHARTON: Dr. Hosbach?

DR. HOSBACH: I'm not going to give you a commercial pitch on what we're doing here. I think -- First of all, I want to clarify one statement, and that is relative to the FDA and releasing lots. They've been working very diligently and they are very aware of the situation and they are trying to work as quickly as they possibly can to release our lots. It is true that we are working hand-to-mouth trying to make up for the shortfall in the marketshare.

Really, let me talk about the issues first and what's compounding some of the situations and then some of the things we're trying to do to remedy the problem and tell you when we might be out of that situation. First of all, I think we can't underestimate what thimerosal did to the situation -- I think it has contributed to having a manufacturer get out of the marketplace -- and it also has significant impact on the way we produce our products. For example, tetanus is the limiting antigen that we have in the production of our D-and-T-containing products. That tetanus goes to Tripedia, and in the past year, it's gone to preservative-free Tripedia. It also goes to Td, it goes to pediatric DT, and it goes to tetanus toxoid. Those are all contributing factors. What we're trying to balance appropriately is the loss of the manufacturer versus where do we place our tetanus products, either Tripedia, Tripedia preservative-free, or in the adult Td products. Hopefully, we'll resolve that in the short term with the preservative-free and we can concentrate fully on version of Tripedia.

In addition, the marketplace has shifted substantially as well for a variety of good reasons, but they have moved to single-dose use of DTaP vaccines, and that is also a situation where it takes a little bit more capacity to do that. Of course, as far as from the timing standpoint, we fill as many multi-dose vials as we can fill singe-dose vials. You get many more doses in a multi-dose vial, as you know. But the market has shifted and we're trying to adjust to that single-dose requirement as well.

In the long term -- longer term for Tripedia and for DTaP, we're looking at introducing a five-component vaccine from Canada and that will alleviate potentially -- it's being reviewed actively right now at the FDA. It was before an advisory committee and we're still discussing what needs to be done pre- and post-licensure for that product. But in the long term, that will alleviate a couple of things, one, the DTaP supply situation, and the T and D made for that product are actually produced in Canada. So it will allow us to free up our T and D manufacturer in the United States

to devote it more toward the Td product for adolescents and adults.

As far as what we're trying to do to alleviate the situation, I think Dean really described it pretty well as what we're trying to do. We're working very closely with the CDC. I appreciate Bob and Dean's help in trying to identify areas of need in public health and to let you even -- in any circumstance, we try to, throughout the course of the year, have a 60/40 split, 60 percent of our DTaP vaccine goes to the public sector, 40 percent goes to the private sector, and we are unwavering about that. We try to make sure that we're fair and we also try to make sure that whoever needs, we try to do something for them. If we cannot, we will refer them -- we become the -- You remember "Miracle on 34th Street"? We will refer them to -- We're the Macy's guys. We'll refer them to SmithKline if we are unable to fulfill an order and see if they can pursue it there.

From a Td standpoint, that's a much more difficult situation. I can tell you that we plan to produce 13.9

million doses, which would be above what was available this past year. However, we're still managing supply. We're limiting customer orders, both in the private and the public sector. We are -- Actually, what we do is we call drop-shipping for distributors if we're limited their orders, but we also are the ones who ship out the orders. So we have control of this particular product because of its short supply situation.

We hope by the end of the year that we'll have implemented a plan of production that will allow us in the subsequent year, 2002, to have about 20 million doses available and, therefore, we'll be able to meet what needs to be filled as far as the pipeline, as well as -- as far as stockpiles or any stocking up that states may need to do. In the interim, we're sending out a letter to all hospitals and the directors of all hospitals, giving them our 1-800-vaccine number. That's the only commercial I'll give you, because I think it's an emergency situation. If they need vaccine, we're available 24 hours a day, seven days a week. Call us at the 1-800-vaccine number and we'll

try to do what we can, but we are limiting orders across the board.

DR. WHARTON: Are there questions for Dr. Hosbach?

(NO RESPONSE)

DR. WHARTON: If not, is Mr. Kempf or someone here from Baxter Hyland?

MR. LEE: Hello. I'm Walter Lee from Baxter Hyland Immunovaccines. And as Mr. Mason had mentioned in his presentation, at this moment, Baxter is not supplying DTaP-combination vaccines and Baxter is here at ACIP today to better understand the situation around the DTaP product shortage and also the potential impact on the American public. We're also here to listen to the considerations of this body. We would like to ensure that we're taking all of these considerations into account in our future planning for DTaP products. Thank you.

DR. MODLIN: Rick?

DR. ZIMMERMAN: Is thimerosal the main issue that led to your decisions?

DR. HOSBACH: No, it is not.

DR. MODLIN: Dean?

MR. MASON: I'll just give the big question. Does Baxter Hyland have plans to re-enter the U.S. market with DTaP? And if so, approximately when?

MR. LEE: Baxter Vaccines is considering the re-entry of the vaccines -- of the DTaP-combinations and there are a number of factors to consider, including the evolution of what the American public market will require, including recommendations, as well as another -- a number of other technical factors. So we would be happy to update this body at future time about the plans.

Thank you.

DR. WHARTON: Are there other questions for any of the manufacturers present today?

(NO RESPONSE)

DR. WHARTON: If not, we will move on to the next presentation. Dr. Lynn Zanardi is going to briefly go over the recommendations that were issued last November regarding use of tetanus and diphtheria toxoids.

DR. ZANARDI: Good afternoon. I would like to take

this opportunity to update you on the Td shortage. During the last meeting in October, we had just learned of a shortage of Td vaccine, and we introduced some priorities for use of Td. This was later published in the MMWR in November. And just to refresh your memory, they are the following.

Of highest priority was use in travelers to countries where the risk for diphtheria is high. Second on our list of priorities was for use in prophylaxis and wound management. This was followed by completion of a primary series in adults for those who've not received their full primary series. This was followed by a booster dose for pregnant women and women at occupational risk for tetanus disease. This is followed by the adolescent booster. And last was the adult booster.

You've heard most of this in Dean's presentation. Initially, we thought that the shortage would be resolved by now or by the end of the first quarter of this year, but with the removal of tetanus-containing products from the market by Wyeth-Lederle, the shortage

continues and Aventis is the only nationwide producer. Aventis is shipping out limited doses of tetanus toxoid in their shipments and, due to the long period of time that it takes to make tetanus toxoid, the shortage is expected to continue through most of 2001. When we look at our surveillance data, we do not see any evidence of increased disease, particularly tetanus. However, due to reporting delays for tetanus reports to come through CDC, this isn't surprising. The actions that we are taking in response to the Td shortage are to continue our prioritization. Aventis is directing doses to emergency rooms and trauma departments. We do get some calls from emergency departments or trauma units claiming that they do not have tetanus vaccine, and when the Aventis number is given, they don't call back. So it sounds like emergency room departments and trauma centers are able to fulfill their needs for wound prophylaxis. We will conducting ongoing review of reported diphtheria and tetanus cases through our surveillance data and, finally, I leave you with the question of, can other Td

manufacturers be attracted to the U.S. market?
Are there any questions?
DR. MODLIN: Questions for Dr. Zanardi?
(NO RESPONSE)
DR. MODLIN: I guess not. Thank you.
DR. WHARTON: You've heard in the presentation so far that we're hopeful that the DTaP situation will be a manageable one, but in case it isn't, we wanted to have some discussion about how available vaccine should be prioritized, and Dr. Bisgard is going to lead that discussion.
DR. BISGARD: I want to start off with, if a shortage does occur, we would like the ACIP to provide us guidance on the following three items.
Number one, should doses one to three be prioritized for optimal protection of infants; number two, should we suspend or defer DTaP dose four; and number three, should we suspend or defer DTaP dose five.
I want to switch to diphtheria -- Well, let's first talk about the shortage.
There was a shortage of DTP in 1985 when two or three

manufacturers had problems with their -- meeting their release guidelines, and at that time it was recommended to prioritize giving the first three doses for optimal protection of infants and they recommended delaying both dose four and five until increased vaccine availability. It turned out the shortage only lasted four months. It had been predicted to last a year. It was also recommended to not substitute DT for DTP and not to give partial doses of DTP and to establish recall systems to vaccinate children with the deferred doses.

Now to turn our attention to diphtheria antitoxin levels. You need a level of 0.01 international units per ml for protection and a level of 0.01 to .09 will give some protection. So this is the target level, 0.01.

These are data from the multi-center acellular pertussis trial, at least for the vaccines listed there. And as you can see, there are differences in the GMT and the proportion of children that reached that protective level, although all were above 85

percent protected after dose three.
And this was a study looking at two different Lf diphtheria toxoid-containing vaccines, 15Lf and 25Lf and two different schedules, 2, 4, 6, and 15 months and 3, 5, and 12 months. I'll just focus on this study.
After the three doses, almost 80 percent had a protective level and that dropped and then was -- after the booster dose at 15 months of age was at about 100 percent. Again, that dropped by four years of age.
I didn't speak about the epidemiology of diphtheria in the United States, but we have fewer than three reported cases a year and we haven't had a case in a child since the early 1900's, but from the immunogenicity data presented, it seems that the booster in the second year of life and at the preschool entry appear to be needed to sustain protective levels against diphtheria.
Now, pertussis, I think you've all seen this data.
Incidence of pertussis from 1983 through 1999 has increased among infants less than one month of age in

the blue line and two to three months of age in this orange line, but has remained relatively stable for infants four to 11 months of age.

And these are data on cases and incidence in the United States in 1999, and these data are pretty similar to the past five or six years in which infants have the highest number of cases and incidence and children one to four years of age have slightly higher incidence, and children five to nine, we know there is waning immunity with the pertussis vaccine. We do have quite a few cases in young adolescents 10 to 14 years of age.

These are efficacy estimates of the four currently U.S.-licensed vaccines, all the trials we've done in different places with different schedules, and also the differing aspects. So you can't really compare them head to head.

I'll just walk through these. Infanrix-vaccinated children 2, 4, and 6 months of age, there's a 17-month trial follow-up period. So children were about 23 months of age at this point. Efficacy was 84 percent.

Then there was an observational part of the trial

which was unblinded, and children were about four years of age at the end of that, and the efficacy was the same. Certiva, a 3, 5, 12 schedule with a 17-and-a-half-month follow-up, so children were about two and a half years of age. Efficacy was 71 percent. Then they followed up children for another six months and efficacy was 77 percent. ACEL-Immune in Germany, four doses, 3, 5, 7, and 12, followed up for 25 and a half months, or about an age of three and a half years. After four doses, efficacy was 85 percent. After three doses, it was estimated to be 73 percent. There was no additional follow-up. And in the case-control study of Tripedia, 3, 5, 7 doses, efficacy was 80 percent.

So the implications for pertussis is that we know that primary series is needed to protect infants. We also know from the those studies that protection with the acellular vaccines may last several years following the primary series.

So what are the pros and cons of deferring or suspending a dose? For dose four, the pros I came up with were that likely protection against pertussis and

tetanus would follow doses one through three. And because these children are still young, catch-up vaccination may be easier. However, the con is that there probably is not adequate protection against diphtheria, especially if children are travelling to diphtheria-endemic regions.

And for suspending or deferring dose five, the pros are that the doses one through four would ensure the greatest protection for young children and adequate protection against diphtheria and tetanus. However, if you're deferring dose five, there is waning immunity to pertussis that might lead to more school outbreaks in elementary schools and catch-up vaccination may be more challenging in this age group.

So I'm turning it back over the Committee at this point.

DR. MODLIN: Let me first ask if there are questions for Dr. Bisgard. Myron?

DR. LEVIN: Myron Levin.

Do you have an estimate of how many doses would be saved by each of the last two strategies?

DR. BISGARD: Dean Mason and I actually spoke about that, and it would be a short-term delay if we were -- It depends on how long we were deferring or suspending. If it was going to be a six-month defer, you might save -- I don't know, but I think it was about a million doses. So it really depends on --

DR. LEVIN: On how long, of course.

DR. BISGARD: How long, right. I don't know if Dean has anything to add to that.

MR. MASON: An objective on our part, there's 3.9 -- 3.8 million birth cohort. In a perfect world, that would be 3.8 times five doses per year. So that's something less than 20 million doses, but we know that 90 percent of children start DTaP's within 90 days of birth and that there's a precipitous decline as one gets into ages three, four, or five unless they run up against day care or Headstart requirements. Another issue is, of course, you'll have to consider that there are spring roundups for kids entering kindergarten next year. School entry requirements would have to -- there would be a lot of factors to think about, but in a pure

world, if you suspend one dose, you would save approximately 3.8 million doses a year. That's certainly an overestimate.

DR. MODLIN: Natalie, maybe I could ask you what the effect on school entry requirement might be, say, in California, and perhaps others who want to speak about other states, if we were to suspend or to -- well, the delay dose five.

DR. SMITH: It would obviously take a massive implementation effort, a lot of -- Systems are set up to require those doses and they are sometimes computerized. So there would be a lot of changing in that sense. I was -- We did have a meeting of all the state and territorial managers last week in Denver and there was a whole lot of concern about this. But I guess the main message they put forward was, just tell us what to do and stick with it so that if we have to suspend that fifth dose, we do it and we go through all the processes we need to not require it.

DR. MODLIN: I guess the other question that we haven't really addressed yet is what -- at what point -- what

would trigger the decision to institute such a policy, when would we know that this is the right -- the necessary thing to do. Obviously, this is not something the Committee can necessarily decide upon. I think it would have to obviously left up to the program to make a decision as to when you feel there no longer is sufficient vaccine to continue to provide all five doses. So I think it would be important for us to have a little bit of thinking and discussion around that point as well.

Jon?

DR. ABRAMSON: Jon Abramson.

The question that I have relates to the mortality and severe morbidity associated with pertussis. It's clear that it's highest in the first year, but do we have data that tells us what it is in the second year? Do you understand my question? Because you're trying to get at the issue of, is it okay not to give the 12-to-18-month one. What is the mortality and significant morbidity in the second year of life?

DR. BISGARD: We have about 15 reported deaths due to

pertussis every year, and most of them are less than -- are in children less than six weeks of age. And we have data on hospitalization among older children but, again, most of the hospitalizations are less than -- in children less than six months of age. There are some in those six months to 11 months and one year of age, but it's a lot less.

DR. ABRAMSON: And those would be interesting to see.

DR. MODLIN: Georges, do you want to provide anymore historical perspective on the events of 15 years ago? Georges, very perceptively, went through his files two or three weeks ago and helped me out in terms of helping understand what we went through at that period of time.

DR. PETER: Well, the discussions were very similar in that one of the manufacturers had dropped out of the market in production and another had production problems. So we were left with one supplier. We made specific recommendations, as I believe we have the information our packet of information, and by the time it came to implement those recommendations, the

shortage had not materialized. But basically, the recommendation was to defer the fourth and fifth doses. We did not get into issues that related to -- as you discussed here about whether to choose dose five or dose four or whether simply to defer dose four for six months, and we did not -- Of course, the situation was quite different because then we were dealing with whole cell vaccine. Whereas, with acellular vaccine, it appears that the duration of immunity may be longer than after three doses of whole cell vaccine.

DR. MODLIN: Presumably, if we did reach such a point, it would be ideal to try to, in some respects, have this apply equally to the public and to the private sector. So I guess the question is, how might that be coordinated? And I might ask Jon, or Larry, or both, or Georges to address the issue of what the Academy may be doing faced with similar numbers and a similar problem.

DR. ABRAMSON: Yeah, I think this would be a discussion -- I'm sorry, Jon Abramson. This will be the discussion that we'll have at the end of March at the

spring COID meeting. I don't know what we'll do. I mean, the thing that bothers me the most is to say that you're going to suspend the fourth dose if we don't understand what the mortality and morbidity data are. Pertussis is the main thing we have to worry about, at least in the short term. So if we can understand that, and there is significant -- I realize it's going to be less than the first year, that this is truly significant, the morbidity and mortality in the second year, then I think the answer becomes a lot clearer.

DR. MODLIN: Walt?

DR. ORENSTEIN: I would just say, I think one -- at least one of the vaccines, it looks like protection extends well into the second year, clearly in terms of mortality. I think Kris mentioned the major issue was in the first part of the first year of life. So I think that the morbidity is substantially less. I think to begin -- What I remember 15 years ago is we just said the first three doses are paramount, and I think we just need to give them the highest priority, and I don't

think we've really tried to differentiate whether we should be dose four alone or dose five alone. I think there was considerable concern at the time of dose five in the sense of prolonging immunity into the early school age years, but I think that what we did at the time was just to say dose one, two, and three and not worry about trying to differentiate dose four versus dose five.

DR. MODLIN: Rick?

DR. ZIMMERMAN: Rick Zimmerman.

It sounds like one of the issues is really almost a policy analysis issue. Is it dose four -- are you going to hit day care requirements, and the potential -- is there going to be a gap when children are younger and have smaller airways, versus dose five, which all children are going to be affected with school entry law potentially. So that's -- it seems it's a weighing of those two issues in making the decision. It would unfortunate if you had -- if you took, I think, both off, because then you would have two groups that you're really dealing with.

DR. MODLIN: Georges?

DR. PETER: Well, I do think that to issue some guidelines now in case of shortages would be very helpful to alerting the pediatricians and family physicians. I think that was a major aspect of the -- of the preparation in 1985, that recommendations were made in advance of the time when actually shortages developed.

Secondly, I don't know if we know what percentage of children get the fourth dose, at 12 months, 15 months, or 18 months. My impression is a lot of children get it between 12 and 15 now instead of 15 to 18, and I'm not sure that we know the data or the implications. The schedule years ago was to give DTP at 18 months of age, and the only reason it was changed to earlier, I believe, was related to administration of the doses concurrently with other vaccines. So, indeed, a postponement -- I mean, changes in the past were made to fit the schedule and a slight delay in the administration of the fourth dose might be sufficient to tide us over until we had adequate supply.

DR. MODLIN: Suggesting that children shouldn't receive the fourth dose until 18 months of age in the case that are shortages. That might -- It doesn't -- It's a very short-term solution.

DR. PETER: Which may be a short-term problem.

DR. MODLIN: Which may be a short-term -- hopefully, a short-term problem. Peggy?

DR. RENNELS: Peggy Rennels.

A concern I have about dropping or postponing the preschool fifth dose would be that those children may be lost forever if you don't get it into them before school.

DR. MODLIN: Or you would rely on the schools for some sort of a recall system which would presumably have its own problems, but we almost certainly would be relying on the schools in most cases to follow-up, which -- Other comments or questions? I guess, procedurally, we really haven't thought this through.

DR. LEVIN: Can I ask one other question?

DR. MODLIN: Yes, of course, Myron.

DR. LEVIN: The reason for asking how many doses we're

talking about for each strategy is, what is -- is there a prediction what the shortfall will actually be? I mean, I saw all kinds of figures of who's not doing what, but I'm not sure I know how many doses we're trying to save in a six-month period.

DR. MODLIN: I don't --

DR. LEVIN: That would determine the strategy.

DR. MODLIN: Yeah. I sense from what we heard from the manufacturers is we don't know. It's a little unpredictable at the moment. It will probably be clearer in four to six months. Is that the message?

DR. LEVIN: Because you can have a step-wise policy of what to do if you knew that it was going to be a short -- a small amount or a large amount and keep changing your --

MR. MASON: It's a critical question. The first area is, obviously, we need a sensitive surveillance system programmatically, that if it reaches an end stage of x number of states reporting spot shortages, do we need to enact something rather quickly. In terms of the actual amount of the present shortage, it gets into

proprietary information about the number of lots that are pending release for each company with the FDA. I think Phil had a great point: the FDA and the manufacturers are very aware of the problem and they're working cooperatively, but the pipeline only generates x amount each month. That's all I can say.

DR. MODLIN: Dennis?

DR. BROOKS: I just want to reflect on the Harmonized Schedule, in that if you make these recommendations, would you have to put it on the bottom of the schedule or legend or something like that? Because most providers seem to go to that schedule immediately when they're looking for information.

DR. MODLIN: Well, we were just thinking about procedures and hadn't really thought that through completely, but I assume that, with the hope that this would be a short-term solution, this would be something in the essence of an update to readers or an announcement in the MMWR that would in some way or respects be time-limited, in which we would transmit the idea that there would be further clarification of

the situation within a timely period of time. Would that be what you're thinking of, Melinda?

DR. WHARTON: Yes.

DR. MODLIN: Phil?

DR. HOSBACH: Phil Hosbach, Aventis.

I wish I could be 100 percent reassuring. We are looking probably in the three- to six-month time frame of substantial improvements and a lot of it really hinges upon continued release of the products, we don't have any hiccups, and every year there's always hiccups with lots now and then. And when we're in a situation like this, it just exacerbates the problem. Also, just relative to us being able to turn over completely to preservative-free Tripedia will also be a predictor of when we're going to be able to come out of some of this.

DR. MODLIN: Jon, if this is a three- to six-month time frame, would you feel a little more -- saying when -- about the advisory regarding the fourth dose as opposed to the fifth dose?

DR. ABRAMSON: Yeah. We knew that.

DR. MODLIN: Let me get a sense of the voting member of the Committee, how they -- Please go ahead and make comments, but I really would be curious specifically as to your opinion about if we do need to make a decision, what the decision should be in terms of an either/or or if.

Dave, why don't you go ahead?

DR. JOHNSON: I would be in favor more of delaying or deferring the fourth dose. And the other point I wanted to raise was the possibility of deferring it for children who are not in day care. I don't have a good sense for other states but, really, only about half of our kids in that age range are actually in day care where they're required to show evidence of that. So maybe we would defer those kids that aren't in day care and that might be enough to get us over the hump. But either way, I would be inclined to look at the fourth dose as opposed to the fifth dose. I think there would be less disruption there.

DR. MODLIN: Jon, do you want to respond?

DR. ABRAMSON: Well, yeah. Jon Abramson.

We try to get at this issue of day care with the pneumococcal conjugate vaccine, and you can read numbers anywhere from 20 to 80 percent if we're using the same definition, no less. So that -- I've come to look at that as a nightmare.

DR. MODLIN: Rich, did you have a comment?

UNIDENTIFIED SPEAKER: No.

DR. MODLIN: Okay. Others? Myron?

DR. LEVIN: Can I ask Dave why he chose four or five? Just go through the pros and cons of that again.

DR. JOHNSON: I would be inclined to look at deferring four. I'm not talking about suspending four. I'm talking about deferring it for six months or whatever it would take. I think there are a number of interactions in the second and third year of life that would allow that child to be caught up with the fourth dose. And I think Peggy brought up a good point that, sure, we have the child in school after kindergarten, after first grade, after second grade, but it's a great deal of effort, it would seem to me, to try and go back to all of those kids if we miss the opportunity at five

years of age to get them the fifth dose. I think it would be easier to catch up children on the fourth dose and the intervening opportunities before school entry.

DR. MODLIN: Natalie?

DR. SMITH: Yeah, I would agree. I was going to say essentially what you just said in that -- that if you don't get that shot or it's deferred, the fourth dose is deferred, they still have a chance to hit the school laws when they enter kindergarten. So those kids will be caught somehow. I mean, it's not ideal. And to recall, as you said, all those kindergarten students and expect the schools to do that I think is somewhat unrealistic.

Then, thirdly, I am worried about pertussis school outbreaks. It would be nice if those kids, as they enter kindergarten, get that booster dose.

DR. MODLIN: Peggy, did you have anything else?

DR. RENNELS: I agree.

DR. MODLIN: Okay. I think -- Is it fair to -- Yes?

DR. DESEDA: Could it be possible -- Deseda. Could it be possible that -- If this shortage lasts too long and

it becomes a big problem, we have to change recommendations that have been, you know, available for years. Is it possible that in the crisis to import a number of vaccines from the same companies overseas facilities? Would the FDA give some dispensation or is this too farfetched?

DR. MODLIN: I hesitate to answer for the FDA. Karen?

DR. MIDTHUN: I mean, the only mechanism we have for that is under an investigational new drug application. If it's not licensed in this country, then it could only be used under an investigational application.

DR. MODLIN: I think it's important to keep in mind the perspective. This committee will be meeting every four months, and we will have the opportunity to review this and to adjust and to adapt as needed.

Is it fair to say that there is a consensus that if we do need to advise on delaying a dose that it be the fourth dose? Any disagreement with that?

Melinda, maybe the best way to deal with this would be ask that we put together just a brief paragraph that might serve as language for a notice to readers, and

maybe we could review that tomorrow at sometime and then we can get a formal vote on that.

Walt?

DR. ORENSTEIN: I presume that if it gets more severe, that dose five would be the next thing. I think that it would be useful to -- at least for us, to know the prioritization, and dose one, two, and three would be kept unless absolutely problematic.

DR. MODLIN: Which we perhaps could include. We're getting into real problems there, obviously, we all recognize, but I think that in terms of providing advice to the program, I think that's appropriate.

Bonnie?

DR. WORD: Just a brief question. Maybe it was asked -- or it was said and I missed it.

I'm not quite sure what the cut-off level is when you're defining the word "shortage," when you were going to -- I mean, I know you're deciding, if we have a shortage what we're going to do or what we would recommend, but when do you -- what --

DR. MODLIN: I had raised that issue earlier, and I'm not certain as -- it's up to the Committee -- we can advise --

DR. WORD: Or the CDC can --

DR. MODLIN: I'm afraid I'm going to have to leave it up to the program to make a decision as to when that point has been reached and, in advice with the AAP and the private sector, make some decisions as to what point in time to publish a specific recommendation and direct the program and the distributors to -- and the programs to act accordingly.

Walt, did you have anything else?

DR. ORENSTEIN: I was just going to say, I think what we would do is clearly -- there is no hard-and-fast rule and I think what we would do is talk with FDA and with the manufacturers and, just as you said, the states and try and make our decision, as much as we did last time back in the mid-'80's.

DR. SNIDER: And just to elaborate on that, I think there would be consultation, not only with the states but with at least you, Jon, and perhaps some other

members of the ACIP. Obviously, the CDC Director would be involved in a decision like this, as well. If not, the Secretary of HHS. So --

DR. MODLIN: Certainly, if it were in -- we thought that it were appropriate and desirable, we can convene the Committee via conference call in between our regular meetings and have, in fact, done so several times in the last couple of years. And we can actually -- we've gotten to a point where we can do that more quickly and efficiently than we have in the past as a result of some changes in the policies and procedures. So that's certainly an option as well. But we'll review some language tomorrow, if that's okay and, therefore, maybe go on to the next item on the agenda unless there are any other -- anymore comments about this.

We are running a little ahead of time. Roger, are you all set? Roger Bernier is going to give us an update on thimerosal-related issues.

DR. BERNIER: Thank you. Actually, I'm just going to give an overview for a couple of minutes and there will

be two principle speakers in this session: Dr. Heilman from NIH and Dr. Mootrey from the National Immunization Program.

I'd like to say that, initially, when we were planning this session, we thought it was going to be the time to come back to the Committee and say that we expect that we will have a second DTaP vaccine which is thimerosal-free as of the early part of 2001 as we had predicted last summer, and given that we do have these two vaccines, does the Committee, in fact, wish to express a preference for thimerosal-free DTaP. But as events have outpaced us, that question became moot. So we have not come to you today to talk about that issue.

It does appear that the manufacturer is optimistic that that second DTaP product will be available, or at least approved for use, in the first part of this year as we had predicted, but since there will only be two manufacturers at that point with thimerosal-free vaccines, the preference issue is not something that you have to face today.

So what we thought we would do, take a little bit of

time not with a decisional item but an informational item where you could hear a little bit about some of the research that's going on relating to thimerosal. Given that we have made the progress that we have in reducing exposure to thimerosal and now, very soon, we may well have reduced that to zero for the routine immunization schedule, the primary drivers for the research have to do with other countries where thimerosal is still being used and also having to do potentially in the future with issues that may be faced in the compensation program. The search is not being driven primarily by policy decisions that we need to make now for the use of these vaccines in the U.S. There are two speakers, as I mentioned earlier. Dr. Heilman, from NIH, will talk about both some results that have been obtained in one of their studies and also will talk about plans for future studies that they have underway. Dr. Mootrey will talk about the future of an epidemiologic study that CDC is trying to pull together. Not all of the research that we know about will be presented today. There are other research

projects underway. For example, in the U.K., we understand that they are looking at this issue in a population of general practitioners. And we would appreciate mention of any research that anyone knows about at this meeting so that we can keep track of that. If you are aware of other projects that are not mentioned, please bring them to our attention.

So without any further comment, I'll ask Dr. Heilman to come forward and talk -- she'll talk both about the results and about the future studies. Carole is Director of the Division of Microbiology and Infectious Disease at the National Institutes of Health.

DR. HEILMAN: Thank you, Roger.

I thought I would just start out introducing who NIH is and the role that we play in vaccine research and discovery. And this is just a little diagram here to remind me to tell you that NIH, particularly NIAID, is very much involved with vaccine development and discovery. That's our primary job and the primary focus of our activities.

In so doing, we do actually have a number of

investigators that we can often call on, and that's indeed what we did this time, to answer additional questions that may have some public health implication. We also have, as part of our development -- vaccine development activities, we also have quite a large infrastructure. We do quite a bit of clinical trials, phase one through, in some cases, phase four trials, and at any point in time, we have about 50 vaccine trials ongoing. I say this because -- both in terms of the infrastructure that we have to call on but also in terms of our interest and our experience in vaccine safety issues.

So with respect to the issues of thimerosal, we really came about this asking two fundamental questions, and that is, the guidelines that were used for decision-making around thimerosal were quite indeed the guidelines that were based on the information from methylmercury. So, again, this is methylmercury with chronic dietary exposure, and the question that we had, are those guidelines indeed appropriate for guidelines for thimerosal, which indeed is a different compound as

ethylmercury, which indeed is injected IM intermittently, a different route.

The second question that we asked was, if exposure to methylmercury and ethylmercury -- do both of them actually result in the same levels of mercury in the brain, which is the bottom line of concerns with respect to thimerosal.

So in doing this, we were able to focus on two populations here, humans and animals. We did the humans first, and the reason that we did the humans first was because we really had a short -- very, very short window of time before we were going to be losing thimerosal vaccines. So we asked one of our vaccine and treatment evaluation units at Rochester, which quite happened -- it also happens to have one of the best groups of toxicologists involved in mercury evaluations -- They partnered with our VTEU investigators -- to take a look at children were have -- I'll go to that one, but the second one that we were doing is also animals. Let me go to the first study. The first study was, again, as I say, conducted at the

Rochester VTEU, and the goal there was to really assay the levels of mercury in the serum and urine of children receiving routine immunizations. Now, it just so happens that we were able to get a population who received at their two-month and their six-month dose vaccine regimens containing thimerosal and also a population that had vaccines that were thimerosal-free. So we did have those two populations, and we were able to compare the levels of mercury in serum mercury, in particular, in children who received vaccines containing thimerosal with those that received thimerosal-free vaccine. It was a very simple kind of protocol, and because we had to institute it quite quickly, what I'm going to show you, the results of that, is a little more complicated.

We were able to get 63 full-term infants. 40 of them were involved -- 40 of them had as their routine immunization thimerosal-containing vaccines. The Elmwood Pediatric Practice, that was the two vaccines that they used at two months, as well as six months. And we were also to get the Naval Medical Center who

used thimerosal-free vaccines as part, again, of their standard care.

What I'm going to show you -- I'm going to have to go through this for you -- is a scatter plot of the results. And plotted on the Y axis is the nanogram per milliliters of serum mercury. Plotted on the X axis is the days post the last vaccination when the serum was taken.

The line that's going at the 1.4 ng/milligram of serum mercury is the controls. Those are an average of our 20 controls. And what I do need to point out to you is a mistake and that is the red dots over there are actually those children that received less than or equal to 50 micrograms of total mercury. They're all two-month-olds. The average amount of mercury they received was about 38 micrograms. It ranged from 25 to 50 micrograms. The blue dots or the blue squares are those children, again, all six months of age, that received greater than 50 micrograms of total mercury.

Now, there's a few things to point out about this graph. The very -- most important thing for me to

point out is that this graph is exaggerated to make a few points and to really try to see if there's a trend, but under no cases were the levels of mercury found anywhere near the EPA, the FDA, or the ASTDR guidelines. They were at least 1.5 logs lower than any of those guidelines. And to remind you, those guidelines are at least a log lower than any of the toxic amounts of mercury found. So all of these levels of mercury are perfectly within the normal guidelines. So that's important to know. As I said, this graph is exaggerated because we wanted to see if there were any apparent trends, is there anything that we can say about the vaccines and the mercury content. And I think it's probably fair to say there's no trends. There's no real relationship between the total amount of thimerosal-containing vaccine that a child has received and the amount in terms of nanogram per milligram of serum mercury in their blood. The vast majority were at the same levels of children who had received thimerosal-free vaccine.

Having said that, there's three dots that are

outstanding there and I wanted to talk a little bit about those three children. Again, let me remind you, this is an exaggerated graph to make a particular point and they would be essentially background if you were asking a different question.

If we look at those three particular kids and take a look at, you know, who are they, what are some of their characteristics, well, there's a few things we can say about them. Again, they're all two months of age. These children did not have any -- there was no temporal relationship in terms of when they received the vaccine at the clinic. They all received 38 micrograms per mil of -- I'm sorry, a total of 38 micrograms of thimerosal-containing vaccine. It was much less than some of the blue dots that received greater than -- at least 100. We can also -- The only thing that I was able to see that may, indeed, have potentially any relationship to this was we were able to assay maternal hair. And although I have no idea on the breast-feeding patterns of any of these kids, two of these three had maternal hair levels that were

greater than one part per billion. Now, again, I have to put that in perspective. The average that a normal person could be expected to have is four parts per billion amount of mercury. If you have a tuna fish sandwich, you will have greater than four parts per billion in your hair. So these just had greater than one, but I will tell you that that one over there also had close to two. So there wasn't any particular relationship that we could necessarily say, but that was the only characteristic.

We did have one -- one mother in the thimerosal-free group that also had greater than one part per billion maternal hair mercury and the child's level was, again, less than 1.5.

The bottom line of this, we really didn't learn very much, but it gave us -- it asked -- it probably gave us more questions than it did answers, and that probably led back to the very first question and that is, is there indeed a relationship between methylmercury toxicity and ethylmercury in thimerosal. So in order to address these kinds of questions, we've opted to go

to five separate protocols, which I'll just briefly outline. They're in various stages of development right now. I also wanted to publicly thank the National Vaccine Program Office who has felt that these were important enough studies to also contribute funds towards this effort.

Two studies we'll talk about are in rhesus macaques and the other three studies are in mice, and we're partnering with our NIEHS, which is the National Institute of Environmental Health Safety which has remarkedly good toxicologists.

All the assays will be performed at the University of Rochester, which, again, has been the gold standard for our human studies.

So the first study that we're looking at in the primate is to really do a pretty good determination, and this is really talks of the kinetic information regarding peak blood and brain levels of mercury in juvenile macaques. We're going to expose them at weekly intervals for about four weeks to thimerosal at 50 micrograms per kilogram per day plus infant vaccines,

and this will be done IM. We'll also look at methylmercury at 50 micrograms per kilogram per day, again the oral, which will be our control -- We're also going to look IM to see if there's a different distribution pattern.

To ask the question about whether or not there may have been, you know -- as the children are younger, maybe they just can't metabolize or the distribution patterns may be a little bit different, we're going to then jump down to really infant macaques. Again, we'll do a similar kind of regimen, but they will more closely mimic the two-month, four-month, six-month kind of immunizations that we care about. These will be sacrificed. We'll be looking at brain scans in doing a complete body absorption.

We're going to then move into the mouse studies where we can just get more numbers and do some additional kinds of studies. One of those will be a dose-escalation study, in which we'll be providing multiple doses of mercury to see whether or not we can really push the system more than we could in the macaques

studies. These will be done at single time points, and we'll also do the oral and IM route as we've done before.

We also wanted then to take a look at the cellular patterns of distribution and the different forms of organic mercury within the brain, and we'll do very intense brain scans along that to see exactly how they're deposited if they are deposited. Then a possible question is whether or not thimerosal, in combination with immunization, i.e., immune activation, had any effect in terms of altering the brain levels of mercury. So we'll look at that kind of a question in great detail.

These studies are -- Almost all of the protocols are just about written and these are all the people that will be collaborating this effort, and we're very lucky in terms of -- within NIAID. Luckily, in the division of AIDS, of all places, we had a person whose specialty was methylmercury. So she helped us in development of these protocols.

Thank you very much.

DR. MODLIN: Thanks, Carole. Any questions for Dr. Heilman?

DR. HEILMAN: We should know about methylmercury and ethylmercury than you ever wanted. So . . .

DR. MODLIN: Stan Plotkin?

DR. PLOTKIN: I would like a clarification, Carole. I mean, what you showed was, in these 63 infants, there were no toxic levels.

DR. HEILMAN: Correct.

DR. PLOTKIN: What I wasn't -- What wasn't clear to me was, what were the levels in the controls who received no thimerosal?

DR. HEILMAN: That was the one that went across at 1.5 nanograms. It went no higher than 1.5.

DR. PLOTKIN: I see. So all of those --

DR. HEILMAN: That was the highest level, was 1.5.

DR. PLOTKIN: -- were distributed below the line.

DR. HEILMAN: Uh-huh (affirmative).

DR. MODLIN: Jane?

DR. SIEGEL: Jane Siegel.

What did you find in the urine levels?

DR. HEILMAN: There was absolutely nothing -- no patterns whatsoever in the urine levels. We looked at those especially and there's nothing -- even a plot there.

DR. MODLIN: Carole, do you have hair levels on all of the mothers or just did you just snip hair from those from which you had selected slightly higher levels --

DR. HEILMAN: No. We actually had all maternal hair from all of the mother/infant pairs.

DR. MODLIN: And how many of them were actually able to measure a measurable amount of mercury in their hair?

DR. HEILMAN: This -- The measurement, if I'm correct, it went down to about 0.1 parts per billion. You could measure that.

DR. MODLIN: As the limit. Thanks. Yes? The microphone.

MS. REDWOOD: Yes. I had just a couple of real brief questions.

The sex of the --

DR. MODLIN: Could you identify yourself, please?

MS. REDWOOD: My name is Lynn Redwood.

The sex of the three outlying children, do you know if they were male or female, since males are four times more sensitive to mercury than are females?

DR. HEILMAN: I do have that information, but I don't know. I would have to look that up.

MS. REDWOOD: The other question I had is the levels you were saying early on were 38.5 which is only about half of what children have been previously receiving in terms of then thimerosal exposure, and I guess I also have some concerns about the small number, only 62 infants in this --

DR. HEILMAN: Absolutely. No, again, please understand this is not a definitive study. It was to really, quite frankly, give us some information of what to even look for when we do the animal studies.

MS. REDWOOD: Well, when you look at academia, one in every 500 children were sensitive. So I think with a population of only 62, you're probably not going to see those children that are highly sensitive to mercury. Thank you.

DR. HEILMAN: Absolutely.

DR. MODLIN: Larry?

DR. PICKERING: Carole, what were the -- you mentioned breast-feeding, but I missed -- was there a difference in breast-feeding patterns between the two groups?

DR. HEILMAN: Unfortunately, that information wasn't collected, and that was unfortunate.

DR. MODLIN: Further questions or comments?

(NO RESPONSE)

DR. MODLIN: Carole, thank you very much.

DR. BERNIER: The next speaker is Dr. Gina Mootrey, an epidemiologist in the National Immunization Program here at CDC. She'll talk about some of the plans that CDC is examining for an additional epidemiologic study.

DR. MOOTREY: Good afternoon.

Today I will briefly provide you with some information about one epidemiologic study that we are just starting the work on. We're still in the protocol development phase of this study and I suspect either myself or others will be back here at subsequent dates to give you more information about it.

As background information, you probably remember that

back in June of 2000, the National Immunization Program convened a panel of external individual consultants to review the results of NIP's data analysis that was done using the Vaccine Safety Datalink Project. The VSD, Vaccine Safety Datalink, otherwise -- I'll call it VSD throughout this talk. The screening analysis examined the potential association between infant exposure to thimerosal-containing vaccines and selected neurodevelopmental disorders and renal effects.

The analysis found that cumulative exposure at different months during infancy was associated with unspecified development delay, ticks, speech and language delay, and attention deficit hyperactivity disorder, or ADHD. There were also a number of other conditions for which they did not find any association, including autism.

The external consultants that reviewed this data analysis found several potential limitations of the analysis, and I have some of them listed here. They found that there was a potential for ascertainment bias or confounding related to health-care-seeking behavior.

In other words, the children who made more use of health care services and, consequently, were more likely to have received all of their recommended vaccines could also have been more likely to have been diagnosed with the outcomes of interest thereby biasing the results towards finding elevated relative risks associated with higher vaccine exposure.

Another limitation of the study was the uncertainty of the meaning or significance of the exposure estimates. In other words, there's a paucity of data from animal experimental or human observational studies on ethylmercury or the extrapolation of methylmercury to ethylmercury.

There were also concerns about the inexactness of the neurodevelopmental diagnoses that were used in the screening analysis -- ICD-9 codes were used -- and there's also a question of consistency of the diagnoses across different clinicians, clinics, and HMO sites. The study did not obtain any data on the possible familial or genetic predispositions to different neurodevelopmental outcomes and the analysis had a

limited ability to distinguish between risks attributed to thimerosal versus those from other vaccines or other vaccine components.

Although a weak statistical association between exposure to thimerosal-containing vaccines and some neurodevelopmental disorders was demonstrated, the consultants concluded that the VSD results do not offer adequate evidence to support or refute a causal relationship. However, they felt that the implications could be profound and therefore further investigations were warranted.

One suggestion for further investigation was to analyze similar data sets. This was done at the third HMO site, Harvard Pilgrim, and those results have been presented before ACIP at a relatively recent meeting. The results of that investigation conflicted with the results from the screening analysis that was presented before the review committee.

Another suggestion from the review committee was to perform epidemiologic studies that were designed to control a priori for potential biases, better define

and assure quality of diagnoses, and to collect data on other factors. The thimerosal cohort study that I'm going to describe is an attempt to address those suggestions.

The purpose of designing this new study is to attempt to validate the previous VSD results and to overcome the potential health-care-seeking bias. Additionally, the new study will measure specific neuropsychological functions and status through individual testing of children. Whereas, the previous study evaluated clinical diagnoses of neurodevelopmental conditions using automated data and ICD-9 codes.

In designing this study, there are several challenges. We need to define accurate and appropriate exposure groups; define sensitive, specific, and consistent outcome measures; and identify feasible study sites. Specifically, in regards to exposure considerations, we need to identify the critical timing of exposures, such as at birth, early in infancy, or later in infancy. We need to identify the levels of exposure and we need to identify and control confounders such as child and

family medical history, birth weight, socioeconomic status, home environmental, maternal IQ, and certain maternal prenatal behaviors.

The outcomes that we will look at in this study will focus on the ones with positive statistical significance in the earlier VSD study: psychological disorders, such as ADHD, language a and speech delays, and other nonspecified developmental delays. There will also be an assessment of intelligence, achievement, child behavior, memory, visual motor functioning, and motor skills. The specific tests designed to evaluate those components have yet to be selected.

Considerations for selection of the study site, or sites, include access to a sufficiently large cohort of eligible children. We need to have good records for a vaccine lot and manufacturer so that we can adequately -- accurately assess the thimerosal content they may have been exposed to, we need to know the actual vaccines that were administered, and we need to assure that similar vaccination policies and health care

services are offered at each site so we don't come up against the same health-care-seeking bias that was a difficulty in the previous study. We have not yet identified the actual site or population. We may end up using the Vaccine Safety Datalink sites. We may expand that to other managed care organizations. We are also exploring the possibility of using the randomized cohorts from the Italian and Swedish acellular pertussis trials. It remains to be seen. Issues yet to be resolved include the required sample size, the extensive variability in thimerosal exposure within the study population, the availability of children who received a birth dose of hepatitis B vaccine, and the other number of children with zero exposure.

We will have a -- it will be a stratified random sample and we will stratify by age, sex, health care site, and thimerosal exposure. Children six to eight years of age will be eligible for study participation. We've selected this age group for a number of reasons. Pragmatically, this is the critical period when

decisions are being made about school placement and the need for special educational services. Neurodevelopmental is relatively stable, there is good normative data for the neuropsychological tests for this age, and most children of this age are able to perform the neuropsych tests.

Okay. So when do we expect to accomplish what? Well, by mid-March, which is not too far away, we will have reviewed all of the -- well, the relevant literature, we will be consulting with internal CDC and ATSDR experts, we will have the first draft of the protocol written, and we will have an internal review of that protocol and rewrite of that protocol based on comments. By the end of the month, we will distributed the protocol to a group of independent external reviewers and then bring them in to actually have a meeting to discuss this. The meeting looks like it is going to be March 26th and 27th here in Atlanta. It will be an open meeting but with limited seating, and we have not yet formed -- we have not yet asked the reviewers for participation in this but that is ongoing

right now.
Then continuing on with this time line, by mid-April, we expect to have the final protocol submitted for -- to NIP, and following that time, we will bring in an independent research contractor to conduct this study, submit to IRB protocols, develop standardized data collection tools, and begin.
Any questions?
DR. MODLIN: Questions or comments for Dr. Mootrey? Dr. France?
DR. FRANCE: I just thought I would bring to your attention -- This is Eric France from Kaiser Colorado -- that -- what jumped out at me when you focused on the six- to eight-year-olds, that is, if you do look at for managed care organizations in the United States, to have information on lot number and eight-year-olds, it's probably only one of 10 children who actually were born in a managed care organization that will still be a member six to eight years later for which they would have the information on lot number. So you might find it challenging to find the sites here in the United

States where you have that sort of continuity so that you have that high degree of record-keeping on manufacturer information.

DR. MOOTREY: Yeah. And we recognize that as a challenge. However, using an age younger than this, the test administration would be more difficult. So trying to use the age group, the youngest age group in which we could really have good testing and still have accurate information on vaccinations administered, yes, would be a challenge. And that's one of the reasons I said we're looking at different populations and may go beyond the Vaccine Safety Datalink, actually surveying different managed care organizations, to see exactly what kind of records they do have available.

DR. MODLIN: Yes?

MS. REDWOOD: Lynn Redwood again. I just had one quick suggestion.

You mentioned critical timing of exposures, and I would like to ask that you also include in there some question about whether or not the mother had been exposed to Rhogam during the pregnancy. When you look

at critical timing, prenatal exposures are very important. And with 15 percent of the population being Rh-negative, I think that would be a very important variable to include in your data, because those exposures occurred two, three, sometimes four times during the pregnancy, as well as postnatal thimerosal exposure.

DR. MOOTREY: Yes. As we have not yet developed the questionnaire that will go along with this, there's quite a bit of opportunity for adding additional questions.

DR. MODLIN: Neal Halsey?

DR. HALSEY: Yeah. Neal Halsey from Johns Hopkins University. I would like to comment on both of the presentations.

I think the studies that are being planned will go a long ways to answer the questions that we did not have answers to when the concern arose back in July of '99. So I applaud everybody for the effort that's going into this. But I do think there's one factor I didn't hear discussed in either of the two approaches that was

of concern to many of us, and that is, the background level of exposure varies considerably for the methylmercury and the EPA estimates were that, I believe, seven percent of the pregnant women in this country have had a background level of methylmercury exposure that exceeded the EPA guidelines. I didn't hear in your presentation a careful analysis, retrospective history from the mother of -- to estimate what that methylmercury exposure was, which will also vary geographically around the country. So the concern was particularly with those infants.

And I didn't hear, Carole, in your presentation, the need for studies to look at whether or not there's an additive effect of the ethylmercury exposure on top of the methylmercury. I heard comparison. Now, I could have missed it in both of these, but I didn't hear that. And to me, I think that's an important factor and a very important variable in trying to assess whether or not there is concern about adding this ethylmercury exposure on top of that small percentage of women who are already loaded with methylmercury at

the level that EPA was concerned about.

DR. MOOTREY: We did intend to include in our questionnaire an assessment of consumption -- fish consumption or other exposure to methylmercury, recognizing that six to eight years later, a food recall may be somewhat limited, but we were going to make an attempt to obtain of that information.

DR. MODLIN: Carole?

DR. HEILMAN: Yes. Although I've talked about what the protocols are being considered right now, especially in the macaque study, what I didn't say is protocol two and three are being -- at least we're going to hesitate on moving on them exactly right now until we get some initial information to see where -- what are the pharmacokinetics of the two. There very well may be that there's a reason to consider the additive part of that and we'll bring it up to the group. So it's still open for possibilities.

DR. MODLIN: Peter?

DR. PARADISO: Peter Paradiso.

You commented that the goal was to validate the VSD

study results, but I didn't hear that it was to validate the Harvard Pilgrim study results, which were in some cases not just non-confirming but quite strikingly different. If I remember correctly, the effects in premature children and some of those effects that might not have been expected may suggest not a causal relationship. I was just wondering why you chose --

DR. MOOTREY: I didn't mean to leave them out. They actually were the third VSD site and they're now part of the VSD. So I guess you could say, which part of the VSD study would we end up validating?

DR. MODLIN: Gina, if you contact either the Pro's Network or a group of similar practicing physicians or pediatricians who are research-oriented, you may find a number of practicing pediatricians who have stable populations and excellent records regarding immunization going back as long as six or eight years or even longer. So maybe expanding beyond just the obvious HMO's with large databases might be worthwhile for you. It's just a suggestion, but it would be yet

another source to get at the issue of good record-keeping over a long period of time.

DR. MOOTREY: Thank you.

DR. MODLIN: Yes, Dr. Mahoney?

DR. MAHONEY: Martin Mahoney.

I agree with you, this study you're proposing is fraught with many methodologic land mines. A couple of suggestions for your consideration.

One, I think you're going to need to attempt to control for this medical-seeking -- potential medical-seeking bias that your reviewers in the past have brought up there for you, you're going to need to look at use of medical care services and validate that information that the parents provide. So it takes you back again to a good information source. You might want to consider a military population, a stable military population where they would have good records on dependents, at least for an extended period of time as a possible source for doing -- a possible cohort for doing this thing.

DR. MOOTREY: Thank you.

DR. MODLIN: Thank you. Other questions or comments for Dr. Mootrey or Dr. Heilman? Roger, are we -- Where's Roger Bernier?

DR. BERNIER: Right here. I think that -- There are no other aspects to our presentation other than to remind anyone if they are aware of any other studies underway or if they have other further suggestions, please contact us at the break or during other times of the meeting.

DR. MODLIN: Terrific. Thanks. It's been a good session. We're running a little early. We'll take a break and reconvene at 4:15.

(RECESS FROM 3:44 P.M. TO 4:16 P.M.)

DR. MODLIN: Could I please ask everyone to be seated?

The next item on the agenda, I think, will be a presentation involving the details of the type 1 sabin strain polio outbreak in Hispaniola that's occurred in the latter half of last year. It was a very intriguing event and I think will be interesting for all of us to hear.

Dr. Sutter is going to open the presentation and we'll have subsequent Dr. Olen Kew and Dr. Ciro de Quadros making presentations. I'm going to ask that we hold questions and comments until all three have presented and then we'll open the topic open for discussion after all three have had a chance to present.

Roland?

DR. KEW: Thank you very much, John.

Good afternoon. I'm happy to be back. It seems like the meeting is getting bigger every time I come back here. Today we would like to update on the outbreak of poliomyelitis in the Dominican Republic and Haiti. And what we would like to do is to give you an overview of the epidemiology, the control measures, the virologic data, and then at the end also put it in a bigger prospective and give you just a couple of slides of a progress report on polio eradication and talk about the implications of this outbreak.

We are very fortunate to have Dr. Ciro de Quadros here, the Director of the Division of Vaccines and Immunizations of the Pan American Health Organization

who will lead off. Dr. Olen Kew, Chief of Molecular Virology Section at CDC will follow. And finally, I will go.

So without any further ado, Dr. de Quadros.

DR. de QUADROS: Thank you very much, Roland. I would like to thank you very much, the ACIP for inviting us to participate and to relate to you some of the data that we have already collected in this outbreak. And this is really a result of a very close cooperation of the Pan American Health Organization and the Centers for Disease Control, which I think really translates what really the Pan American Health Organization is, which is the combination of all knowledge that we can have here in this region. I think this is a good demonstration of that Pan American in this recall.

The background that we have is that the last case of polio in the Dominican Republic was in 1985. In Haiti, the last case was in 1989. And as you all know, the last case in the Americas was in Peru in 1991. And in 1994, after intensive work by the International Certification Commission and National Certification

Commission, the Americas were certified as polio-free, meaning that the Commission declared that there was no indigenous transmission of wild poliovirus in the Americas. And then in 1991, we had a case in the OR, which we call it a compatico case. It had a sequelae which was typical of polio but had no specimen collected. So it became classified as compatico, but later on was discarded by the National Commission and International Commission because it did not fulfill all the conditions.

In the Dominican Republic between '83 and '93, there was over 60 million doses of OPV applied in National Immunization days and mopping-up campaigns. In 1987 and '88, there was a national (inaudible) in which over 300,000 houses were visited, 458 cases of acute flaccid paralysis found, and none was compatible with poliomyelitis.

The coverage and number of cases shown in this transparency or in this slide, coverage has remained about 80 percent over the last few years, which drops in '91, '92 and '98, '99, and the last case, as you

saw, is there in 1985.

In Haiti, the situation is quite different. As you know, Haiti suffered major problems with the whole government, with embargo during the several years, and the program immunization really has deteriorated considerably from what it was several years ago. There are years even that we did not have actually vaccination in the country. There was no polio reported in (inaudible), but coverage was, as you can see, dismal low -- below 50 percent.

If we look at the proportion of districts in those two countries for which we have data, the proportion of districts with coverage below 80 percent, you can see that basically the majority of districts in the Dominican Republic for which we have data have very low coverage with few exceptions in 1993 to '95 and that's were last districts with low coverage, but this, I think, shows to you the very poor level of coverage in the two countries.

If we look at some of the indicators for -- surveillance indicators, in this one we show the

proportion of notification sites reporting weekly, you can see that in the Dominican Republic, the situation was a little bit better than in Haiti, but there was a deterioration of those indicators over the last few years. This was a phenomenon that we saw in many other countries in the Americas and here was really watched in others. And reflecting part also the complacency because of (inaudible) for many years.

If we look at the acute flaccid paralysis rate per 100,000 children under 15, which is basically one of the best indicators to monitor surveillance and the expected minimum is one per 100,000 per year, you can see that in both countries, that indicator was not really up to par. So surveillance has deteriorated definitely in the two countries.

The cases of acute flaccid paralysis properly investigated with the collection of inadequate sample for the laboratory. Also, you can see Haiti, basically. We didn't have the specimens. While in Dominican Republic, we had a period in that we had a good proportion of cases with specimens and, again, in

the last two years in deterioration.
The proportion of enterovirus isolations from the two countries, in most of these specimens initially are sent to a reference laboratory for the Caribbean area, which is in Caribbean Epidemiology Center in Tobago, and you can see the proportion of enterovirus isolation was mostly, with exception of 95 to 97, we see some expected international disturbance of between 10 and 20 percent of isolates of enterovirus.
Now, if you look at the situation then of the present outbreak and we look at the year 2000 and the first two months of the year 2001, we had 12 confirmed cases in Dominican Republic. There are still several cases that are pending investigation. About, I think, 18 or 19 cases that are pending investigation and several have been already discarded, but were 12 confirmed cases now in the Dominican Republic starting in July, and the last case was in the first two days of January. It was the 2nd of January, that last case.
This was the rate and case by age group. Most of the cases are in the group one to four years of age and

most of them are also unvaccinated. The coverage in the areas in the Dominican Republic and Haiti were the lowest in the whole country.

In Haiti, we have so far only one isolate from a patient. It was in August, and some other cases have been discarded and there are still three cases pending. This case in week 35 had acute flaccid paralysis but had no specimen collected. So we keep that as a compatico case for further studies to be done, but so far we have just that single case in Haiti.

These are the location of the cases. The case in Haiti was in the northern part in Cape Haitian. There are other cases in the Dominican Republic sort of in the many roads that goes from Santa Domingo into that area and then you had around those places.

After the cases were discovered, there was intensive search for cases in both countries. In Haiti, those areas that are shaded are still to be searched. They were searched and we found acute flaccid paralysis cases. Most of them had specimens negative. And then in the areas which the dots, they have been already

heavily searched and no cases of acute flaccid -- no cases of acute flaccid paralysis were found. Searches are still going on in this part of the country. But so far, all the searches in Haiti did not uncover any additional case.

These are the confirmed cases in the Dominican Republic along this road. This is the last case detected in the beginning of January. It's quite interesting, because as I'm going to refer later, in December, 16, 17, and 18, they had a very heavy national immunization days in the Dominican Republic with the vaccination of 1.2 million children, which is more or less the cohort of one to five. And this kid who was the only kid not vaccinated in the village where he lived -- He lived in sort of a hill. He lived with his grandmother and the grandmother didn't bring the kid. It was an area also that two vaccination teams thought that the area belonged to the other one and that house was left. So it was a quite interesting situation.

This is the overall distribution of all cases that have been confirmed. The cases in red are the cases

confirmed. Then the cases that are already discarded and then some pending cases that the results from the lab are not yet available.

And for the year 2001, we had one confirmed case, as I mentioned, and then there are several cases, 14 cases that are pending in the same area of the outbreak. These are acute flaccid paralysis cases pending, the results from the laboratory. So that's the present situation in that regard.

And this just summaries the whole laboratory work. We had -- In the Dominican Republic, we had 12 cases and nine of them were -- the virus was isolated from the case itself and three of the cases were confirmed because the virus was isolated from close contacts. So there were actually 17 isolates of the derived virus but only 12 paralytic cases. And there were some Sabins also found, some known polyenteroviruses, 22, several negative, as you can see, about 67 negative, 11 from patients, and 56 from contacts, and there are still some pending cases, 68 pending cases. In Haiti, just one case confirmed, one derived case. Still, we

have some -- some three cases pending results of the laboratory and -- and several were negative, both from cases and contacts.

The activities that followed the discovery of the cases which were caught by the normal -- you know, whatever surveillance they had at that stage -- Actually, it was quite surprising because the case in Haiti, it's about three hours' walk from a dirty road. So it's very difficult to access that. Even with that situation, the case was discovered, these (inaudible) taken, and the case was reported. So in the very poor surveillance environment, still we could get that. And the same with the cases in the Dominican Republic. Initially, the cases were suspected to be toxication because that's an agricultural area where there is lots of agri-toxics being used. So there was lots of investigation in that respect, but also they had the stool samples for collection.

So in both countries, there was intense active search in most of the country. There was environmental sampling that was done in collaboration with the group

from the CDC. Those samples which were from both countries are now being sent to a laboratory for examination and see the extent of transmission -- of the circulation of the virus. As I said, there was a mass campaign in the Dominican Republic in December with 1.2 million children vaccinated which was basically 100 percent. There is a second mass campaign that just finished this Sunday. They held it Friday, Saturday, and Sunday. The data that I got last night is provisional because still data is coming from the field that tells us that already, yes, the data had 1.1 million vaccinated. We think it will be approximately the same number. Then there will be a third campaign held in April for that.

In Haiti, there is a mass campaign that is going on today, at this moment. It's a very difficult country to work at this moment. They tried a mass campaign in January. The coverage was below 30 percent. Heavy rains all over the country, very poor planning, and now they are doing a campaign that is a rollover in different districts and hope that the situation will be

improved, but it's a very difficult country to work at this moment. You know it's a country that's just got an official government taking over and the parallel government also being nominated. So it's a very difficult situation.

So the main implications as we see for the Americas and possibly also for the rest of the world is that we are now -- the CDC is reviewing now all the Sabin isolates from '94 to the year 2000 to determine if this had happened before and went undetected because sequences were not done as a routine. We continue an active search now, not only in the two countries, but we are identifying high-risk areas in other countries in Latin America and searches will be conducted. Of course, this was the lesson to every country, that they have to maintain a very high level of acute flaccid paralysis at all times and also maintain a very high level for OPV coverage in all countries to continuation of the NID's, and we have now to wait for further research before we decide on discontinuation of vaccination and how that will be done. I think that Dr. Sutter will

address this issue in his presentation.
Thank you very much.
DR. KEW: I very much thank the Committee for inviting me to present and tell a little bit about the virologic side of this very interesting outbreak, and it really started last summer when Victoria Morris Glasco from the (inaudible) lab notified us that we had a type 1 poliovirus, first from the Dominican Republic and then later from Haiti, where there was considerable interest on the part of the epidemiologists whether this was a wild virus or a vaccine-related virus.
And with her constant prodding, we decided we better sequence these viruses, even though we had, not as a matter of routine, been sequencing vaccine-derived polioviruses. It was unusual, in fact, type 1 vaccine-derived polioviruses associated with AFP cases.
So with that, we proceeded to sequence, and the first one had about 18 neucleotides different from Sabin 1, which was much higher than what you normally see from both healthy children who have received vaccine or VAPP cases. And the second one had 24 neucleotides

different from Sabin 1 but, more importantly, many of those neucleotides were shared in common between the two, indicating that there was some kind of epidemiologic link between a case in the Dominican Republic and a case in Haiti occurring both in the same summer.

So we then proceeded to get a number of other isolates. We've got a large number now from the (inaudible) laboratory and they, as a group, have about 97 percent VP1 sequence identity to the Sabin Type 1 OPV strain. That's about three percent sequence difference, which is well above the threshold we normally see. The isolates are unrelated, less than 85 percent VP1 sequence identity to type -- wild type 1 polioviruses. I'll tell you a little bit more about what that 85 percent really means. The unrelated two viruses previously found in Hispaniola or any other part of the Americas are unrelated to wild type 1 polioviruses currently found in other parts of the world. The viruses formed two closely-related clusters, and I'll show you a tree in a moment of that. The single

isolate from Haiti represents one cluster and the 18 isolates from the Dominican Republic represent a second cluster.

The interval that we're going -- that we sequenced is VP1, which is about 15 percent of the genome. This is for the routine characterization. The shaded areas here are the antigenic sites which have also changed in this virus.

This is the relationship between the Sabin 1 from Haiti and Dominican Republic to wild type 1 polioviruses.

Now, what's circled here -- I hope you can see the laser dot -- are the isolates we previously received from Haiti and the Dominican Republic. So this is the wild type 1 genotype previously indigenous to that island.

Related to that was viruses found in Brazil. This is close to the last virus from Brazil. This is the last type 1 -- wild type 1 from Central America and Mexico. And then over here are the viruses from the Dominican Republic and Haiti, the first two isolates, and then this is Sabin 1 right here. Then this is Columbia in

1991, the last isolate from Columbia; and then these are wild type 1's from all over the world, Sudan, Chan, Liberia, Pakistan, China, Bangladesh, Cameroon, Guinea, Nigeria, and so on, essentially a sampling of the contemporary type 1 lineages and genotypes found worldwide. Again, the viruses from Haiti and the Dominican Republic clustered tightly in VP1 sequence with Sabin 1.

Now, these distances, apparently impressive as they are, really are a great underestimate of the true genetic distance between this cluster and the rest of these because of saturation of variable sites. So the 85 percent really represents a great underestimate of the true genetic distance between this cluster here and the rest of these. So these are really quite, quite distinct.

This is another tree where we have the relationships between Sabin 1, the Haitian -- single Haitian isolate, and the cluster from the Dominican Republic. And you could actually the topology of this tree by moving the Sabin 1 over here, putting it at the root and putting

it out here somewhere, because it truly is parental to these. And then you can see that the Dominican viruses form a genetic cluster quite separate from the Haitian lineage, but both of them are quite closely related to each other and to the Sabin 1. And you can also see a tendency for geographic clustering of these isolates. So these are from Santiago here. This is La Vega. This is Espillat. This is Santa Domingo and another one from Santa Domingo, and these two from Santa Domingo don't look -- even though they're separated only by about five or six weeks really are distinct lineages.

Now, these viruses really are now wild poliovirus by any definition other than their immediate ancestry. They have similarities to wild poliovirus in the capacity for sustained person-to-person transmission. They have a significant paralytic attack rate. I think it's difficult to actually give a hard and fast number to that, but it's certainly significant. There is reversion at the critical attenuating sites. The single most important attenuating site for type 1

poliovirus is in the five prime untranslated region representing from (inaudible) where it's representing about half of the total attenuating -- attenuation phenotype, and that site has been reverted in the all the isolates we've so far sequenced. They also are non-vaccine-like and are antigenic properties so the standard antigenic test, which are also used to distinguish vaccine viruses from wild, would pick these up actually as non-vaccine-like or, presumably, wild. These viruses also replicate at super-optimal temperatures. 39.5 is what we tested. It's about a thousand times higher titer than your standard Sabin 1 at that temperature for the same input titer of virus. So it's, again, behaving like the old RCT 40 test, if any of you are familiar with it. It's very much like a wild poliovirus.

They also undergo recombination with non-polio enteroviruses, very like wild polioviruses do as they circulate in the community. They keep picking up sequences from their evolutionary cousins of the poliovirus enteroviruses, and so have these viruses.

Now, we've estimated the times of circulation of these vaccine-derived polioviruses and we've done this by looking at the VP1 sequence differences among the clinical isolates that Victoria has sent us, and the rate of poliovirus VP1 evolution is approximately three percent synonymous substitutions per year. That's about one to two nucleotide substitutions per week. This is the most rapidly evolving virus that we know of in nature.

And the rate of evolution for type 1 poliovirus appears to be remarkedly uniform and similar for different genotypes. So using this value of three percent, we estimate that the originating, initiating OPV infection occurred somewhere around August, 1998. That divergence of the Dominican and Haitian lineages occurred somewhere around June, 1999.

Now, there are some assumptions for these calculations and they are, at this point, still fairly crude. We assumed that there's a constant rate of fixation synonymous with VP1 substitutions over this time period. That's an assumption that is unproven, but

it's certainly reasonable and based on other observations. Also, it's on the assumption that the VP1 evolution rate for the Dominican and Haitian lineages is similar to the rates determined for other circulating wild polioviruses. That's an unproven assumption, but at this point it would be difficult with the current sequence database that we have to actually internally calibrate the evolution rate simply because we have a short observation time, only a few months, about six months. And mutation is stochastic. It's kind of a plasson process. So right now, we have fairly wide confidence intervals. We can narrow those down by sequencing complete genomes and narrowing those confidence intervals, but they're still going to be fairly wide because the period of observation is necessarily short, and with Ciro's effort, it's going to remain short.

This is another form of the tree where we actually now have a scale of time, and what this is, is now scaled to some fraction of -- this is the year 2000 and some fraction of the year, and these essentially are the

branches -- the tips of these branches are now essentially ordered in chronological order. And we estimate from this, based on the previous assumptions that the rate is about three percent synonymous substitutions per year, that the Haitian lineage diverged from the Dominican lineage about July, 1999, and that the Dominican lineages started to elaborate from some common ancestor around the spring of 2000. These viruses are also recombinant, as I had mentioned. White would indicate Sabin 1 sequences only. The single Haitian isolate has a recombination crossover site at this point. This is the capsid region here. This is the five-prime untranslated region right about at this position. It is an important site, that determines the attenuated phenotype, or largely determines the attenuated phenotype, and then these are nonstructural proteins in this interval here, in 2A, 2B, 2C, 3A, and so on. And the nonstructural protein sequence is derived from some other -- not necessarily poliovirus sequences, but almost certainly a species seen in non-polio enterovirus. The Dominican Republic

isolates share a little bit of this sequence, but then there's been a superimposed recombination with a separate different non-polio enterovirus indicated by the blue color. So these are recombinants.

Now, this allows us then to make a specific hybridization probe, which will pick up viruses which are Sabin-derived in this interval, Sabin sequences in this interval, but have non-Sabin sequences in this interval, and we can have a rapid screening for the recombinant viruses.

Now, there are other examples of circulating vaccine-derived polioviruses. One example is in Egypt where viruses which had originally been thought to be wild type 2 polioviruses were sent to us by Dr. Tari Neghee of the Vaccine Lab in Cairo, and when we sequenced them, it turned out that they were Sabin-derived but quite diverged from Sabin, about four to six percent diverged. And the last wild poliovirus isolate from Egypt was seen about 1979.

What we observed then was continued evolution from the period of 1988 to 1993, but we could extrapolate that

using assumptions rather similar to what we had used before for the Haitian viruses, but with internal calibration because we had a longer period of observation. We estimated that circulation had initiated from a single event starting about 1982. And there's a similar observation in Guizhou, China, that Jon Rabee [phonetic] and his colleagues have described briefly in the Chinese literature.

As Ciro had mentioned, there is now surveillance for circulating vaccine-derived polioviruses. Sequence studies from other PAHO countries did not find any highly divergent isolates up to 1997. What was conspicuously absent were isolates from Hispaniola, which we very much wanted to have but they were not able to obtain for reasons that Ciro had just told you. They weren't available. Analysis of more recent PAHO isolates in progress, there are on matches for the Hispaniola viruses found so far in other countries in the Americas, and virtually all of the isolates have a greater than 99 percent VP1 sequence to the respective OPV strains.

There are also sequence studies ongoing of current vaccine-derived isolates from AFP cases from all regions. We've already started. We've got a big shipment from the Eastern Mediterranean region representing all their Sabin strains or AFP cases in our collection at the present time.

I think that summarizes what I have to say, and I think I'll turn the rest of the presentation over to my colleague, Roland Sutter.

DR. TOMPKINS: John, could I ask a question while we're waiting?

DR. MODLIN: Yes. Lucy?

DR. TOMPKINS: Lucy Tompkins.

Do I have it right that what you think has happened molecular-epidemiologically is that the vaccine strain reverted sometime in July -- around July of '99 in Haiti and then its derivatives, which are more or less still revertants -- in other words, have they accumulated further reversions to virulents and then went onto the Dominican Republic? Is that how it goes?

DR. KEW: Our estimates, and they're only estimates at

this point, would be that the initiating event was as an OPV dose given to a child in mid-1998, that the environment surrounding that child, that is, the coverage rates in that community were such that the virus could transmit efficiently to the next child and that child could then initiate another infection. And under such events, a continued evolution of the virus permitted increased replicated fitness of the virus such that it could initiate person-to-person transmission which continued along a single common lineage to what we're seeing now until about mid-1999. Then it split into two lineages, a Haitian lineage, which may not be representative of all that was in Haiti by any means, and the observed Dominican multiple lineages, but we think it was from single initiating event.

DR. TOMPKINS: Is the virulence of the Dominican isolates any different from the one Haitian isolate that you have, just on the basis of what you know so far on those trees?

DR. KEW: We can't -- We cannot tell you very much

about the virulence in children other than that the attack rate in the Dominican Republic, where surveillance is quite good, appears to be comparable to what you had with type 1 wild, and Ciro could address that, I think, in more detail.

Experimentally, they have been tested in transgenic mice, a couple of them from the Dominican Republic, and they're quite virulent transgenic mice. There are additional tests ongoing in other laboratories which will include the Haitian virus. The relationship between experimental virulence in mice and what you actually see in humans is unclear, but it's certainly another indication that the virus is a hot virus. And that's predicted by the genetic properties of these viruses. They have the sequences which correlate strong with increased neurovirulence, both the Haitian and the Dominican.

DR. SUTTER: Thank you, Olen.

What I would like to do is actually start off with perhaps a little bit of good news, a progress report on the global polio eradication initiative.

You have heard a lot about the outbreak already, so I would will go through the next slides very quickly, some virology.

There are some unexpected findings and some immediate implications, which we already heard as well. I will talk a little bit about stopping polio vaccination options and I will talk a little bit about IPV, what is the decision-making process in terms of who will be making these decisions and when these decisions need to be made for stopping vaccination. I will offer some conclusions.

In terms of global polio eradication progress report, in 1988, when we started, there were about 350,000 cases occurring annually. Last year, in 2000, 2,599 have been reported, and we don't think that this number will go up much more. We think it will be around 3,000 when all the countries have reported. Last year, we had more than 7,000 reported. So this represents quite a significant drop.

Type 2 has not been isolated in more than a year. It was last isolated in northern India. So, hopefully, we

are done with one type, but there are still some areas in the world where surveillance is not that great. So we can't be certain at this point.

Just to give you an example of one country, this is India, and just looking at accurate flaccid paralysis cases with poliovirus isolation, from 1998 to 2000, you can see that we have seen a huge decline in the number of cases, from more than 1,900 cases here to 1,100 cases here and 266 last year. You can also see that the virus is now pretty much focused in northern India, with just very, very few cases outside of Yutarpredesh [phonetic] and Pehar [phonetic].

In terms of surveillance, just indicated the countries that are nearing certification standard level surveillance in yellow, and you can see here that most of the world is getting yellow. And we have seen much progress in the African region as well, and I think next year if I were to show you this slide in a year, you would see lots of yellow in Africa as well.

You have seen and heard about the outbreak already, so I will not get into this or the virology. I think what

Olen already alluded to, we had examples where type 2 did circulate and cause cases, but we had never had, before this instance, type 1. And clearly, type 1 is the most attenuated of the -- of the Sabin viruses. So, for us, that is a little bit unexpected or surprising.

Why the Dominican Republic? I think you heard about that as well. Coverage clearly was quite low in the most effective areas. I put the question mark behind Haiti because we only have one isolate. There may be another possible in Haiti, but coverage has been much lower, even than in the Dominican Republic, and it's still puzzling why that virus didn't take off and cause more cases in Haiti.

I think also we heard about the immediate implications. Clearly, we need to maintain surveillance capacity, not only in the Americas but all the other regions and countries that are now polio-free. Immunization coverage must be maintained. There's clearly a price to be paid if not. We don't know whether this outbreak and circulation of this virus will affect the

certification of this region. I think the Global Certification Commission will look at the data and will have to come to a decision.

In terms of the global program, clearly, we need to cover our backs as well and while still moving as quickly as we can to eradicate wild poliovirus, we need to make sure that vaccine-derived virus will not emerge behind us.

We need clearly to do more research. At this point, we believe that this is a rare event. Although we can't be certain because we haven't looked at all the -- all the Sabin isolates from around the world to see whether we have other instances.

Why did this occur, what -- under what conditions, and how can we prevent it from occurring in the future? Just in terms of what the options are for stopping vaccination -- And I just bit a little bit of slang here -- starting with cold turkey, and that's really after certification which has stopped, which is probably not the safest thing to do and, hopefully, nobody will advocate for that. The big bang is really

to have a global immunization day, not -- you do lots of national immunization days but do a global immunization day to maximize immunity and then stop. Other suggestions have been to go from a trivalent OPV to a bivalent because it looks like maybe type 2 is gone or nearing elimination. Maybe we could stop that part and see what happened with type 2 in the environment in these countries, and so on, and then move to a monovalent. Clearly, we can go from an OPV to an IPV, and some people are still advocating to go to a new vaccine, although that doesn't seem a very feasible option at this point given the time to test things and safety issues.

For some of us at least, we think that this outbreak is a wake-up call for us and provides us with some guidance how to stop, and we believe that OPV should stop after eradication. OPV not only causes vaccine-associated polio, but it also can re-emerge as we just have heard.

The cessation of OPV must be coordinated. OPV strains must also be contained. We cannot let them back into

the environment or into children. Clearly, we need high OPV coverage until cessation.

Some believe that the highest immunity that one can obtain is actually immediately after eradication, and so there is a trade-off with waiting or doing something else.

The role of IPV clearly -- or IPV has become more prominent again, and what is happening now, what we are seeing is that industrialized countries clearly move to IPV. They are starting to switch, as we have seen in the United States as well. So we see a two-class system emerging where industrialized countries go to IPV and developing countries stay with OPV. It's clearly an issue with feasibility for global IPV. Especially the manufacturing capacity is not here at the moment, and I think it would take between three and five years to actually gear up. So it's something that could not be done immediately.

There's also an issue of what schedule, sequentials, or combined, or IPV-only schedules. These need to be looked at. I think the IPV-only immunogenicity is

another issue. There's no country, no developing country at the moment, that uses an IPV-only schedule. So we have very, very little information about IPV immunogenicity in developing countries. And in all -- I think virtually all of the studies that look at IPV in developing countries, it was done in a situation where OPV was used very heavily and OPV's certainly, in most cases, did contaminate the IPV groups.

We need to worry clearly about the injection safety. Hopefully, with combination products, this would not be an issue. Of course, also the IPV used for outbreak control or whether one needs to have OPV in stock for outbreak controls.

So in terms of research issues, there are a couple. One is just the schedules as well. WHO is using a schedule of six, ten, and fourteen weeks. That doesn't work terribly well in developing countries. These children have a very high level of maternal antibodies. So a schedule of two, four, and six months would work, but it would -- would entail that WHO changes the schedule.

I think the immunogenicity of IPV -- I think still needs to be looked at in developing countries as well, including mucosal immunity, simply because I think we never had a situation where we had clean groups to look at and to study. We don't know what coverage of IPV would be needed to limit OPV circulation in tropical countries.

Some countries with suboptimal coverage, what can we recommend for them? Do they need a combined schedule, a sequential schedule of IPV and OPV, or just continue with OPV?

There have been several meetings that the World Health Organization has convened in Geneva, and at the meeting in March, 1998, one of the recommendations was that OPV should stop and IPV can stop when there is, one, eradication of wild poliovirus, laboratory containment of polioviruses, and evidence that Sabin virus will circulate only for a limited period of time.

In terms of decision-making process, WHO would like to bring this issue and the solution -- have the solution endorsed by the World Health Assembly which is really

the governing body of the World Health Organization. And they're hoping to have an information paper this May to the WHA and then a discussion in 2003, and hopefully, by 2004, we'll be in a position to make recommendations.

So, just in conclusion, my favorite quote: "In battle, no plans survives contact with the enemy." And I think this outbreak has shown this again. Clearly, even in an eradication program, we need to continue with the research and we need to learn these lessons and apply them rapidly. We're not sure at this point to what degree the outbreak in the Dominican Republic and Haiti will affect the stopping strategy. We think it will, but further research is needed so that we have the best science that can drive this process.

Thank you very much.

DR. MODLIN: Olen, thank you. Also, thanks to Olen and Ciro for some eye-opening presentations.

We do have time -- I know that this is a subject that will generate an awful lot of interest, so let's get going. Sam?

DR. KATZ: Perhaps I missed it in Ciro's presentation, but what degree of sampling has there been in the Dominican Republic among non-ill children to see, is the virus circulating? As we know, you may have 100 children excreting virus for one paralytic case, or 200, or 1,000. Do we know anything about the denominator background?

DR. de QUADROS: There was not a national survey -- a national sampling survey in the population, but the contacts -- several contacts of cases, we collect specimens, and they are not so many. I think, all in all, no more than 200 contacts have been collected. So there was not a national sampling. The environmental samplings, there weren't -- they did give some information on the country as a whole, but not in the population itself.

DR. KATZ: So how many were there in those 200?

DR. de QUADROS: We got about, I think, eight with viruses. There are still some pending. I think there is about 50. I think 59 are still pending -- contacts.

DR. KATZ: Thank you.

DR. MODLIN: Stan?

DR. PLOTKIN: Well, I have two comments. One is that I would argue that if this type of occurrence is rare, it is only rare because coverage has been relatively high in those places where OPV campaigns have been done. Because knowing the process of developing attenuated strains, it seems to me that as long as you have serial human passage, you will eventually arrive at virulent viruses. The problem -- well, not the problem, but the thing that's prevented that in most cases is that there has not been the extent of serial human passage as there was in the Dominican Republic, but in a circumstance where vaccination is dropping off for whatever reason, then the chances are going to be maximized for an excreted Sabin type 1 strain to -- or rather, any Sabin strain to lose it's attenuating mutations and become virulent again.

My second comment speaks to something that Roland said about the use IPV. Indeed, the prospect of furnishing 500 million doses or so of IPV, it would be somewhat daunting at this point, but it's not totally out of the

question if it were planned. But the more important point, it seems to me, is that combination vaccines for the developing world has got to be the wave of the future. In other words, everyone of us wants to get the vaccines that we use in the U.S. into the developing world. And the way to do that, as in the U.S. for that matter, is with combined vaccines. If those combined vaccines contain IPV, the cost issue at least specifically for IPV disappears, and another advantage of that, which Roland knows better than anybody else, is that you get better immuno -- better seroconversion if you're using IPV and OPV together until such point as you decide you can stop OPV, in which case you still have the immunogenicity and protection of IPV.

DR. MODLIN: Thanks, Stan. Neal?

DR. HALSEY: A question for Olen Kew.

I mean, the hypothesis with regard to the origin of the virus that you put out is that a vaccine dose was given to a child that was then shortly thereafter transmitted to another child and another and another, and that at

some point it acquired the characteristics of also increased transmissibility and virulence. Is it not also feasible that this was a virus that was given to somebody who had a prolonged excretion and the mutations occurred in that immunodeficit individual for whatever period of time was necessary and then it was transmitted to somebody else and started those outbreaks? And is it possible that both the Haiti and the Dominican Republic isolates are two different origins? How firm are you in your belief that they really had a common ancestor?

DR. KEW: I'll answer your second question first because it's the easy one.

It's very clear that they have a common ancestor. They have too many common sequences that are not the normal attenuation reversion pathway. So we checked that out immediately. And also they have common non-polio enterovirus sequences in at least a small window indicating that they did have a common -- a recombinational history, too, which got largely obscured by secondary combination event.

We cannot exclude the possibility that there was a immune-deficient child or a person that was a participant or intermediate in this process, but we don't think it's a necessary hypothesis. It may be true, but we, at this point, have no way to determine one way or the other.

DR. MODLIN: Myron?

DR. LEVIN: Are these recombinant viruses readily neutralized by titer-specific antibody?

DR. KEW: Yes.

DR. LEVIN: Good.

DR. KEW: These viruses -- To answer your question in a little more depth, there is enormous antigenic variation among polioviruses for all three serotypes, but the range of that variation is limited. So the rate is high, but the range is low. What we're seeing now is the kind of evolution you see with the wild polioviruses. Once they've been essentially evolved away from the rather atypical Sabin immunogenicity back to a wild virus immunogenicity, they're very, very similar to other wild polioviruses and present no

additional threat because of their immunogenic properties.

DR. LEVIN: Yeah. Well, it goes to the question, would OPV be appropriate in preventing transmission?

DR. KEW: I don't think there's any question it would be.

DR. LEVIN: Yeah. Thank you.

DR. MODLIN: Olen, why you're at the microphone, could I just -- a follow-up question on what Lucy asked earlier, and I think I also got a -- Obviously, these viruses have lost the attenuating mutation in the five-prong non-coding region, but there are, as you indicated, other attenuating mutations for type 1 that have been well-identified and some of which are in VP1. Have those been lost as well?

DR. KEW: We haven't gone through the complete catalog of changes yet but, yes, a number of them have been lost as well, and there are some also attenuating changes in the non-structural protein genes. Of course, those have been essentially switched out with nice, fresh --

DR. MODLIN: With the recombinant.

DR. KEW: -- yeah, recombinant circulating viruses.

DR. MODLIN: Those have been recombined.

I guess the second question is, the use of the transgenic mouse model makes an awful lot of sense because it's easy to do, but, of course, we've got the old style monkey neurovirulence model that's been developed at the FDA and whether or not, in this situation, this wouldn't be an appropriate use of that model to go back and look, because that seems to be the -- correct me if I'm wrong, sort of the most conservative assay that we have for neurovirulence for any poliovirus. Is that still the case?

DR. KEW: I think as a safety test -- I think there's people that know a lot more about this than I do. As a safety test, the monkey neurovirulence test is still the gold standard for testing of OPV. Rarely have wild polioviruses have been tested for neurovirulence except in the early days of characterization of wild polioviruses. These viruses now that we're looking at, vaccine-derived, appear to be very much like wild

polioviruses and they are, again, paralyzing children. So the child neurovirulence test has already been run on these. It is a very unfortunate thing, but it's been run on these and these viruses are hot and there's already some indication that that correlates with what's found in the mouse model.

DR. MODLIN: Thanks, Olen. Dave Fetson?

DR. FETSON: Dave Fetson, Aventis Pasteur MSD. Perhaps Roland, or even Ciro, might be able to answer this. Does the research agenda that you've set forth now include, in addition to virologic and epidemiologic studies, a social science research agenda which asks people in developing countries what kind of strategy they want for the end game for polio vaccination?

DR. SUTTER: Thank you for your comment. At this point, in 1997, following the report of Olen Kew that actually showed that vaccine-derived virus can be replicating in an immunodeficient case, we put together an initial research agenda. Most of these -- the research has actually been done. And now there is a process underway to define our next, you know, two- to

three-year research agenda. We are doing this with WHO and, hopefully, within the next three to four months, we'll actually finalize that. So at this point, I can't even tell you whether something like that would be in there but, at this point, I doubt.

Thanks.

DR. MODLIN: Jon?

DR. ABRAMSON: I was going to follow up on Neal's point. You, again, touched on it.

With the data that was presented in October that suggested that you could find virus in some people 10 years out, how -- how are you going to feel comfortable stopping immunization with IPV for -- after a short period of time?

DR. SUTTER: There are no easy questions today.

But I think what we are still trying to define -- and I think that is still ongoing, some of these studies -- what is really the likelihood or -- of immune-deficients actually excreting. That's one thing. And the other thing is particularly whether we see the same things in developing countries as well. I think for

most of us we believe that most industrialized countries will not stop vaccination for quite sometime. So this is probably not something when the world as certified as free of wild poliovirus that, you know, countries will say this is the time to stop. So . . .

DR. MODLIN: Dr. Deseda?

DR. DESEDA: I have a question and a comment. My question is, what about the ages in the confirmed cases in the Dominican Republic? I just wonder about that. I would think they would be infants. But the other point is, in Puerto Rico, we have a very large community from the Dominican Republic, many of whom are illegal aliens. We've had several vaccination days coinciding with the ones in the Dominican Republic to try to capture these children. We are also recommending people who travel to the Dominican Republic to get one dose of IPV. I don't think there's any danger in Puerto Rico because we have very good vaccine coverage, but I wonder what would happen to other people from other Central American or Latin American countries who travel quite frequently. And in

the Dominican Republic, there's a very big resort in terms of tourists, and for Europe also.

DR. MODLIN: Ciro?

DR. de QUADRO: I think I showed on one of the slides the distribution by age group, and the majority are in one to four. So the majority are kids are below five years of age.

We have the same advisory to travelers in the Dominican Republic, to be sure that they are vaccinated before they go there, most of the Dominican Republic and Haiti, and of course, there the other point is that they still do not see the importance of surveillance in the other countries that have much contact to the Dominican Republic. For instance, we have maybe an airplane full of Argentineans almost every day coming to the Dominican Republic. So both they are ensured that these people are protected, as well as surveillance when they go back where they are. But it is a difficult thing that we have to face now.

DR. MODLIN: Phil Brunell?

DR. BRUNELL: Phil Brunell.

Olen, I wonder if you would expand on the origin of these viruses. One of the mechanisms, which I think is the one you're leaning to, is sero-passage has changed this virus back to a wild, but I'd like to ask the question about whether essentially a big bang happened here. Because it sounds as though this virus is very unusual in the -- in the rate of mutation. I mean, you mentioned this. It's extraordinary. So was there something special about this particular strain or was this something that evolved gradually as one might expect if you passed poliovirus through the human species? I think the implications of this, I think, are obvious and that is, if this is an unusual event and you keep using OPV, this can -- the chances of this occurring again are greater than if you switched to some other strategy. On the other hand, if this has evolved by sero-passage through the human species, then you had better get OPV out there and use it more intensively.

DR. KEW: As Roland said, there's no easy questions this afternoon. There's actually several parts to your

question, so I'll try to break it down into its component parts and address them individually.

First of all, what you don't want to do is separate the virology from the epidemiology, the conditions in the field from the properties of the virus. I mean, they're so interlinked that you have to look at this as a presentation showed in its entirety. There's no evidence that extended evolution of OPV viruses occurs through person-to-person transmission in an area where there's vaccine coverage. Where we've seen this evolution continuing through person-to-person transmission has only been in areas so far where there is suboptimal vaccine coverage.

The second point is that the vaccine viruses themselves are highly mutable. Poliovirus is the most mutable virus that we know of in nature. Most of the mutations that we observe are synonymous. About 90 to 95 percent do not change the virus amino acids and presumably don't change the virus properties in a very significant way. However, the vaccine strains are adapted for replication in subculture around 34 or 35 degrees. So

they really are cold-sensitive variants which have a relatively low replicated fitness in humans. At the molecular level, one of the components of attenuation is that the translation efficiency, the efficiency at which the viral RNA serves as a template for protein synthesis is significantly lower for the vaccine viruses than it is for the wild polioviruses. So there is a strong selective pressure in the human intestine to reverse those mutations, attenuating mutations, which reduce the overall replicative fitness for the virus. Now, what's excreted by normal healthy vaccinees, particularly for types 3 and types 2, are revertant viruses which have increased replicated fitness and, in the case of type 3, a fairly high up to very high neurovirulence. We don't know whether the transmissibility has increased, but we suspect that it probably has, although we don't know whether it's been fully optimized. For type 1, which what Roland alluded to, there is also this process of reversion which goes on, but it's slower and there are additional mutations which tend to stabilize the attenuated phenotype such

that type 1 is less mutable back to full neurovirulence than type 3, or indeed even type 2.

So that comes back to the environment in which this event occurred. These infections dead end in communities with high vaccine coverage: the United States; Cuba, where they've done many, many studies; and a number of other places. And even in India where we've looked carefully -- not we, but the Indian virologists have looked very carefully, they've seen no evidence in areas of high vaccine coverage of person-to-person transmission of Sabin strains. However, in areas of low vaccine coverage, the conditions exist such that those viruses that are excreted by an individual might next infect another individual and this excreter already has a higher replicated fitness. Now you have a potential for re-passage and a continued evolutionary selection for even higher replicated fitness. You have a virus which has essentially recovered all the properties of a wild poliovirus. We think it happens most readily with type 2, but now we see it also can happen with type 1.

DR. BRUNELL: But I thought you said there was something rather unusual about the rate of replication in this strain.

DR. KEW: No.

DR. BRUNELL: I'm sorry. The rate of mutation in the strain.

DR. KEW: No, no. These strains, we don't know what the rate of mutation is and it's hard for us to carefully measure it because of the rather narrow time window that we have to work with. So we have wide confidence intervals. But it looks similar to what we see with normal wild polioviruses, but the evolution rate does not appear to be atypical at all, and that's the underlying assumption for our estimates.

DR. MODLIN: Olen, thank you. This presentation has been, obviously, extraordinarily interesting. It also will serve as a nice background for our next presentation which will focus on dose reduction, and particularly on dose reduction of IPV.

Are you ready, Paul? Just in terms of introduction, I think many of you will recall that Chen Lee, before he

left the Committee, urged us all to -- urged us to re-examine the bases for some of our recommendations and thoughts about the immunization schedules that we recommend and, in particular, about the need for all of these doses that we recommend. As a result, we've had a working group that has been meeting now for about three or four meetings under the leadership of Peggy Rennels to examine this issue regarding several of the antigens that we've used. And we've identified two antigens for further examination, one of which is IPV. It seemed to be, in many respects, the easiest to look at first.

Peggy, did you have anything else that you wanted to say in the way of introduction about the overall process? We're ready to go prime-time. Paul has been leading the subworking group that's been looking at IPV.

Paul?

DR. OFFIT: Right. So what I'm going to do is, in about 10 minutes, just briefly report the results of our working group, which was charged with trying to

answer this question: Can we reduce the eIPV immunization series from four to three, or less than three doses?

The Dose Reduction Working Group is shown here. And in order to answer this question, we've actually divided it up into three smaller questions. The first is: Do three doses of eIPV induce adequate levels of circulating, virus-specific antibodies? Secondly, are these antibody responses induced after three doses of eIPV long-lived? And third, do three doses of eIPV induce long-lived, virus-specific memory responses?

So we'll answer the first question first. Do three doses eIPV induce adequate levels of circulating, virus-specific antibodies? The easiest question. There are several studies that look at this. We're just going to summarize here a few, and we've group, for the purposes of this slide, three studies because they were very similar. The N in these three studies was between 65 and 330 people, and the studies were performed in New York and Maryland. The dose rage is shown here, and you probably all know this, but the

formulation which we currently use today for eIPV contains quantities of antigen of 48 and 32 D antigen units for types 1, 2, and 3, respectively.

The poliovirus is grown -- for these studies were grown in VERO cells, which are African monkey kidney cells.

eIPV was administered at two and four months of age and again in the second year of live and bloods were obtained one and two months after each dose.

As you can see here, after dose two and three, 99 to 100 percent of children had circulating, virus-specific neutralizing antibodies in the first McBean study. This was also true in the second McBean study. And also high levels of virus-specific antibodies were found in this study by Howard Faden.

One side point to make is this study that was done by John Modlin, this was a study performed in Baltimore, Maryland, with a N of 99. The eIPV antigen units are shown there. In this case, the poliovirus vaccine was not grown in VERO cells but rather was grown in MRC-5 cells, which are human diploid lung cells. Again, eIPV was administered as two doses in the first year and one

dose in the second year of life and bloods were obtained two months after dose two and three -- after dose two and three months after dose three.

The only thing to point out here is that there was a relatively lower percentage of children after dose two that had virus-specific neutralizing antibodies, and Dr. Patriarcha [phonetic] also alluded to studies which were not published but were in his domain that suggested virus grown in MRC-5 cells may not induce as great of an immune response after the first couple of doses for type 3 as distinct from the AGMK cell-derived viruses, or VERO cell-derived viruses.

So I think we can conclude from those studies that 99 to 100 percent of children developed circulating, poliovirus-neutralizing antibodies after three doses of eIPV, that these -- It's important to point out that these studies were performed with two doses given in the first year and a third dose given in the second year of life, and there is at least a question about differences in vaccines prepared in MRC-5 and VERO cells.

The next question is, are antibody responses induced after three doses of eIPV long-lived? The best study to answer this question would be one that examined poliovirus-specific antibody responses found 15 to 20 years after three doses of eIPV. That study would best be performed in a country that didn't have circulating wild type poliovirus or circulating vaccine virus. Unfortunately, this study hasn't been done. So we're left at looking at studies that were performed in Sweden and France where, in the case of Sweden, the length of -- the longevity of virus-specific circulating antibodies was looked at after four doses of eIPV, in France, after five doses of eIPV, and in both cases, 15 to 20 years after that immunization schedule, responses were long-lived. So although that's encouraging, I think we can say that at least for our purposes, there are no data available on the capacity of three doses of the eIPV given within two or five years of age to induce long-lived circulating antibody responses.

The last question is, do three doses of eIPV induce

long-lived, virus-specific memory responses? What's the rationale behind the importance of memory responses? As you know, incubation periods for polio-induced CNS disease are fairly long, in the seven- to 30-day range, and one can argue that a long incubation period will allow adequate time for differentiation -- for activation and differentiation of memory B cells to antibody-producing B cells and, thus, protection against disease. And usually the length of time it takes for activation and differentiation of memory cells is about three to five days, so within the incubation period of the disease.

There were a couple of studies that have looked at this. The first is shown here by Murdin and colleagues. In this case, anamnestic response was defined as a high-titered response greater than that found after the first two doses. And children were immunized at two, four, and 18 months of age with eIPV and had anamnestic responses to dose three given at 18 months and to dose four given at four to six years of age.

The next two studies were done by Howard Faden. In this case, children were immunized at two, four, and 18 months of age with eIPV and had anamnestic responses to OPV when it was given at five years of age, and in this case, anamnestic response was defined as high-titered response significantly greater than that found at four years of age. So not sort the more classic definition of anamnestic response in that you have a careful -- a kinetic-type response, but certainly a reasonable standing.

But, in summary, again, one can say that at least for our specific question, there are no data available in the capacity of three doses of eIPV given within two or five years of age to induce long-lived virus-specific memory B cell responses.

So the conclusions are shown over the next several slides. Three doses of eIPV with the third dose given in the second year of life does induce adequate levels of circulating virus-specific antibodies, and although the answers to questions two and three aren't immediately available, at least as relates to our

specific situation, one can at least take some heart in the fact that it's likely that responses are long-lived or that memory responses are generated. Again, there's no specific data to answer that question. And in addition to those concerns are the following.

No country has experience with only three doses of eIPV. Denmark gives three doses of eIPV, but that's followed by OPV. The eIPV-only schedule has just been introduced into the United States. Some physicians give the first three doses by six months of age. If we drop the fourth dose, some children may only get that series in the first year of life and antibody responses may decline more rapidly after that priming series.

Neurovirulent poliovirus has re-introduced into the Western Hemisphere, as you've just heard. The advent of combination vaccines makes it preferable to give three doses within the first year of life. Doses given beyond the first year of life are likely to be important in the induction of memory responses.

And finally, if we recommend a three-dose schedule, some children may only get two doses, which is likely

to be inadequate.
So, in summary then, the working group does not recommend switching from a four- to three-dose series for eIPV.
Thanks.
DR. MODLIN: Thanks, Paul. Any questions or comments?
(NO RESPONSE)
DR. OFFIT: It was either that clear or that unclear, I guess.
DR. MODLIN: You've done your job well. I hear a little bit of a sigh of relief over here to my right. Karen, I don't know if you have any comments to make at all?
DR. MIDTHUN: No. It was a very clear presentation.
DR. MODLIN: Terrific. Thank you. Rick?
DR. ZIMMERMAN: Rick Zimmerman.
I am intrigued by the possibility of dropping four to three doses, and I realize we're not there, both on the question of the logistics of what's going to happen with combination vaccines, as well as the question of duration of immunity. I don't have a way to predict

the future with what's going to happen with global eradication, but I think it would be a sad situation if we didn't have data and we were continuing to use IPV five or 10 years from now in a four-dose series because we hadn't collected the data to look at it. I realize there's some logistic issues, but I hope this issue doesn't drop from the radar screen and that the studies can be done to look at the duration of immunity with the three-dose series so we can look to see, is it possible to drop it in the future.

So I hope we don't lose the idea. I recognize the impracticality of moving that way now.

DR. MODLIN: Did you want to respond, Paul?

DR. OFFIT: I guess I would ask how you would do that study. I mean, for three doses, looking at either long-term immunity or long-lived memory when we currently have a four-dose schedule in the United States by five -- four to six years of age, how would we do that study?

DR. MODLIN: Bob?

DR. CHEN: I guess the -- This may have came out too

recently in the February 1st issue of *American Journal of Epidemiology*. The Dutch did a nationwide sero survey, as many of you know. The Dutch has a five-dose eIPV schedule, and what they found was that the general population, the seroprevalence for type 1 was 96.6 percent, type 2, 93.4 percent, and for type 3, 89.7 percent. And then in their Orthodox Reform group, the respective seroprevalences were 65, 59, and 69 percent. So it raises the issue that even with the five-dose eIPV schedule, with type 3, it started to get kind of borderline, and that's with the 97 percent coverage rate in Holland. So that might be additionally helpful.

DR. MODLIN: Thanks, Bob. Any other comments or questions? We will have a similar discussion regarding H flu tomorrow that we've put off. Also, let me just ask real quick, Melinda, if we'll be ready to go at 8:00 in the morning with some -- to finish up the discussion on vaccine supply with determination.

DR. WHARTON: We've got some draft language we're putting together right now.

DR. MODLIN: Okay. Let's -- Actually, we also, I notice, have a period for public comment that we have scheduled for now, at the end of the day. Is there anyone who's been signed up or anyone who's not been signed up to make any comment regarding an issue that we've covered or an issue that we haven't?

Yes? Actually, no, we're done, I think. Let's start at 8:00 in the morning, and we will start with the review of the DTP vaccine supply.

Walt?

DR. ORENSTEIN: I think there's another presentation. People are packing up, but I think there's a discussion of the OPV stockpile.

DR. MODLIN: Oh, I beg your pardon. I beg your pardon. I did miss -- I'm sorry. There is one more part to the polio discussion. I beg your pardon. I missed the -- Prompt, trying very hard. I'm sorry, Trudy.

DR. CONO: Good evening. Thank you. I'll make this a very brief pre-dinner overview of the process through which CDC has been working to establish an OPV stockpile in the event of an outbreak of poliomyelitis

in the U.S.

Just a brief of the U.S. polio immunization policy. In January of 1997, the U.S. moved from an all-OPV vaccination schedule to an IPV-OPV sequential schedule. This was followed in January, 2000, by movement from the sequential schedule to an all-IPV schedule. So by November, 2000, OPV was no longer available in the U.S. OPV was no longer being produced and any stores, whether they be public or private, had surpassed their shelf life expiration date.

So why create an OPV stockpile? As this Committee has affirmed, OPV remains the vaccine of choice for mass vaccination to control polio outbreaks. Furthermore, OPV has higher seroconversion after one dose as compared to IPV. OPV provides a greater degree of intestinal immunity as compared to IPV and OPV provides beneficial secondary spread of vaccine virus.

Is the U.S. at risk of an outbreak of poliomyelitis? Well, at first glance, we might think the answer is no. The U.S. has high vaccination coverage. In the National Immunization Survey, parents of only 1.9

percent to 3.1 percent of children reported their child had no polio vaccine by 19 to 35 months of age. Furthermore, the Western Hemisphere had been certified free of indigenous wild poliovirus in 1994. However, as we're aware, there are pockets of under-vaccination in the U.S., whether they be in religious communities, amongst philosophic vaccine objectors, or among groups of refugees, immigrants, or other people who have difficulty accessing vaccine services. We also have learned of neurovirulent poliovirus in the Western Hemisphere.

As we talked about in the earlier presentation, there has been the outbreak of poliomyelitis on the island of Hispaniola. Puerto Rico lies about 75 miles away from the eastern coast of the Dominican Republic. As Dr. Deseda pointed out, there is frequent travel between the two regions by ferry boat and by airplane, and it's estimated that between 200 and 300 immigrants from the Dominican Republic reach Puerto Rico each week.

So what are some possible sources of OPV vaccine for use in the stockpile? One possible option is through

the former U.S. manufacturer, Wyeth-Lederle, the producers of Orimune, or perhaps through other manufacturers, and one that has been identified is Glaxo SmithKline.

As for Orimune, it is no longer produced in the United States. However, CDC has identified approximately 850,000 expired doses in storage with Wyeth-Lederle labs. The potency of this vaccine is uncertain. Preliminary testing at FDA suggests that the vaccine may need U.S. potency specifications. However, further testing is going on at NIBSC in the U.K. If potent, this vaccine could become an interim stockpile. If it did, however, because it is expired vaccine, it would be used under an investigational new drug protocol.

Glaxo SmithKline was the sole respondent to a CDC solicitation for OPV manufacturers. Several GSK products are under consideration for use in the stockpile. These products are not produced in the U.S. and are unlicensed in the U.S. and, therefore, would also be used under an I and D held by CDC.

So, in summary, at this point, there is no OPV

stockpile in the U.S. In the short term, the Wyeth-Lederle product may be an option pending potency testing issues and an I and D. And over the longer term, the GSK products may be an option, also pending I and D.

Thank you.

DR. MODLIN: Thank you, and my apologies for the oversight.

Questions regarding the stockpile? Stan?

DR. PLOTKIN: Yes. I would like to just ask whether you're requesting trivalent vaccine or monovalent vaccine, and if you're not asking for monovalent vaccine, why not?

DR. CONO: I believe that the original solicitation was for trivalent. I'm not sure about monovalent. Perhaps contract people might be able to address that.

DR. MODLIN: I don't know if Dean is here, but I expect Walt might able to address the issue.

DR. ORENSTEIN: I don't think -- The issue of monovalent stockpiles is one actually that has been considered at WHO with regard to after stopping polio

eradication. There is some controversy, particularly with monovalent type 3 vaccine. The concern here was to get vaccine that was already available and could be used in a larger number of people with trivalent vaccine being the predominant vaccine. As you probably know, Stan, even the issues of going to bivalent vaccine have been of concern. I think it's certainly something we could consider, but I don't think we've thought about just getting a product that's been used in other places and is licensed somewhere.

DR. MODLIN: Peggy?

DR. RENNELS: Twice today -- Peggy Rennels. Twice today, the issue of using vaccines that are unlicensed in the U.S. but licensed in other countries under I and D have come up. For wide-scale vaccination, is that really a feasible way to do it?

DR. MIDTHUN: That's the only way the FDA can do it. I mean, obviously, it is difficult to give vaccine on a very wide-scale basis under I and D. Clearly, there are consent forms that would be need to be obtained on every individual. You would have to have in place an

actual protocol with provisions for how you're going to do this. So, yes, it requires a protocol, it requires a consent form, and the issues associated with that. So it is cumbersome, but that's the only mechanism we have available for doing this.

DR. MODLIN: Lucy?

DR. TOMPKINS: Why can't the FDA invent a new procedure for outbreaks of infectious diseases?

DR. MIDTHUN: That's not up to FDA. I mean, there might be some other level within the Federal Government that could potentially address that, but we have to go by our regulations and that's what they ask us to do. Now, if some other body comes up with some other mechanism and tells us to do things differently --

DR. TOMPKINS: Would that be the Secretary of HHS? No? It would have to be legislation?

DR. MODLIN: I would -- Chuck Helms is not here, but I would be very surprised if that issue has not come up with the bioterrorism work group. Maybe it may have been discussed by NVAC or the NVPO. I don't know if Marty or Georges have anything to add to that issue in

terms of actually trying to effect the change in regulatory policy for contingency purposes. I think it's a very valid -- but we would add it to the list.

DR. MYERS: I'm not a lawyer, so I probably shouldn't respond, but at least in other discussions, the higher body that Karen is referring to is legislative.

DR. MODLIN: Yes.

DR. SNIDER: Although there have been some discussions about whether the President, under an Executive Order, could make a judgment and suspend the current rules. But clearly, that would be a major effort, either by the highest level in the Executive Branch or at the Legislative Branch, having to take action. I think the issue of trying to do something proactively, though, is something that is on the plate and is of concern to the people who are working in the bioterrorism arena. I think that analogy is a very good one because we are beginning to recognize that there are a number of problems that we will encounter around diagnostic kits that are not necessarily approved as devices around vaccines that may

not -- may be under I and D, around drugs that may be an off-label use, and that somehow in doing bioterrorism preparedness, we may be able to find a way to deal with other emergency situations that are not necessarily bioterrorist events, but nevertheless are emergency events.

So I think that the continued exploration of the bioterrorism group into trying to smooth the way to dealing with an event of bioterrorism might provide some answers to how to be proactive and not have to have a Presidential Executive Order or congressional action taken in an emergency situation.

DR. MODLIN: Yes?

DR. PALKONWAY: (Inaudible) Agency. In Canada, there exists a so-called special access program which could circumvent a lot of license a product under certain circumstances. If you have to deal with a large-scale situation like an outbreak, we also have programs dealing with such specific programs. But this such program exists in Canada, so you could consider this to study, the Canadian program.

DR. MODLIN: Thank you. Any further comments or questions?

(NO RESPONSE)

DR. MODLIN: If not, we will adjourn for the day and we will start at 8:00 in the morning. Thank you.

(Whereupon, the meeting was adjourned at approximately 5:50 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 23RD DAY OF MARCH, 2001, IN ALPHARETTA, FULTON COUNTY, GEORGIA.

PAMELA T. LENNARD, CCR, CVR

CERTIFICATE NUMBER B-1797
(CCR SEAL - NOTARY SEAL)

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 8:00 a.m. on Thursday, February 22nd, 2001, at the Marriott Century Center Hotel, Atlanta, Georgia.

C O N T E N T S

(continued)

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(By Group, in Alphabetical Order)

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Dartmouth Medical School
Lebanon, New Hampshire

Executive Secretary:
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P R O C E E D I N G S

8:00 a.m.

DR. MODLIN: Good morning. We're going to continue on this morning with the last item on yesterday's agenda, which is the second half of the Dose Optimization Working Group's presentation. The sub-working group has been chaired by Dennis Brooks, and Dennis is going to present the data review and the recommendation of that group on hib vaccine.

Dennis?

DR. BROOKS: Good morning. Like John said, we just want to continue with the Dose Optimization Working Group's findings at this point. You will note that there was a previous handout yesterday. Today's handout was changed a bit, so I would suggest you just make some changes with pen and ink.

The composite of the working group included the following people, with extreme help from Peggy Rennels and Trudy Murphy.

The working group actually had a very difficult time with this question. The question was: Can we possibly

decrease the number of doses of PRP-T and HbOC from four to three? This was -- There are several products here in the United States that are used, but these two products actually use a three-dose primary series, as well as a booster, and these were the ones that we wanted to focus on completely. We gathered as much information as we could, looking at data related to immunogenicity as well as efficacy, and we're primarily focusing on two models that are currently in use.

The two models are the Scandinavian Model, which is a two-dose primary series with a booster; and the second model is the UK Model, which is a three-dose primary series without a booster.

As I said previously, the products that are currently in use in the United States include PedvaxHib title and ActHib. PedvaxHib currently has a two-dose and a booster. So we are actually looking at the other two, as I said before.

Immunogenicity, what we looked at was the response of PRP-T and the HbOC. The immune response to those particular two followed a similar pattern. After dose

one, there was a minimal response; there was a limited response after post-dose two; and a good response after post-dose three. That is currently illustrated in the graph here from the [inaudible] article, which showed that after -- if you look at PRP-T, HbOC, after post-dose one, minimal response; after post-dose two, somewhat of a response; and then a really good response after that. Of note is the PRP-OMP, which is the hib titer, the PedvaxHib, which had a very good response after post-dose one and reached effective level after post-dose two. But, again, we're looking at the other two because I think those are the two that we were wondering whether we could decrease their dosing.

In terms of efficacy, all of the conjugated vaccines had a protective effect against hib. I don't think there was any question about that. But overall, the efficacy could be affected by the disease burden of the population; if there was a high disease burden, age of onset of disease, if there was early onset of the hib disease; and immune response to the first and second dose, which we illustrated in the previous slide.

This particular grid looks at some of the studies that were done prior to the use of the various vaccines. The Finnish work was obviously one that was done extensively. PRP-D did not show an improved efficacy or a significant efficacy in Alaskan Natives, and I think that was basically because of the high disease burden and the early onset of disease. HbOC and PRP-T actually showed some good responses after three doses, certainly very effective at 100 percent and 94 percent. And the Navajo tribe, which also had a significant burden of disease, responded fairly well to two doses of the PRP-OMP, but, again, early onset disease, early -- good immune response to post-dose one.

The Scandinavian model, which basically most of that information came from the Peltola study, was a two-dose primary series with a booster. There is apparently a low burden of disease relative to the United States and a later onset of disease also.

The following grids actually try to summarize some of Peltola's work. If you look at -- There's a two-dose primary series, primarily using PRP-T, given at three,

five, and ten months of age. Probably there's a two-month swing in there somewhere. And if you look at the effectiveness in the population, it had greater than 95 percent and 96 percent for overall hib disease by 1996, which showed some good work for the Norway people.

The Finnish people actually use HbOC. They had four to six -- It was given at four and six months, again later on in the disease process, and at 14 to 18 months. The efficacy, which you can look at again, greater than 95 percent for meningitis and 100 percent for hib disease by 1996. Obviously, the Finnish people are doing quite well.

In Sweden, we looked at PRP-T also at three, five, and twelve months of age, with a two-dose primary series, and the effectiveness was greater than 95 percent for meningitis. Interestingly enough, they had 75 percent for hib disease by 1996. The reasons for that are a little unclear. Again, there is some population extrapolation issues.

Denmark, again PRP-T, three, five, and twelve months. Efficacy was certainly within acceptable range.

Overall available data for all hib disease was not available.

In summary, the two-dose primary series with booster showed high effectiveness in Scandinavia with PRP-T or HbOC. There is currently no available -- no experience with this particular schedule in the United States.

The United Kingdom's experience was looked at also. Unfortunately, Dr. Salisbury is not here right now. So, I mean, he would obviously have quite a few comments related to that, but the hib disease was introduced in 1992, currently, use of PRP-T at two, three, and four months of age. And as is highlighted, there is no booster in the second year of life, which makes it very interesting.

The pre-vaccine hib disease was 23.8 cases per 100,000 and post-vaccine was 1.8 per 100,000. So, obviously, they're having some effectiveness.

As of 1995, the overall estimate of efficacy of three doses of PRP-T in the U.K. children was 98.1 percent with very tight confidence intervals, actually. But if you broke down the age range, you would find that as a

child approaches 24 to 35 months, the efficacy drops to 94.7. I think that that was overall in all the articles that we saw, that as the child gets older, the efficacy of the PRP-T went down somewhat, and that seemed to be acceptable to them.

In conclusion, the PRP-T and HbOC are poorly immunogenic after a two-dose primary series in the U.S. children and, thus, may not provide sufficient protection. A two-dose primary series at three and five months followed by a toddler booster seems to be effective in the Scandinavian children, although the effectiveness for overall hib disease was Sweden was questionable.

Conclusion two -- one of the overriding factors in all the work that we looked at was that you should extrapolate effectiveness in Scandinavia to U.S. populations and, apparently, you should not extrapolate effectiveness in any other population also. I think that's one of the things we found was an overriding issue. The potential differences with age of risk of onset, unknown differences in circulation of hib and

the controversial question of genetic differences. Conclusions from the U.K. model, based on the data available, there is decreased efficacy as the child gets older and approaches between two and three years of age after the three-dose primary series with PRP-T without the booster.

And the recommendations of the group were, basically, that the data was inadequate to support a reduction in number of doses of PRP-T and HbOC from four to three in U.S. children. Certainly, we welcome any questions and any dialogue related to the haemophilus review.

DR. MODLIN: Dennis, thank you. Very nicely presented and thorough summary.

Are there questions or comments regarding h. flu? I don't see Mike Decker in the audience, if Mike would have any comments. Phil?

DR. HOSBACH: There are a couple of other ways of looking at this, and one is to look at the hib failures in the United States and see how many of those kids are incompletely immunized. Of course, you don't have a -- I don't think you have a good denominator for that. So

that may be a problem.
I'm really surprised at the English data because even in the absence of immunization, kids will gradually acquire hib antibody. And my recollection is, by four years of age, the vast majority of kids unimmunized with hib antibody. And finally, I remember when this vaccine was in development, Dan Grannof [phonetic] immunized kids with unconjugated vaccine to see if there was immunologic memory, and I don't know whether there are data of this sort to support or reject what you are proposing in terms of doing away with the booster or an accelerated or decreased number of doses in the schedule.
DR. BROOKS: We don't have any data on the unconjugated use of the vaccine that I could particularly find. Maybe Peggy knows something about that. In terms of the herd immunity, which it sounds like you were talking about related to U.K. experience, I think there's still surveillance going on about that. But overall, I do believe that the efficacy did go down as the child got older. But it leveled off somewhere

around 95 percent, I think.

Any other comments?

DR. MODLIN: Myron?

DR. LEVIN: Myron Levin.

You have here in one of your slides the incidence data after 1995. Do you have more recent incidence data, and how might that compare to the U.S. incidence data?

DR. BROOKS: I don't have the incidence data. Trudy Murphy could probably give you some idea on the United States data.

DR. MODLIN: Trudy?

DR. LEVIN: And can I just --

DR. BROOKS: Sure, yes.

DR. LEVIN: So I guess the question -- the thing that, of course, was -- is disturbing and that you put in your summary is that, in the older children, the efficacy was a little bit less than it was --

DR. BROOKS: A little bit less, three percentage points, yes.

DR. LEVIN: I don't know how many numbers are involved here and how hard that conclusion is. Maybe you can

comment on that.

DR. BROOKS: I have that article, but I don't have the number right off the top of my head.

DR. MODLIN: Walt?

DR. ORENSTEIN: I just wondered if I'm missing something here, but at least the way I look is the efficacy is really no different between the two, at least if I look at the overlapping confidence intervals, and I don't know if there's more data or -- As I see it, they're equal efficacies. Even though the point estimates may be a little different, there is substantial overlap in the confidence intervals, and I don't know if the Committee can consider that or there's something else that makes you think that there are real differences in efficacy.

DR. BROOKS: I --

DR. MODLIN: Walt, let me challenge you on this. If you were going to be making a decision as to whether or not to drop a dose, would you rather go with the confidence limits or the point estimates here?

DR. ORENSTEIN: I think I would want to know, as Myron

said, what has been happening since 1995. I mean, there's five years more presumable experience on it, but I would like to know also -- my presumption is there might be tighter confidence limits in there and better estimates of what the efficacy really is. I'm not saying that we ought to change, but it certainly doesn't look all the impressively different to me.

DR. MODLIN: That's a good point. Trudy?

DR. MURPHY: I'm not sure which question to address. As far as incidence in the U.S., it's been running in the one per 100,000 -- one to two per 100,000. It's very low, but those -- that's based on passive surveillance for the most part, although there are a few areas of active surveillance. So it's very low. As far as drift, we did try to obtain some more recent data from the U.K. and were not successful. So this was the most recent published data.

DR. MODLIN: Dr. Fetson?

DR. FETSON: David Fetson, Aventis Pasteur, MSD. I think that one of the factors that is worth considering is the fact that the British have not felt

it necessary to change their policy on the basis of the data that they've generated. So despite the 94.7 percent effectiveness point estimate in the children over two years of age, they've not changed their policy. They feel very, very comfortable with it and their more -- most recent publications have documented a very substantial measurable effect on invasive hib disease in older children and adults with their three-dose policy. So they feel that it's an effective vaccine and their policy is working.

DR. BROOKS: I think we wrestled with this concept in terms of the efficacy of the United States versus the decreased efficacy in the older children in the U.K. experience. I think the question is, are we willing to accept a four point or three point change in efficacy with decreasing the dose, the booster dose. I can't give you an answer for that. I think we felt that we should probably continue with what we were doing. I don't know if Trudy or Peggy have another response to that, but it was something we wrestled with significantly.

DR. MODLIN: Stan?

DR. PLOTKIN: I think in my opinion, which is obviously the only one I can express, the overwhelming reason for maintaining this is because combinations will be available and will be too tedious to take hib out of a combination to eliminate a dose. I do detect -- And Phil brought this up. I do detect some intellectual inconsistence in that I think most of us believe that memory is extremely important in the efficacy of hib vaccines. And the data that I'm aware of show, in fact, the two doses are quite efficacious, at least in most populations with the vaccines that are now in use. I'm not advocating two doses. What I'm saying is that I think probably we could do without four doses of hib, but I certainly not recommend in the practical circumstances that we have eliminating that fourth dose. It will gain us nothing in the long term.

DR. MODLIN: Thanks, Stan. Yes, Georges?

DR. PETER: I certainly support continuation of the present U.S. policy, but two questions that we do not, as far as I know, have the answers. One is whether or

not a change in the carriage of haemophilus influenza type B has occurred in the vaccine era. In the pre-vaccine era, it was three to five percent approximately and whether the vaccination has impacted on carriage rate in any way in older persons -- in other words, have the reservoir been effected -- we do not know the answer to.

Secondly is we do not have data and will not, I suspect, for some years on whether or not the [inaudible] Wright curve still applies for antibody concentrations now that we have a vaccinated population. In other words, one might speculate on the situation where natural boosting no longer occurs as regulating older persons unless you have immunologic -- simply because we don't have as much circulation of the organism, but that's purely speculative.

DR. BROOKS: And thank you. We did read your article.

DR. MODLIN: Unless we still have circulation of -- What is it? -- K-100 antigen and, therefore, contributing to immunity on that basis.

Anyway, I certainly don't hear the -- any beating of

the drum for a change now and it may be that this question will -- and probably will become moot with the introduction of combination vaccines, but at some point in time, it may be worthwhile revisiting a question if there -- particularly if there are data from abroad that would help us to understand a little bit more just what the long-term protection is going to be.

Dennis, thank you --

DR. BROOKS: Thank you.

DR. MODLIN: -- very much for a nice consciousness-raising presentation.

Let's go on and finish up with some unfinished business from yesterday, which is the draft of what I presume will be an update in the MMWR regarding the availability of DTP supplies and contingency plans in case a shortage should occur.

Melinda, do you want to take us through this?

DR. WHARTON: It's --

DR. MODLIN: Or Kris, I'm sorry.

DR. BISGARD: All right. We put together some -- a quick paragraph. This one is sort of background

information and we will have to add some tetanus and diphtheria language, but it does provide some of the data that Jon was asking about yesterday. In 1990's, 81 percent of 102 pertussis-related deaths were among infants less than four months of age. And I have a graph of hospitalization data. I'm sorry -- This should be a stack bar, but there are most -- there are a lot of hospitalized cases, 60 percent of pertussis cases in children of less than six months of age are hospitalized and then that decreases to 24 percent in children six to 11 months of age, 17 percent in children one year of age, eight percent in children two years of age, and then four percent in the three-to-nine-year age group. So it decreases rapidly.

DR. ABRAMSON: May I ask a question?

DR. MODLIN: Sure.

DR. ABRAMSON: Are you saying these children between one and two years of age --

DR. BISGARD: Yes.

DR. ABRAMSON: -- is that correct?

DR. BISGARD: Basically, 12 months to 23 months.

So I don't think we need to vote on this, although I would appreciate comments. And the language that Melinda and I drafted are the following:
Because pertussis is most severe among infants and current available supplies of DTaP are limited, the ACIP, in consultation with other groups, including the American Academy of Pediatrics and the American Academy of Family Physicians, recommends the following to assure the vaccine supplies are sufficient: for all infants to receive the initial three-dose primary DTaP series. Effective immediately, all health care providers should defer administration of the first DTaP booster of the five-dose series, which is dose four, usually given between 12 and 18 months of age, until adequate supplies are available to administer recommended doses to all children. When adequate, DTaP vaccines become available, steps should be taken to recall all children who did not receive the first DTaP booster for remedial immunization. And in order to insure immunity, the pertussis, diphtheria, and tetanus during the elementary school years, administration of

the pre-school booster at ages four to six should continue in accordance with existing ACIP recommendations. And probably one other bullet that we should add is that children travelling to endemic -- diphtheria-endemic countries should receive that fourth booster as well as children among -- in some Indian reservations in South Dakota.

DR. MODLIN: Any discussion? Let me ask you or Melinda, this obviously is an update that would go into effect once it's published. So, again, maybe just a question about -- This is something I presume that you're going to keep in your back pocket and publish it at that point in time that you feel would be appropriate and necessary. Is that right?

DR. WHARTON: Yeah, yeah. This is something that we would like to have guidance from the Committee in the event that in conversations with FDA and the manufacturers as well as our other partners, that it appears that we have a sufficient problem that we need to provide guidance to providers about how to grapple with the shortage and then we would publish this. And

we should be able to get into MMWR with a very short turnaround.

The other point to make is that we've written this as the sort of minimalist intervention with only the fourth dose. And the last item on the overhead about the preschool booster, if the problem appeared to be sufficient that it required dropping the fifth dose, that language would be changed, but what we've shown you is the minimalist approach that we would use in the event it appears that action is required.

DR. MODLIN: Comments, questions? Myron?

DR. LEVIN: Anybody who reads who's in the field would first say, how long, how long is this going to last? So should we -- And I know you don't know how long, but should we have some -- is there some kind of conservative statement we can make saying that --

DR. WHARTON: Well --

DR. MODLIN: The only thing is, it says when supplies become available steps should be taken, but maybe --

DR. WHARTON: We certainly could provide some background language about what's going on with the

shortage and that we hope by the end of the year that supplies would be adequate, so that people understand this isn't for the next six years we expect things to be this way. We certainly could put that in.

DR. SMITH: You might also, as happened with flu, refer them to the web site or have an update they could check.

DR. MODLIN: Good point. Phil?

DR. HOSBACH: Yeah, I have two comments.

One is, do you want something in here about out-of-home care, that kids who are in out-of-home care should receive vaccine even though they may be in that 18-month-old group, because that'll be required in many states for attendance.

And the second may be a matter of semantics, but I think some people consider the fourth dose not a booster, but part of the primary -- part of the immunization series. So I think I would probably take out of that statement in the second line "booster" and just leave it as the 18-month-old dose.

DR. MODLIN: Jon, would you -- I know you have a

comment. Would you respond as well the Phil's comment about considering the fourth dose a booster here?

DR. ABRAMSON: I mean, I would certainly consider the fourth dose a booster dose, but let me make two comments.

The data that you showed still makes us wonder what the hospitalization rate is, and I've been through this too many times. What we assume and what is reality don't necessarily click. If you have that hospitalization rate data, then we need to see it in order to make a better judgment about whether it's the fourth dose or the fifth dose that ought to go out.

And that piece of data in our spring meeting, I hope we can come back and give you agreement with the policy, but the hospitalization rate flows with that disease rate -- And let's say it 17 percent or 20 percent of the hospitalizations -- that's going to be a very serious discussion.

So it is the hospitalization rate. I don't -- I think there are very, very few deaths between one

and two years of age, but I don't know what the hospitalization rate is. So that to us -- to me, as we present it at the spring COID meeting -- will be a piece of -- critical piece of data that, if Walt or somebody else can be given as they come up with it, we would like to have.

DR. MODLIN: Georges?

DR. PETER: Jon, several points. I don't disagree with you, Jon, but I would add that we do not know the benefit of the preschool dose in terms of reducing the reservoir that affects the incompletely-immunized young. So one could make an argument that the preschool dose is equally important.

The second point is that the definition of a primary series of pertussis vaccines [inaudible] 30 years ago was established as four doses, and that was with whole cell. And I think today, a redefinition by the FDA might indeed be helpful unless you've already done so, but we wrestled with this language in the Red Book some years ago. And I think the data at least would suggest that the fourth dose of acellular today is truly a

booster.

DR. MIDTHUN: Can I address that? Karen Midthun. I think with the acellular pertussis vaccines, it depends on the vaccine. Can you hear me?

UNIDENTIFIED SPEAKER: Could you start over again?

DR. MIDTHUN: Yeah. Karen Midthun, FDA. I think for the acellular pertussis vaccines, it depends on the particular vaccine that you're considering. For example, the SKB Infanrix vaccine, there, clearly, efficacy was demonstrated after immunization at two, four, and six months. And as we saw yesterday, the protection was, you know, followed up for several years thereafter.

With the Certiva DTaP vaccine, for example, that was the one from -- currently with Baxter, there the efficacy data in Sweden were based on a three-, five-, and twelve-month immunization schedule, and in trying to see how that really translated in a two-, four-, six-month schedule, there was a bridging study done with regard to immune responses in comparing them. And what was found was that immunization after two, four,

and six months in the U.S. gave you significantly lower immune response and after three, five, and 12 months in Sweden, and whereas immunization after two, four, six, and 15 months of age gave you similar responses or actually a little higher than you saw at three, five, and 12.

So that vaccine, for example, was licensed for a four-dose series.

DR. MODLIN: So the semantics will need to remain a little fuzzy, I think is the answer. Thanks, Karen. That's helpful.

DR. SMITH: We can talk about the semantics, but I think the reality in the field is that a lot of practicing docs don't know what a primary series versus a booster is, anyway. So I think there would have to be an accompanying Q-and-A document to address -- do more explaining.

DR. MODLIN: Okay. I assume that you guys can dance around that issue fairly deafly.

Is there any other comments regarding -- Really, the basic issue here is fourth dose versus fifth dose.

Dave?

DR. JOHNSON: I guess I'm a little bit concerned about John's comments, and I'm not sure that we have concurrence from the Academy with this kind of statement and I would be worried about having the statement possibly published without that concurrence. I --

DR. MODLIN: I don't want to speak for Jon, but I don't think we're going to have concurrence until the Committee has had a chance to meet.

DR. ABRAMSON: This is an issue that is going to have to be 12 people around the table to decide.

DR. JOHNSON: Right. I appreciate that. But the question was one of outstanding hospitalization data and these data weren't adequate, Jon, you didn't think to help your group make that decision?

DR. ABRAMSON: Yeah. I do think the group would want to see the hospitalization rate. I understand what Georges is saying, but you say the same thing if you have a pool of two- to five-year-olds who are passing around pertussis, you worry about them also as a source

for other -- you know, a six-month-old with pertussis. I think we need to see the hospitalization data.

DR. MODLIN: Am I correct that the Red Book actually recommends hospitalization for kids under six months of age with pertussis? And if that's the case, could there possibly be some -- I don't want to say -- it wouldn't be an artificial difference in hospitalization rates, but it could be that kids with similar degrees of illness may be more likely to be hospitalized if they're younger and if that would be an issue.

DR. ABRAMSON: I have my Red Book authority looking this up.

DR. MODLIN: I think that's the issue. Georges?

DR. PETER: While Dr. Pickering is checking on the information from the Red Book, I wonder whether any advantage would exist from at least a MMWR publication about the potential for a shortage. Remember, this is a public meeting. The press is covering it, and some misconceptions could develop that we actually have a shortage when indeed we don't. So a statement in MMWR indicating the potential for a shortage and that

recommendations would be issued at this time, no change in current policy is warranted, I think would be very helpful.

DR. MODLIN: I agree. It's a good point. Could --

DR. SNIDER: John, could I just get just a little further clarification Jon about the Academy's possible position? Are you saying that you would favor delaying the fifth dose over the fourth dose if there was some threshold met for hospitalization?

DR. ABRAMSON: And there was a high hospitalization rate in children after six months of age, after they get their booster -- after they get their six-month dose, their third DTaP. If there was a high hospitalization rate between then and five years of age, I think that has to go into the decision about which dose, if you had to eliminate a dose, would you eliminate. It's not going to be an easy decision. If the hospitalization rate is low, then I think we will go along with the -- with removal of the fifth dose.

DR. BISGARD: I have one more piece of data to add,

John. I don't know if --

DR. MODLIN: Sure.

DR. BISGARD: I did get some data from the National Immunization Survey, 1999 data from Emanuel Moriese [phonetic], and 90 percent of children are immunized with the fourth dose between 12 and 20 months, 80 percent between 12 and 18 months, and the mean and median are both 16 months of age for that fourth dose. So that might give you a little more data.

DR. MODLIN: Larry?

DR. PICKERING: Yeah. John, to answer your question, the Red Book states that infants younger than -- after giving the details of the severity of the illness, particularly in prematures, that infants younger than six months of age with potentially severe disease often require hospitalization. It doesn't say they need to be, but it's very clear from the description it's a severe disease and that needs to be considered, but it is -- it is not implicit.

DR. MODLIN: Okay. Rick?

DR. ZIMMERMAN: Do we have that graph broken out by

three-month periods for the pertussis hospitalization rate in the second year of life, or is that just every six months? Can you put that graph back up?

DR. WHARTON: Again, I'm not -- I'm not completely sure what, in addition to these data, are needed. These are based on the reported cases of pertussis nationally in the United States and the intent was to present this as a stacked bar graph. The software had other ideas. So it came out as side-by-side bars, but these would -- together the yellow bars and the green bars account for all the reported cases of pertussis in that age group and the yellow bars indicate the number of cases that were hospitalized. So --

DR. ABRAMSON: I'm sorry. We missed that. We were sitting here thinking that was incidence data.

DR. WHARTON: The incidence line is the purple line. So, I mean, I think these are the data that were being requested.

DR. BISGARD: And it is in your copy.

DR. WHARTON: I gave you a copy --

DR. ABRAMSON: All right. Well, that would be very

helpful in the discussions.

DR. LEVIN: But those people between ages one and two did get the fourth dose?

UNIDENTIFIED SPEAKER: Don't know.

UNIDENTIFIED SPEAKER: We don't know. They may well have.

DR. BISGARD: We don't the immunization status. Although vaccination history is not well reported, of those that we do have good reports, most of these children are under-vaccinated.

UNIDENTIFIED SPEAKER: Are under-vaccinated?

DR. BISGARD: They're under-vaccinated.

DR. MODLIN: They have disease.

We need to wind this up pretty quick. Barbara?

DR. WATSON: Barbara Watson from Philadelphia. Just to back your statement, since '93, all the cases that we've had of pertussis in the six- to 11-month and over one year have been under-vaccinated, either only one dose or two doses of pertussis vaccine, and I think that's relevant for the --

DR. MODLIN: Okay. Phil, I'm sorry, we probably need

to bring this to some closure. I don't -- Dixie, I don't feel that we really need to vote on this since it's a consensus of the Committee, unless others feel differently, unless you would rather have a vote, Melinda. I think you had the advice that you need.

DR. WHARTON: I think if the Committee is comfortable with us using this as draft language, then it will, of course, be subsequently edited and worked on some more.

DR. MODLIN: And if at some point it really looks like there's a significant need to divert from this, then we'll either have some degree of consultation or even have a conference call meeting of the Committee, if necessary.

DR. WHARTON: We'll continue to keep you and perhaps Dr. Rennels advised as things progress.

DR. MODLIN: Are other members of the Committee comfortable with that approach? Dave?

DR. JOHNSON: Just to confirm something that we mentioned before, I think Georges brought it up, presently an article that would talk about the absence of a shortage but the possibility of a shortage and

that more information would be forthcoming.

DR. WHARTON: I think a very brief one- or two-paragraph notice to readers is an excellent idea. And perhaps we can also incorporate whatever is going on with Td vaccine that we can say at the same time as an update to the previous notice to readers.

DR. MODLIN: Terrific, great. Thank you. Kris, thank you very much.

Let's go on to the updates from each of the DHHS ex officio members. We typically usually start with Alison, but I promised that we could put Alison down the list. So, Walt, why don't we start with you, if that's okay.

DR. ORENSTEIN: We have provisional data for the year 2000 and this is a table initially generated from April 1999 in the MMWR for eight of the vaccine-preventable diseases of childhood

or -- with rubella complication, Congenital Rubella Syndrome, provisional year 2000 data and percent decrease, and I think the important point has always been that last column. We still see reductions of 95

percent or more.

A couple of things to highlight here is we think this will probably be the first year we've ever gone below 100 cases of measles in the United States. We've been at 100 before, and to put in perspective 10 years ago, we had almost 28,000 cases of measles in the United States.

Number two is we have a record low for mumps and our feeling is the almost exclusive use of combined MMR vaccine, which has really helped in reducing that health burden. The other thing to mention is that rubella, while not a record low at this point, is still quite low and is still primarily a disease of young Hispanics who were born and raised in countries that, until recently, were not practicing rubella vaccination. And hib may actually go down because we have a lot of unknowns in this number and as serotype information comes in, that number may actually be reduced.

Immunization coverage continues to be at record or near-record highs. This just shows you what was going

on in the '60's, '70's, and '80's and how much higher immunization levels are today. We are approaching 90 percent for most of the routine vaccine-preventable diseases. For varicella, we've had exponential rises recently into the mid-60's range and a little bit of slowing in the last six months. We'll just have to follow that. But immunization levels are still very, very high.

At the end of January, I think a historic meeting was held, convened by the American Red Cross and a joint declaration on measles was issued. For those who don't know, measles is still the greatest vaccine-preventable killer of children in the world today. WHO estimates that about 900,000 children under five die annually from measles, the majority of whom are in Africa. The American Red Cross convened a group of agencies, and I'll show you, and they issued a declaration. We're hoping, in fact, that the American Red Cross will take a very active role in promoting measles, as well as including rubella as an opportunity with some of the campaigns for measles. So this declaration is being

promulgated through the Red Cross. To give you an idea of the organizations that have signed on to this declaration, they include the American Academy of Pediatrics, the CDC, the Gates Children's Vaccine Program, the International Pediatric Association, March of Dimes, the Pan American Health Organization, the Task Force for Child Survival and Development, the U.N. Foundation, UNICEF, USAID, and the World Health Organization. So I think the goal here is to eliminate this -- or to substantially reduce this major cause of mortality.

Also on the good news side is there have been some major budget increases for immunization in the 2001 budget. We had had -- or having infrastructure money in the 317 Grant Program. We had a substantial increase, a 42.5-million-dollar increase for infrastructure, and we're working with states to get that money spent expeditiously and appropriately. And although much of this will likely go for children immunization, which was the real request, we are strongly encouraging states to use at least some of it

for adolescent and adult immunization, and we feel this is potentially an important pot of money after our experiences with influenza this year and the need for an adult infrastructure, that this is an opportunity to use that. And I think the other thing, we're working with the states. A major reason we had the big cuts in our infrastructure budget is the states were not able to gear up and spend it, carried over accumulated, and the Congress began cutting the base instead of the carryover. So our goal is to try and get this spent and spent appropriately.

20 million dollars were added for vaccine purchase; five million dollars for global polio eradication; and five million dollars for vaccine safety, which we intend to use to support the development of what we are calling clinical immunization safety assessment centers to do clinical evaluations and not just epidemiologic work, as well as expanding our Vaccine Safety Datalink.

And the last thing I wanted to talk about is immunization registries. We had discussions of this, but they are functioning in places. States tell us

that about 21 percent of children under six have their immunization histories included in some form of local or state-population-based registries. All 50 states are developing them. The Healthy People 2010 goal includes the goal of 95 percent of children under six in fully operational registries. We've used registry data on IPV in Oklahoma, particularly, in looking at whether IPV was having an adverse impact on immunization coverage, which it was not. This just shows you data from Oregon where about 85 percent of the birth cohort has at least two doses of vaccines registered in the registry and this looks at the number of children and shows what happened with thimerosal recommendations and their change. The yellow is doses given within five days. The orange is doses given within 56 days of birth. And you can see, there was a marked drop with the change in recommendations and then the concern which was shown in the MMWR last week is that when thimerosal-free vaccines became available, very slow implementation and, as of yet, not a return to baseline levels of use of hepatitis B vaccine in the

first 56 days of life and particularly the birth dose. So just to show you that we are making use of registries in this country.

Thank you.

DR. MODLIN: Thanks, Walt. Questions or comments for Walt? Bill?

DR. SCHAFFNER: Walt, we always appreciate the -- your second slide, which is the comparative morbidity slide. I wonder if you might take three thoughts.

The first is, it would be helpful to have the ages represented on that slide because we use it all the time. The second is, it occurs to me that we might begin to consider including varicella, hepatitis B, pneumococcal infections, and influenza in that. And of course, my last suggestion is that you create two slides. We would like to see an annual adult immunization slide.

(LAUGHTER)

DR. MODLIN: I'm sure Walt will take that under advisement, Bill.

DR. SCHAFFNER: Thank you.

DR. MODLIN: Georges?

DR. PETER: Approximately, I think it was last fall, wasn't it, Sam, that the Institute of Medicine issued its report on "Calling the Shots," which related to the infrastructure and I don't know if the 42.5 million increase -- or really, 60-plus-million-dollar increase in 317 reflected Congress' reaction to the IOM report, but the IOM report was pretty comprehensive. I wonder to what extent it has been appreciated by our elected representatives in Congress and to what extent initiatives are underway to implement some of those recommendations.

DR. ORENSTEIN: I think it is a very good question. I presume -- And Sam is on the IOM Committee and is holding the Executive Summary in his hands. Several things, one is, I presume at the time the Congress added this infrastructure money into the budget they had access to the IOM Report. We knew officials from the IOM had briefed the Congress. So I'm sure they -- I can't be certain, but I presume they took that into consideration in the increases that we

got. We are continuing to work with the Institute of Medicine. And next Monday, in fact, is a meeting of a new advisory committee to look at how we begin to take the show on the road, and there will be a series of three regional meetings planned to not only look at federal inputs, but to try and get greater state, local, and private sector inputs into our immunization system. So that should be over the course of the next year.

There are a series of other steps that we are doing to look at implementing some of the recommendations such as more transparency and grant awards, development of formulas and the like, and we're working with the Association of State and Territorial Health Officials to try and implement some of those recommendations.

DR. MODLIN: Dennis?

DR. BROOKS: I don't know if you can comment on this, but the issue of funding for registries and long-term maintenance seems to come up all the time. Do you have any comment on that?

DR. ORENSTEIN: I think one is certainly the 42.5

million dollars could be used to the extent that states had it for registry-building, enhancements, and maintenance. There have been discussions -- The National Vaccine Advisory Committee has given recommendations for developing a sustained support mechanism. We do not have that at the moment from the federal level. There are potentials that states have, such as the Medicaid program. There's a process for obtaining Medicaid funds that could substantially enhance funds available for registry development. There have been discussions about. I think, clearly, some of it will have to come from state and local resources.

DR. MODLIN: Myron?

DR. LEVIN: Walt, are all these registries homegrown and are they all different, or is there any kind of template being made that could be used by all states?

DR. ORENSTEIN: They're generally homegrown. The feeling has been that they will be used most if they are tailored to meet local and state needs, and there has been effort to try and get them to communicate with

one another. There's a series of functions that have been developed. And in a recent MMWR, we've listed -- I think there are 13 functions that we think registries need to fulfill.

On either side of you, Natalie and Dave, you may want to comment further from your prospective about -- about these issues, but the feeling has been that we didn't want a federal or -- a template. We did develop, with the National Vaccine Advisory Committee, what we felt were minimum data that should be in a registry. So that is standard.

DR. LEVIN: I mean, I ask the question for two reasons. The one you covered was communication between states, but the other is, instead of reinventing part of it each time, is there some way you can give someone a jump start by saying, here's the basic plan, and then, you know --

DR. ORENSTEIN: There's been a lot going on. This was one of the big things that the Robert Wood Johnson Foundation began with the All Kids Count program. There is a group called AIRA, American Immunization

Registry Association, that has had meetings and we've had -- our last meeting was in Rhode Island. Our next one is in July in Arkansas, and there has been substantial sharing between the states of experiences and what works. I think the big -- probably the big impediments are what Dennis mentioned, the issue of funding and the other provider participation. Private provider participation has been the biggest barrier.

DR. MODLIN: Walt, we had a nice presentation on immunization registries here, I think, now about two years ago, and maybe with the turnover of the Committee and just for all us, it would be interesting to hear an update on what progress has been made. Maybe we can add that to a future agenda.

DR. PETER: John --

DR. MODLIN: Georges, yes?

DR. PETER: I believe, Walt, that the report of the NVAC on registries and a national system is pending in publication and I think the next meeting would be an appropriate time to have a presentation describing that report and the progress and lack of progress that's

been made.

DR. MODLIN: Good point. Terrific.

DR. ORENSTEIN: NVAC has been the group working most closely on immunization registry issues.

DR. MODLIN: Sam, last comment on this?

DR. KATZ: Well, I had two, if I may, John. Sam Katz from Duke.

One was, as far as the measles, the American Red Cross is concerned. Although it's headed American Red Cross, I think their goal is to mimic Rotary and have international participation by the Red Crescent, the Red Cross organizations throughout the world and mobilize, not just fund-raising, but volunteers consortia, collaborations, and it may -- it may be very exciting. We're all optimistic, though. It's a tough job.

The other, in relation to what Walt said and very nicely, for those of you who go home, one of the striking things in this Institute of Medicine study -- And I hope -- you know, the summary is only a 13-page thing you can read in ten minutes, but the striking

thing is how little many states have put into their program as relying so heavily on the federal funding with the Vaccines for Children program, with CHIP, with Medicaid. A lot of states have just sort of coasted along saying, well, we don't need to put money into the immunization programs, and I think that's part of what the dissemination committee that Walt mentioned, which starts next Monday, will be looking at, how individual states will rectify some of these inequities.

DR. MODLIN: Thank you. Let's move on, if we could, to an update from the FDA. Dr. Midthun?

DR. MIDTHUN: Sure. Can you hear me?

I'll just provide a brief update. We had a Vaccines and Related Biologicals Advisory Committee meeting at the end of January, and the main topics of discussion at that meeting were the influenza virus vaccine, strain selection, and as you heard, the two -- it was recommended that the two A strains be retained and that there would be further discussion required to determine the B strain that should be selected. And the other focus of discussion was the licensed Limerix Lyme

Disease vaccine and discussions regarding the safety data for that vaccine, both pre-licensed and accrued since the time of licensure.

We have an upcoming advisory committee meeting that will held March 7th, 8th, and 9th, and on the 7th we will be discussing Glaxo SmithKline's license application for their combination DTaP/IPV/hepatitis B vaccine. Then on the 8th of March, we'll be discussing a general -- it will be a general discussion about approaches that might be taken in licensing new pneumococcal conjugate vaccines. That's an issue in the sense that Prevnar, the pneumococcal conjugate vaccine from Wyeth Lederle was licensed in early 2000 and the issues becomes obviously that it would be very difficult to do a placebo-controlled study in this country to evaluate other pneumococcal conjugate vaccines and what might be other approaches that might be taken.

And then the half-day session on the 9th of March will be to finalize the influenza recommendations. Then I guess one other thing I might mention is that the NIAID

and the Center for Biologics are co-hosting a pneumococcal vaccine conjugate workshop. Actually, it's coming up on Monday. It will be February 26th. It will be a small working-group-type session to talk about what we know about the immune correlates of protection with regard to pneumococcal disease and pneumococcal vaccines.

Thank you.

DR. MODLIN: Karen, could you expand a little bit about the VRPAC discussions surrounding the safety of Lyme vaccine -- Lyme Disease vaccine? I assume it focused on the arthritis issue.

DR. MIDTHUN: Sure. There had been some expression from members of the public regarding concerns over the safety of this vaccine. So the purpose of the advisory committee discussion was to discuss the safety data that were available to date and the plans for the continued safety evaluation of this product. So such what was reviewed were the safety data that were available at the time of licensure. And just to recap quickly, there were no differences with regard to the

incidence of arthritis in the vaccinated of the placebo groups. In the controlled data that were available at the time of licensure, there has been a theoretical concern about the potential for perhaps an association with arthritis with regard to this vaccine. The reason for that is that early studies that have been done which have looked at treatment-resistent Lyme arthritis noted that there was some association with reactivity to OSP-A, which is not normally seen in most people infected with Lyme Disease, and the vaccine itself is a recombinant OSP-B vaccine.

So this was something that had been recognized during the development of the vaccine, and as such, it was looked for during the clinical development of this vaccine and -- and again, I would like to reiterate that no differences were seen. I should note that in the immediate post-vaccination period and the clinical trials, there was an increased incidence of arthralgias noted in vaccine recipients compared to placebo recipients, but these were -- there were transient and there were no long-lasting sequelae associated with

vaccination versus placebo.
In the post-marketing, as part of the licensure commitment, the SmithKline Beecham agreed to do a large post-marketing study to gain additional data and experience and look at this further to ensure that there were no problems in this particular area. They are -- They did initiate after licensure and are in the process of continuing to do a post-marketing study where the ultimate intent is to actually accrue 25,000 vaccinees and, for each of those vaccinees, three unvaccinated controls to further examine this issue. It's a prospective cohort study that's being conducted in Harvard Pilgrim and they are now trying to enlist some other sites. The difficulty has been that they have not accrued vaccinated individuals as quickly as they had hoped. So although the ultimate target is for 25,000 vaccinees, at the current time, there are roughly I think 3,000 so far as accrued. And the hope in enlisting these other centers is it will bring that number up to roughly 9,000. And of course, the intent is to continue accruing. Preliminary data that exists

from that study do not, again, show a difference in terms of arthritis, but those are preliminary data because they have to look at the cases a lot more carefully. So those are preliminary data.

There have been reports to VAERS, a number of different reports, including cases of arthritis, arthrosis. So, again, the concern was, is there something different that we should be doing in terms of this ongoing post-marketing study. And r recommendation of the advisory committee was that they did not really see that there was convincing evidence that there was anything different with regard to the safety profile now as with regard to at the time of licensure. However, the post-marketing adverse events were of concern and there was a desire obviously to get accrual into this post-marketing study to try to get those data more quickly and to explore whether there might be other avenues to gain additional data as well.

And the other discussion was that -- they suggested that we work with the CDC to try to get out a vaccination immunization sheet that would give patients

a better idea of vaccination and what to expect. Also, they recommended that we work with a sponsor to go over the package insert which was a process that was already sort of in progress to see whether we might also revise that to better reflect some of the happenings to date.

DR. MODLIN: Karen, thanks very much. Other questions for Dr. Midthun? Dave?

DR. JOHNSON: Could you update us again a little bit on the time line for the Glaxo SmithKline license application for DTaP/hib/IPV combination and what would be potentially the earliest that it might be licensed?

DR. MIDTHUN: As I said earlier, we'll be discussing this at the upcoming advisory committee and obviously getting the input from our advisory committee regarding how they view the adequacy of the safety and the efficacy data that will be presented. And of course, we'll take that under advisement. I can't predict, of course, what kind of input we'll get but, obviously, once we have that, we'll work with that.

I think another thing I should mention is that there are things beyond safety and efficacy that also are

obviously taken into consideration for licensure. For example, there are maybe manufacturing or product issues, and we really have to make sure that all of those issues have been adequately addressed.

I really can't -- I really cannot give you an estimate as to what might be the earliest time.

DR. MODLIN: Thank you, Karen. Questions or comments?

(NO RESPONSE)

DR. MODLIN: Karen, thank you very much. We'll go onto the report from NIH, Dr. Carole Heilman.

DR. HEILMAN: Last October you had a lot of discussion around the issues of bioterrorism and how that may indeed affect some of the decision-making with your policies. And what I thought I would do is give you a little more things to be thinking about, as I'm sure these issues will come back again.

I really want to focus on some of the areas that are of most relevance to you, but just to put this again in perspective, the NIAID actually does have a pretty vigorous bio-t research agenda and a lot of what we do,

again, are within our mission are basic research and infrastructure regarding right now opportunities to really sequence and annotate a lot of the genomics of bioterrorist organisms.

We also are involved in the design and development of diagnostics, as well as clinical evaluation of new therapies.

But really what I want to focus on with you today is some of the new things that we are doing with respect to design and development of vaccines for anthrax and a little bit of information with respect to some new data with regard to smallpox.

So what I wanted to alert you to is a while back we initiated a protocol with a smallpox working group, which asked the kind of question, could we indeed expand or extend our current supply of Dryvax? And the question was raised based on some earlier data that suggested that a one-to-ten dilution of Dryvax could give a 90 percent immunization rate. So Dryvax hasn't been used for a while. So we took it upon us to answer that kind of question.

So, again, within our VTU structure -- this time we used St. Louis University -- we did a pilot study in healthy adult volunteers who had no history of vaccination. There were 20 volunteers per three group [sic] using undiluted one-to-ten, one-to-100, a very simple design. The endpoints that we used were positive skin lesions, but we also have a lot of immunology that's still in the works. Unfortunately, I'm not going to be able to give you some of the immunological results, but one of the goals of this particular activity was to really look very carefully with modern day techniques to see what the -- what the, I should say, repertoire or what the patterns of immune response are, which may be important as we try to go to licensure for new smallpox vaccines.

So here's the results. We had 95 percent take rate in the undiluted, but unfortunately, it dropped in one-to-ten to 70 percent and it even dropped another significant amount when we did a one-to-100. It went down to 20 percent. And the reason that I bring this up for you is because there may be situations until we

get a new vaccine where decision-making in terms of how to use the limited stocks that we have will come into play. And again, you have situations where as you dilute things out you can cover more but your efficacy is less. So this may be brought to you at some point in time. So I just wanted to share this data with you. Going to anthrax, which is another area that you had again a lot of interest, there was a question asked by Sam Katz at that time, what are you doing on this anthrax vaccine and can we go past MVA -- I'm sorry, AVA? And we are actually working in close collaboration with DOD, and there have been a number of issues within DOD that needed to be resolved. We are very happy to report we had a meeting with them probably two weeks ago and a lot of the issues which were really legal liability issues really we seem to be past right now. So we are entering into a formal agreement with DOD to begin testing three rPA candidates. This is recombinant protective antigen, surface antigen, better purified. Animal study data have suggested that you need less immunizations, maybe

one or two, in order to reach the same antibody level as you would with AVA. There are three variants of rPA under development at USAMRID and at two other companies, DERA and AVANT. Within DOD, there's a consortium and it's essentially an agreement that we would -- they would all work jointly towards the same goal, which was improvement of AVA. And what we're planning to do is to do a lot of the clinical phase one testing for them to be able to help in their decision-making.

The USAMRID rPA is the most developed at this point in time and we believe right now -- We've met with JVAC, which is really the implementation arm of a lot of USAMRID, and we think that the trials can easily begin this year.

And finally, I just wanted to tell you that, even though we're focused on rPA, we're not eliminating other vaccine -- potential vaccine candidates, and we do have an ongoing functional genomics and proteomics project with Office of Naval Research, and we'll be doing a lot of characterization of the gene protein

expression patterns, especially doing germination patterns with anthrax. Obviously, we hope that some of this information will be very useful to either validate or to expand our vaccine development program.

So I just wanted to leave you with that.

DR. MODLIN: Thanks, Carole. Are there any questions? Jon?

DR. ABRAMSON: Carole, I think it was here maybe a couple of times ago that you talked about data from the NIH looking at influenza and reduced dosage for pandemic planning. Where does that stand?

DR. HEILMAN: That was actually presented at the last meeting by Linda Lambert, and we were able to use at least that particular strain in April to show that a dilution of that strain was not significantly different from the antibody responses that you would have seen if you've given undiluted.

DR. ABRAMSON: Are they looking with other strains? I mean, was that the end of the study?

DR. HEILMAN: That was essentially it. You know, if we need to address a particular question again, we'll be

glad to try and do that.

DR. MODLIN: Further questions?

(NO RESPONSE)

DR. HEILMAN: Thank you.

DR. MODLIN: Carole, thanks very much.

Moving on, Dr. Geoffrey Evans, the Vaccine Injury Compensation Program. Geoff?

DR. EVANS: While we're waiting to get it set up, there's a one-page handout and the monthly statistics. Copies are at the back of the room.

What I thought I would do is just amplify on a couple of points that were made in October about where we stand and some recent legislative events.

First of all, in terms of the monthly statistics -- And I know for some of you, this will be your first meeting and you won't quite be familiar with some of the processing terms, but basically, we have -- we're still getting pre-'88 claims filed. These are for vaccines that were given before the program was enacted in 1988, and those are dismissed usually after they're filed.

So far we've received, for the active program, 66 this

year, which is about 17 per month. And the only thing of note under adjudications is that we've just about adjudicated all of the pre-'88 claims. We have a couple of dozen left. And in awards, we've given 1.2 billion to date, with nearly a billion of that represented from the thousands that were received under the older program. 348 paid out of the Trust Fund to date, and currently, the Trust Fund has 1.5 billion dollars in it.

In terms of, quote, unquote, "new vaccines," hepatitis B, hib, and varicella were added in 1997. We've received hundreds of hepatitis B claims when the filing deadline for older administrations passed in 1999. And those are going to be adjudicated probably over the next five to seven years. I've spoken about that before. And right now, the Court is getting geared up to begin looking at these claims. A very small amount of hib and varicella, and DTaP to date is still just 24 claims, and rotavirus, a total of eight.

As I discussed this part October, there was legislation that had just passed called The Children's Health Act

of 2000 which, among its other provisions, allows for petitioners who come into the Vaccine Injury Compensation Program to be compensated if they allege an injury and there's not six months of continued effects, which is required under law. With this provision, if they were to have experienced in-patient hospitalization and surgical intervention, then that would allow them also to be eligible for compensation, assuming that the medical aspects of the case qualified.

Now, what drove this legislation was the fact that the rotavirus vaccine, which is a very strong case to be included as an injury under the program, would -- if adjudicated would leave many of the petitioners unable to receive compensation because most of the cases resolved completely, either after closed or open reduction. So this was put in specifically for that and signed into law and will cover both pending claims, as well as future claims. And we are in the process of -- through publication of a notice of rule-making to add intussusception to the table, and really, all this

does is just further streamline the process. Right now, if someone were to file a claim for -- under rotavirus or intussusception, they would simply need to show the medical records that the event occurred and document as such. And the epidemiology -- the data that came out of the case control settings and other -- datalink studies, we would be able to provide a very strong case that there is an association. I don't think there would be any problem in terms of receiving compensation, but by adding it to the Vaccine Injury Table, then just the mere fact that intussusception was documented is good enough. So there's a legal presumption on that basis.

I just want to clarify one point when it comes to the pneumococcal conjugate. This was a slide I showed last October. And the key change here is the word "officially" in the fourth bullet, which has now been italicized. With the publication on October 6th in MMWR of the notice that CDC now views the recommendation for pneumococcal conjugate vaccine as being one of routine use in children, that qualifies it

for inclusion into the compensation program because there's already an excise tax in place. However, what we're supposed to officially do is publish a notice that the Secretary is announcing that this is the CDC recommendation, and that has not happened yet because we were -- we have included it in the NPRN under "Development," which has, of course, taken a lot longer than we thought it would. And the most recent hang-up has been the fact we have a new administration. And of course, we would like to look at any pending regulation.

So we are going to try to just publish a very quick notice in the *Federal Register* in the next couple of months if we can just announcing that it's now officially viewed by CDC, but for all intents and purposes, it is covered under the program. It is listed on our web site because the effective date of coverage goes back to the excise tax.

If you understand this, you're doing a lot better than a lot of other people. Every year I come and I talk about this legislation. I don't think this has been

re-introduced. At the end of the session, of course, all pending legislation that's not passed expires and it has to be re-introduced, but there's been ongoing efforts to reduce the excise tax from 75 cents per dose to 25 cents per dose. So I would assume that this is going to be re-introduced this year.

And probably more importantly, there is a report that was issued by the Government Reform Committee at the end of last year that came up with three recommendations but not any specific language or guidance as to how to go about this, but basically that the Reform Committee, based on hearings on the Vaccine Injury Compensation Program thought that there should be a review of the current table to make sure it reflects science and try to come up with a reasonable alternative standard for non-table claims. This is due to the fact that in contrast to the beginning of the program in which you had vaccines and conditions listed, there was a fair amount of information in the literature about these conditions. By adding new vaccines, it takes a while for the literature to catch

up and there are very few conditions that are listed under the newly-added vaccines. So for petitioners, for example, with hepatitis B, very few of these claims of the 322-odd claims list a table injury or as a table injury because there's only one table injury listed, and that's anaphylaxis. So each claim has to then be approached on a causation basis, which is a very timely and difficult task for the court and the petitioners. So it has come up as a suggestion that we should look into maybe coming up with a different approach for off-table claims but continue to have a strict standard for the conditions replaced on the Vaccine Injury Table itself.

And the last suggestion had more to do with the Department of Justice, and really resides totally in the Department of Justice, and that just has to do with the process itself in terms of being less adversarial and trying to be more user-friendly and more streamlined.

There were some bills introduced in the last session that have not been re-introduced that I know of that

would have changed the burden of proof and tried to make it less adversarial and it'll be amazing to see what will happen this legislative session.

That's where things stand now. Any questions?

DR. MODLIN: Questions for Geoff? Paul?

DR. OFFIT: Geoff, one quick question.

The compensation for the rotavirus-induced intussusception, is that just when the case occurred within 15 days of receipt of that vaccine?

DR. EVANS: Well, the intussusception rule-making that we're going to propose and that was approved unanimously by the Advisory Commission on Childhood Vaccines would make it 30 days. So --

DR. OFFIT: Even though there was no statistically difference between a vaccine and unvaccinated group in the 15- to 30-day range?

DR. EVANS: If that's indeed -- I mean, this is right now not official policy yet because it has to still be approved within the Department and go through rule-making and public comment, but there would -- we know that certainly the first two weeks, there was clear

evidence and association, and where that -- you know, if it's a bell-shaped curve, where do you cut off? Is it two weeks and one day? Is that not vaccine-related? So our proposal was to go ahead and extend the additional benefit of the doubt for those two weeks. Now, I claimed that we would go forward today on causation. In fact, it's not clear what the court would do if, indeed, we were to contest it, and I would assume that since we have announced publicly that our approach is zero to 30 days that we would concede a case that fell within that range.

DR. MODLIN: Further questions or comments? Yes?

DR. BERNIER: Roger Bernier from NIP.

Geoff, could you comment on the rationale or the thinking as to why there would be a different standard for a table injury as opposed to a non-table injury? If I understood you correctly, you implied that the standard would be different. And how does that relate to the other point you made about desire to have changes in the burden of proof required? Is that related to that or unrelated?

DR. EVANS: The Vaccine Injury Table was established by Congress as a compromised mechanism in 1986. And administratively, the Secretary has made changes to the table twice, in 1995 and 1997. Those changes were based, in large part, on the Institute of Medicine reports which used a causality standard in setting up five categories as far as judging whether it was a causal relation between a vaccine and a condition. So that has been the approach for either adding to or taking off conditions on the Vaccine Injury Table.

With -- If it's not a table injury, the court required that there be a standard of proof for proving causation. In fact, that is also 95 percent. Of course, when you have conditions which there's very little literature or just case reports where the literature is not clear, that's a standard that is very difficult to surmount, and the Court has been rejecting very large percentages of claims that have been presented for off-table conditions.

So if this is going to be the predominant kind of claim -- In other words, if 75 percent of claims that are

going to be filed now in the years to come are going to be for conditions where the science is not clear enough to add them to the table -- there is growing pressure to maybe consider a standard that wouldn't be quite as strict as a causality standard in terms of adjudicating those on a causation basis.

DR. MODLIN: Paul?

DR. OFFIT: I'm sorry. One other quick question, Geoff.

When you said that there was an interest in decreasing the federal excise tax from 75 cents to 25 cents, is that because there is more money in the program now than you need? Is that --

DR. EVANS: Well, that's been the perception. I mean, 1.5 -- it's hard to spend 1.5 billion dollars quickly and --

DR. OFFIT: Why don't you -- Why don't we spend it on studies of vaccine safety?

DR. EVANS: You know, that's been thought of before. I'm being a little facetious.

The real answer to your question is that there's -- and

a GAO basically looked into this. They had two reports, and one specifically focused on the trust fund. And interestingly enough, they didn't come up with a recommendation in terms of what to use the money for, recognizing consumers think the money should only be used for the compensation program. Obviously, governmental agencies would like -- in this area in this time of [inaudible] budgets, they would like to be able to come up with additional resources, but -- and there's also the view that the Vaccine Injury Trust Fund is too big because we're being too difficult in terms of our criteria for compensating cases.
So the fact that it's been so politically-charged and controversial makes that kind of outcome very difficult politically. I would also -- No, I'll stop at that point. I won't get into any more.

(LAUGHTER)

DR. EVANS: Yes?

DR. MODLIN: Dr. Severyn?

DR. SEVERYN: Dr. Christine Severyn, Vaccine Policy Institute.

I just wanted to make the Committee aware, if you're not already aware, that the new legislation that adds rotavirus vaccine to the Vaccine Injury Table only compensates or what would -- puts on that Vaccine Injury Table those cases in which in-patient hospitalization occurred and surgery. The cases that were, quote, "repaired" with an enema are not on this -- not on the Vaccine Injury Table. Is that not correct, Dr. Evans?

DR. EVANS: Well, that is correct. And certainly, there may be some that will not be compensated, it's likely, but the program only pays for unreimbursed medical expenses, and this is a fairly transient condition. Obviously, it's a great stress to the family and can be to the child, but if Congress was going to go forward with providing some kind of relief in this area, they felt that surgery should be the bottom line in terms of what would be compensable because there's a much greater chance of complication.

DR. SEVERYN: So if it's outpatient surgery, it's not on the table?

DR. EVANS: I believe that outpatient surgery would not be any problem. And most children that undergo intussusception surgery would not be on an outpatient basis.

DR. MODLIN: I can't imagine that would ever be the case.

DR. SEVERYN: Okay. But the point I was making is that the children that have it repaired through enema are not covered through the Vaccine Injury Compensation Program?

DR. EVANS: That's correct, based on current law. This is not something that the Secretary could change administratively.

DR. SEVERYN: Yes. But the ACCV, that's a whole other issue.

DR. EVANS: I just wanted to make that one follow-up to Paul. I know I had a senior moment and I forgot. It turns out that Congress recognizing that the Highway Trust Fund was being used for purposes other than what was intended originally by the legislation specifically put a provision in I believe the pneumococcal conjugate

legislation which specifically prohibits the Vaccine Injury Compensation Trust Fund from being used for anything other than compensation and for the administration budgets.

DR. SEVERYN: Some of the things that are coming out at the ACCV meeting, the things that are coming from the Treasury Department, is that the Vaccine Injury Compensation Trust Fund is being used for deficit reduction and other purposes. Is that not correct?

DR. EVANS: That's absolutely --

DR. MODLIN: I think Dr. Evans has already been pretty clear as to what -- as to exactly what it is being used and what Congress has intended it to be used for. It sounds to me like it's going to take an act of Congress to use -- for us to spend a dime of that for anything else. So I think that's probably the bottom line.

DR. EVANS: But I just want to clarify one point. Any trust fund is used for deficit reduction.

DR. MODLIN: Thanks. Geoff, thanks very much. The next report will be from the National Vaccine Program Office, Dr. Marty Myers.

DR. MYERS: As you know, the National Vaccine Program Office operates across the different agencies of the Department and with the U.S. AID and Department of Defense. So my report, while it's the NVPO, is also the interagency vaccine group which is the mechanism by which we operate.

I'm going to give part of the report and then Georges Peter, who is the Chair of the National Vaccine Advisory Committee, is going to give part of the report.

One of the things that NVPO does is administer a program called the Interagency Research Program. This is a small inside-government/across-agency research program that is specifically intended for meeting unmet needs, those things that sort of fall between the cracks, the things that fall between the different funding cycles, and so on. A number of you have attended, for example, a number of workshops such as the thimerosal workshop a couple of years ago that were funded by this mechanism.

The National Vaccine Advisory Committee helps us

establish the priority areas for this unmet need funding, and I thought it would be worth -- just talking about last year's priorities and then I'll show you how the money is awarded across agencies for these particular issues.

For this last year, or this current year, the top priority area is vaccine safety and adolescent and young adult immunization. Last year, it was vaccine safety and the prior year to that, it was pandemic influenza and new priority vaccines, especially tuberculosis. These -- All these topics remain within the priority areas.

I show this primarily because vaccine safety accounts for about 43 percent of the funding, and for those of you who are interested specifically in infrastructure relating to adolescent immunizations, this was an area that NVAC felt that was a major gap. And when we went back and looked at our prior funding, there was none for adolescent and young adult immunization. So this year, there is 11 percent of the six-million-dollar funding is directed at adolescent medicine. And you

can see pandemic influenza is -- the research activity -- Some of the questions earlier about pandemic flu, a number of these studies are being conducted through the unmet needs gap-filling mechanism.

Another issue which has -- that we have been involved with is the laboratory containment of wild type polioviruses. You heard yesterday about the global eradication. That's half the story. The other half of the story is all the samples in various freezers that contain, or have the potential to contain, wild type poliovirus. And those who are interested, the WHO action plan for laboratory containment is -- I gave the web site here. It's hard to find that action plan. And last November, NVPO was asked to coordinate across the agencies an action plan for laboratory containment. Dr. Walter Dowdle, whom many of you know, is directing this initiative.

He asked me to be sure to say that effective containment is a realistic goal, but it's not -- absolute containment is not. As consequence, once an inventory is established and laboratory surveys have

been done, which is intended to be completed by the end of 2002, that at that time, the biosafety level for containment of samples that may potentially wild type poliovirus will begin to increase, first to BSL level 3 and then to BSL level 4.

Just after the last ACIP meeting in October, we held a workshop to consider the prevention of perinatal CMV infection. And there were several things we learned. One, that CMV as a public health problem is much greater than many -- even the CMV community had recognized, but that it's not widely recognized as far as public health importance, being the most common cause of damage to the developing fetus now that rubella -- in this country now that rubella vaccine is available. In looking at disease burden from hearing loss and progressive hearing loss, in the IOM Report looking at vaccines for the 21st century, looking at how the prioritized

vaccines -- CMV, perinatal CMV, began the number one -- should be our number one priority. So this is the reason we held this workshop in October. We looked at

a lot of different ways of approaching candidate vaccines, who the target populations might be for studying vaccine safety and efficacy. There are a number of difficulties and complexities of looking at this particular vaccine.

We heard about a number of the different strategies that were under development and we, at our last NVAC meeting, spent a -- some time looking at what the next steps for the interagency vaccine group should be to try and facilitate the development of such a vaccine. So, for example, one of the suggestions was that the Centers for Disease Control should participate in looking at disease burden. Much of the data that is available is limited to Alabama, and it's not clear whether this data is -- would be universal throughout the country and whether, in fact, we have enough data -- population-based data to be able to make decisions and so on.

Finally, somebody asked some questions about pandemic influenza. Because this is a cross-agency and cross-department activity, the NVPO was asked to coordinate

the technical development of a pandemic plan. Within NVAC, we have a pandemic influenza working group. Chuck Helms is the liaison member from the ACIP. The current plan is at the Department under review. And the structure of the plan is a document that outlines many of the issues and many of the approaches to addressing the issues. And then it has a series of 16 technical annexes that are in various stages of development for how to respond to a pandemic. Many of your states are in the process of doing a -- developing model state plans and the funding for that is from the unmet needs funding I mentioned previously.

In your books are three draft annexes that -- particularly the liaison members, we ask you to take back to your organizations and provide us input of infection control, selecting alternative sites for care, and resource -- management of scarce resources. Annexes are at a point where we would like to have input on those.

The working group had its last meeting in November and these are some of the -- they looked at the draft that

we had under development at that point, and a couple of the points I think are worth mentioning.

The first is, we have a tendency, when we pandemic plan, to think about the worst-case scenario. So much of the emphasis and discussions have occurred, by all of us as we talk about pandemic planning, is to think about 1918, but, in fact, the working group said we should -- we should take into account a severe pandemic like 1918 and we should take into account less severe pandemics like 1968. But in fact, pandemic planning should probably be geared for something in between that and that our model should be more of the 1957 pandemic response with then looking at the others as extreme possibilities.

The response by -- both locally and at the national level should be flexible. So one of the things that happens when people start talking about pandemic planning very early on is who's going to buy the vaccine, and when are they going to buy it, and what about liability and so on, which are very, very complex issues. And the recommendation of the -- or the

discussion that we had with the working group was that a -- these types of decisions needed to be flexible and that would be geared towards the type of pandemic and the severity of a pandemic as it unfolded.

Also at a meeting that was held in September, there was a lot of discussion on the global level about vaccine and where a vaccine should be available, whether responsibilities of developing countries or undeveloped countries on vaccine supply, much less the issues of vaccine within a developed country, and vaccine in short supply, some of the issues that we talked about yesterday. So we tried to model the plan into a scenario that assumes that there will be little or no vaccine early in a pandemic response, which means that the local response planning will be critical for coping with the level of illness, morbidity and mortality.

And then finally, the whole issue of addressing antiviral agents. Several of you asked me about where we were in planning for how to use antiviral agents within a pandemic response. If you think the issues surrounding vaccine are complex, the issues about two

classes of antiviral agents that are delivered by different routes that have varying availability that are already licensed and so on, in a coordinated pandemic response are very, very complex. So as a consequence, the working group is convening a special technical panel in a couple of weeks. We're specifically going to try and develop strategies for how antiviral agents might be utilized to -- as part of a more comprehensive pandemic response.

Now, finally, at the last NVAC meeting and at the last ACIP, I mentioned this, so I thought I would follow up on it. We were going to have a presentation on autism and vaccines and the studies that are currently underway, but as it turned out at the time of the last NVAC last week, there was a Spring Harbor meeting simultaneously. So all of our speakers were there. So we will hold that a half-day of our NVAC meeting in June. We'll include the discussion of current research activities surrounding autism. We hope we'll have the report from the Institute of Medicine Safety Committee that we're going to hear about later this afternoon by

them as a part of that presentation.
I'm going to stop there and maybe we'll let Georges go before people ask questions. This is Georges' first experience with PowerPoint.
DR. PETER: Why did you have to make that comment, Marty?
(LAUGHTER)
DR. PETER: In any case, I want to provide you with a brief overview of our last meeting, which was last week.
First of all, a major issue that surfaced has been the need to review the rotavirus vaccine experience, and the planning for a workshop began last fall and the initial intention of the workshop was to focus on the implications of the Rotashield experience for future development of oral vaccines and rotavirus vaccines, particularly with respect to the international sphere. Since then, the need to review the Rotashield experience has become very evident. The ACIP, of course, now has a working group which will examine this issue and we will be holding a workshop now in

September. Our hope originally was to have it in May or June, but the dates simply were not possible. Then in October, we moved it to September in order to give it as much -- as much advance time before the next meeting of NVAC and the ACIP.

Four of the five sessions will be devoted to a review of the Rotashield experience and the fifth session will be on the generic issue about the implications of intussusception association with an orally-administered vaccine and future development.

A second aspect is one that Marty has spoken of before and is the workshop that was conducted in San Juan last May on the possible effect of aluminum in vaccines and adverse effects, and the proceedings of this workshop will be published in *Vaccines* very shortly.

Third, as Marty mentioned, the cytomegalovirus workshop, and our committee will be developing recommendations to make to the Secretary for future development, and I think the most important point is that the burden of disease of cytomegalovirus is not appreciated and in order to give the appropriate

priority, both in the public and private sector, we need to make sure that that burden of disease is appreciated. I think now that we have newborn screening in many states, routinely I think this burden will increasingly become appreciated.

We continue to follow global immunization initiatives. We have had presentations from a variety of different organizations, including from groups representing the Gates Foundation. And last week, we had a presentation from the Fogarty Center by Dr. Miller on their current developments, and our hope is that the funding for the global immunization initiatives by the U.S. Government continues under the current administration.

And for the past two years, we've been revising the standards on adult immunization in collaboration with the National Coalition for Adult Immunizations and the National Immunization Program. These standards have been tentatively approved by the National Vaccine Advisory Committee and have been reviewed by the working group of the ACIP and also approved. The next step is to circulate these to key partner

organizations, which includes the ACOG, the American College of Physicians, the Academy of Pediatrics, and the Society for Adolescent Medicine, and most recently, the Infectious Disease Society of America. Once we have approval of these different organizations, then we will seek partner organizations in order to have a broad consensus to help to implement these standards. Our plan is to introduce these standards in a publication in MMWR and possibly in a peer review publication next January during Adult Immunization Week.

Then in the course of the summer or during the course of the fall and this winter, we realize that pediatric immunization standards which were originally issued in 1992 were in need of similar revision, and the National Immunization Program, under the lead of Gene Santoli and Lance Rodewald, has revised these standards. They are now undergoing review by the Committee and subsequently will be circulated to other organizations. Our hope is to move rapidly on this revision process and to perhaps have these ready for issuing next

October, too, in conjunction with the adult standards. Mention has been made of the new committee established by the IOM, a vaccine safety committee. This is a committee generated by an initiative of the interagency group on vaccines. The contract for the IOM committee is with the National Institutes of Health and the Centers for Disease Control. The role of NVAC will be as a forum to discuss future issues to suggest to the interagency group for discussion, as well as to give prioritization, and we are a public forum in this respect. And secondly is, we will review the reports of IOM vaccine safety committee. We will hear more about this committee from Marie McCormick later this morning.

The Committee has also reviewed the IOM report which was actually originally published, I believe -- not published, but originally issued over a year ago entitled "Vaccines for the 21st Century: A Tool for Decision-Making." We had a draft report and the NVAC has been able to review it. Of course, our review is now on the NVPO site but up until tomorrow. The final

edition of the report has not been publicly available. We're pleased to announce that the IOM will be publishing and making available to the public this report tomorrow. This report is an interesting one. It has a model for developing -- for establishing priorities for vaccine development with a complex formula. The idea is not to establish the priorities but rather suggest a mechanism by which the U.S. Government can consider priorities. And as mentioned earlier, in that analysis of the 21 examples that were analyzed, leading in the category was cytomegalovirus vaccine.

Finally, we have three new work groups that have been established. One is on the introduction of new vaccines, originally intended to address the issue of financing, which was a major problem last year for the introduction of Prevnar for the private sector, in particular. And when we began to address the issue, we realized that the introduction of new vaccines was a much broader topic. So financing is only one of several issues we will be considering.

A second issue that has -- we've been asked to address by the Association of State and Territorial Health Officers concerns not which vaccines should be mandated but rather guidelines that states may use in establishing mandates for recommended vaccines. And this work group will be open to suggestions for topics that could be discussed in a public meeting at some point as planned.

Third and mentioned earlier was that we will have a work group on strengthening the supply of vaccines and we already have an ACIP representative. This group will be hopefully holding a conference call in the very near future and begin its actions, because we realize the need to begin to make some progress on this issue which is hardly a new one. But the initial charge the Committee is to identify the vulnerabilities in the current supply as well as to identify the challenges. Then perhaps the next step is to formulate some recommendations, but that is not our initial stage of development.

Our next meeting is June 4th, 5th, and 6th. The first

day will be a meeting of the subcommittee on vaccine coverage and the second and third day, June 5th and 6th, will be for the plenary sessions, together with other subcommittee meetings.

I'd be glad to answer questions for the National Vaccine Advisory Committee. I would make one point, since we have such a plethora of committees that advise the Government, the role of NVAC is to advise the Assistant Secretary on programmatic issues. And of course, this committee deals more with technical issues, but I think the collaboration between the different committees is very important. As a result, we have on NVAC an ACIP representative, which is John Modlin. We now have a VRPAC representative as well, Bob Daum, who is the chair-to-be. We also have a representative from the Advisory Commission on Childhood Vaccines, which is Jackie [inaudible], a citizen member and well-known to many of us as the Academy representative in Washington.

So I think I'd be glad to answer questions, formally or informally, and I might say that, indeed, I told Larry

Pickering yesterday that I would never use PowerPoint. I was simply technologically incapable. In other words, I'm an adult with special needs.

(LAUGHTER)

DR. PETER: Well, today I am using this, and I think it's wonderful. Thank you.

(LAUGHTER)

DR. MODLIN: Happy to see you've mastered it. Jon?

DR. ABRAMSON: Yeah. Jon Abramson.

Georges or Walt, perhaps you can help us with -- The Brighton Collaboration is an international collaboration that seems to be trying to do a lot of the same things that the IOM group is trying to do. So I'm wondering what -- They're trying to set up criteria for which to determine whether something should, you know, be purported versus should be studied, et cetera. What is going to be the collaboration, if any, between these two groups?

DR. PETER: Well, Jon, I don't think we've discussed this. I think may -- Bob Chen, I think, has been involved with the Brighton Collaboration, or if anybody

else would like to comment. I think that's an important point that I have not previously considered, but if anyone has any further comments. Yes?

UNIDENTIFIED SPEAKER: Katherine [inaudible]. I'm one of the two coordinators of the Brighton Collaboration. And actually, I don't think there's a contradiction in these two activities right now. What we aim to do is to come with a standardized set of case definitions for adverse events following immunizations. That is a primary goal right now simply to enable comparability of vaccine safety data from clinical trials as well as post-marketing surveillance. So I wouldn't see where they would conflict with what you just presented.

DR. MODLIN: Thank you. Further comments or questions for Georges?

(NO RESPONSE)

DR. MODLIN: Georges, thanks an awful lot.

The last report will be from the National Center for Infectious Disease, Dr. Alison Mawle.

While Alison is setting up, I wanted to make a quick announcement. I think, as many of you are aware,

weather is creating some travel havoc up and down the east coast and it's likely that many of us travelling in that direction, particularly to the mid-Atlanta states, you're going to be delayed. So those of you who are travelling on a government GTO, please see Gloria or Latarsha if you feel like you need to be changing plans in terms of making contingency plans or change in travel plans, which will be critically important. You can do that at the break. Certainly, Gloria and Latarsha are well aware of this.

UNIDENTIFIED SPEAKER: Do you want to elaborate on that, John?

DR. MODLIN: There's a snowstorm.

DR. MAWLE: Okay. I think we're up here. I just wanted to update the Committee on unique exposure that occurred last fall to recombinant rabies virus vaccines. Just to give you a background on this, I think people are aware that all the vaccination of wildlife has been used as an adjunct to the traditional public health methods in controlling rabies, such as immunizing pets. And this was begun originally in 1990

primarily to control the spread in raccoon rabies in the U.S. To date, over 15 million baits have been distributed.

Now, the oral vaccine is a vaccinia construct which was originally derived from the Copenhagen strain of vaccinia, and it contains the glycoprotein from the eRA strain of rabies, which is a canine strain.

Now, in Ohio, raccoon rabies was originally detected, I think it was in 1996, and they started the bait distribution, oral vaccination of the population, the wildlife population, in 1997. They do it twice a year. They do it in the spring and they do it in the fall, and they've had very good success in controlling raccoon rabies and that has declined significantly and it is apparently virtually undetectable right now.

Last fall a woman was bitten on the arm when she tried to remove one of the baits from her dog's mouth. She treated the obvious bite, but apparently, there were a couple of superficial scratches that were so minor that she didn't even really rinse them. Ten days later, she developed an inflammatory reaction around those

superficial lesions and was eventually treated with antibiotics and wound debridement. It was not immediately obvious what the problem was and, initially, she was thought just to have an infection of the dog bite. It was only later when things did not resolve that the connections were made with the actual bait and it was diagnosed potentially as vaccinia exposure.

The wound material was sent to our rabies lab at CDC and the material was cultured on viro cells, gave a classic cytopathic effect, and an EM showed classic poxvirus. The virus was sequenced by PCR and both vaccinia virus sequences and the rabies glycoprotein sequence were detected. They sequenced the actual rabies PCR product and it had 100 homology with the eRA glycoprotein. They inoculated mice with the material and there was -- the mice were fine.

The patient herself had convalescent serum taken which contained neutralizing antibodies to the rabies virus. These are the folks who were involved from both CDC and in Ohio at the hospital and the State Health

Department. And I just want to point out the rabies is very well controlled within the U.S. There was a MMWR published in December that dictated -- described five cases of death in the U.S., which were the first rabies cases since 1998. Four of those five were bat exposures and one was to a dog in Africa, and the vast majority of rabies right now in the U.S. is, in fact, either due to bat exposure or to dogs in other countries. The control program here has been very successful and the vaccinia bait has significantly contributed to that.

I do want to point out that this is very widely publicized when Ohio does this. They've put out press releases. They notify the emergency rooms. People are very well aware that these things happen. And to our knowledge, this is the first time that it's been documented that a human has been exposed and infected by the vaccine.

Thank you.

DR. MODLIN: Thanks, Alison. Questions for Dr. Mawle? Paul?

DR. OFFIT: Alison, just a quick question. What is the bait?

DR. MAWLE: What is the bait? I believe it's chicken necks.

DR. OFFIT: Chicken necks.

DR. MAWLE: Yes. And it's laced with this vaccinia rabies --

DR. OFFIT: And the woman that was trying to pull the chicken neck away from her dog, did she know that that was soaked with this --

DR. MAWLE: No, no. She had no idea. In fact, apparently, they also had some reason to think that somebody had been trying to poison their dogs.

DR. OFFIT: Was there any local -- But when you distribute these chicken necks, do you -- do you inform people locally that these -- this is what you're doing?

DR. MAWLE: Well, as I understand it, most of this is done in rural areas. But, yes, it's in the press. I mean, you don't go to door to door, but, yes, it's widely -- widely advertised, yes. It was eventually this sort of sequence that alerted the ER doc to the

fact that, obviously, this is what it was likely to be.

DR. MODLIN: Stan?

DR. PLOTKIN: I think it should be mentioned that this kind of bait -- Actually, there are two different oral vaccines -- are widely used in Europe. I don't remember the number of doses, the number of baits that have been used, but really thousands and thousands. And again, the safety record has really been excellent as far as human exposure.

DR. MAWLE: Yes. 15 million, about, have been used so far. This is not a common occurrence.

DR. MODLIN: But the vector is considered a non-highly-attenuated vector; is that correct? I assume that that's the case.

DR. MAWLE: It's pretty highly attenuated, yes.

DR. MODLIN: Highly attenuated.

DR. MAWLE: Yes.

DR. MODLIN: Okay.

UNIDENTIFIED SPEAKER: But not enough --

DR. MODLIN: Pardon?

UNIDENTIFIED SPEAKER: Not enough.

DR. MODLIN: But not enough to the point that it didn't cause a wound infection?

DR. MAWLE: Right. Which is still --

DR. MODLIN: Getting back to our --

DR. MAWLE: It can still replicate --

DR. MODLIN: -- statement yesterday.

DR. MAWLE: But it is attenuated.

DR. MODLIN: Okay, thanks. Any other questions for Dr. Mawle? Marty?

DR. MYERS: How did the dog do?

(LAUGHTER)

DR. MODLIN: Do you know?

DR. MAWLE: I don't know. Presumably, immune to rabies.

(LAUGHTER)

DR. MODLIN: Dr. Ruprecht?

DR. RUPRECHT: One follow-up. The patient had dermalitic hyperkeratosis, which is a complicating factor.

DR. MODLIN: Had eczema, or eczema-like cutaneous disease. Interesting.

Okay. We're a few minutes behind. Let's plan on returning from the break at 10:20, if we could.

(RECESS FROM 9:56 A.M. TO 10:24 A.M.)

DR. MODLIN: Could I ask people to please be seated so we can started? Could I ask people to be please be seated so we can continue?

The next item on the agenda will be a review of the General Recommendations Statement. Unfortunately, Lucy Tompkins needed to leave earlier, although Lucy has been chairing the General Recommendations Work Group. Bill Atkinson, who has been centrally involved in this process now for sometime, is going to lead us through the most recent changes in the General Rec Statement. This is a process that is fairly mature, and what Bill is going to do is focus on those important changes that have been made since the last meeting or since the last time that the ACIP has had a chance to review the progress of this group. I hope very much that if we cannot complete our work on this at this meeting, and I think there's a reasonable chance that we will not be able to, the plan will be to ask the Committee to

review a final draft and make a final vote on this at the June meeting.

Bill?

DR. ATKINSON: "Mature" is the proper word. This is, to my recollection, the eighth time that the General Recommendations have been discussed in this forum. At best today, I think I will be able to tell you what's in the document. I would like to put a couple of issues out and see if there's any consensus, or at least opinion, on the part of the Committee/liaisons. I would also like to run through the new parts and explain very briefly why they're there. Then I agree, I think that probably -- this is an onerous document, I would admit. I would encourage, however, that all of you should at least read it through completely one time and I'd like to get comments from everybody. I think we can kill this -- We can finish this next meeting. The three things that -- I would just like to go briefly through the three components. This is the first time you-all have seen a complete -- a complete sort of collection of all the parts that we've talking

about. There are copies in the back of this large document that I will point you to.

The three pieces that have been incorporated into this that have already been discussed and agreed upon by the Committee are -- that have been discussed at three different meetings are the minimal intervals, ages, and grace period issue; the vaccination of internationally-adopted children, which we spent a lot of time on last time, which there's a great deal -- there were some more work group meetings and more wording on that. So I would encourage you to read that section and make sure everybody agrees with what kind of came out of the machine. And then the issue of nonsimultaneous administration of live vaccines.

On these three issues, there's one new thing that I would like at least judge feelings on. A footnote was included on page 7, at the bottom of page 7 in the draft that you have. That footnote was meant to sort of acknowledge the fact that there are state regulations and requirements for school that may be difficult to reconcile with the grace period, the four-

day grace period. That footnote in its current iteration says that "In some situations, local or state requirements may mandate doses of certain vaccines be administered on or after certain ages. For example, many school entry requirements may not accept a dose of MMR or varicella vaccine given prior to the first birthday." You recall that the four-day grace period applies to all antigens, all ages, no intervals. Therefore, by these recommendations, that dose at given at 361 days, four days before the first birthday, would be considered acceptable. Shall I say, would not be recommended to be repeated.

It goes on to say "While health care providers must comply with existing state and local regulations, ACIP hopes that individual states and local areas will consider the new ACIP four-day decision rule and 'grace period' recommendation in reviewing and evaluating their state and local vaccination requirements." This was not originally part of the discussion and I wanted to make sure that everyone was aware that this footnote existed and do anything to do, for it, or against it

that anyone would like to suggest, including drop it entirely.

DR. MODLIN: Natalie?

DR. SMITH: Yeah. I just want to comment on this footnote. The first part is that "ACIP hopes." We're used to translating language from ACIP about "considers" and "recommends." "ACIP hopes" is sort of a new level --

(LAUGHTER)

DR. SMITH: -- for the states to interpret. More seriously, it takes many years to get state laws and regulations in place for many of us. I can think of one antigen that took us about three and a half years to get the state law in place. It's a very arduous process to go back and change laws and regulations. So I would be more comfortable if we just dropped the last sentence. I think it is clear -- States know that these grace periods are going into effect. It was a major topic at a program managers' meeting last week. So I would be more comfortable with the footnote if we drop that sentence and didn't -- didn't have this as a

reason that we had to revisit our state laws, especially around the MMR requirement at age 12 months. And I think the Association of Immunization Managers is also here and may have some comments.

DR. MODLIN: Well, I think -- Sort of in the interest of taking ambiguity to a new level, which is what we -- this committee has been very good at. I guess the real question, though, is here, Natalie, is that if we dropped the last sentence, is there any reason to have the footnote at all? I would be curious at what other people think about that. Peggy, you're shaking your head. How do other members of the Committee feel about this? Rich?

DR. CLOVER: I think it's relevant to have some footnote just acknowledging the fact that this recommendation may cause a problem for a practitioner as it relates to state law requirements, and I think just a statement that just acknowledges that as an issue would be a benefit.

DR. MODLIN: But it is going to create conflict between -- clearly between what we hope will be a standard, a

national standard, and differences between -- for some states, for not all states. So that, in some respects, it's going to actually create difficulty where we had hoped to achieve some unanimity. Is that fair?

UNIDENTIFIED SPEAKER: Uh-huh (affirmative).

DR. MODLIN: Yes?

DR. GREEN: Jessie Green, South Carolina. I think the intent of the grace period will be implemented regardless of whether you include the footnote. If you do include the footnote, I would suggest that you do remove the last sentence. I think it could be problematic.

UNIDENTIFIED SPEAKER: How is that? Why would it be a problem?

DR. GREEN: Well, I think it makes no difference in whether or not immunization regulations are affected by the grace period. That will be implemented in smoothing out the bumps in the road. Perhaps a politician could read this because of the strength of an ACIP statement and want to build a new highway.

UNIDENTIFIED SPEAKER: I'm lost.

DR. MODLIN: Thank you. Dr. Brunell?

DR. BRUNELL: I must say, the first time I saw this, I was very much opposed to even the four-day grace period, and this was based on my experience with measles immunization at the time I was chairman of the Red Book Committee and probably on this committee. And what happened was that we just had a whole bunch of calls about 364 days, what's wrong with 364? And now you're going to have questions -- calls about 360, 359. I think you're just complicating your life by even making this initial change, and to make it more vague is just going to increase the complexity, the confusion, and the phone calls.

DR. MODLIN: We have flip-flopped on this issue and I think it may be helpful to have a little bit of perspective. The whole reason for having the four-day grace period for MMR was to make it consistent with the four-day grace period that we have granted for all the other antigens. So it was an attempt to simplify the system in that respect rather than to complicate it when we were comparing it to DTP and hib and all the

other vaccines that we use.

I hope -- Well, Rick?

DR. ZIMMERMAN: We continue to support the four-day grace period.

DR. MODLIN: Okay. Other comments? Other than Dr. Brunell, are there people that feel strongly that we should not have a four-day -- or feel that we shouldn't have a four-day grace period for MMR? Dr. Johnson?

DR. JOHNSON: I was under the impression in our past discussions that we clearly had considered a four-day grace period or some sort of grace period for other vaccines but that we were dropping that notion for MMR because of -- well, for those very reasons that we have up there, that in many jurisdictions, the law is tied to the first birthday. I'm a little uncomfortable with that language in the last sentence there that's suggesting that ACIP hopes there will be some changes in state law or application of state law or regulations.

DR. MODLIN: Well, as I had mentioned, we have flip-flopped on that issue. And I think you probably

weren't at the last meeting where we flopped. In fact, we did make the decision to include the four-day grace period for all vaccines, including MMR, and it may be that -- Let me ask Walt or Melinda, or both, what would be best for the program here. I don't want to get bogged down in debating.

DR. ORENSTEIN: Clearly, we support the four-day grace period. I think the Committee has supported it. Whether the footnote is needed or not, I'm not sure. I think the big issue, as Rich said, is does there need to support that, in fact, you may not do it. I think that perhaps taking out the last sentence might just do that.

DR. ATKINSON: The last sentence or the last phrase?

DR. ORENSTEIN: The last sentence.

DR. ATKINSON: To include -- So the entire last sentence, "While health care providers must comply," that entire sentence?

DR. ORENSTEIN: Right.

DR. WHARTON: Yeah.

DR. ATKINSON: Okay. No problem.

DR. MODLIN: Is that a reasonable compromise for everyone? Bill, I hope we don't see this in June.

DR. ATKINSON: No. That's -- Hopefully, that's the last of it.

DR. MODLIN: Okay.

DR. ATKINSON: One thing I would like to get a quick opinion on, in the 1994 General Recommendations, this was -- this is a comment by one of the reviewers, there was a whole -- two pages of definitions, essentially a glossary. I, personally, don't think it was particularly useful. I left it out. Some reviewer suggested it be put back in. Does anyone have any strong opinions one way or the other, whether there should be a glossary of terms or not? You can just -- Maybe you can just tell me this on comments or not. I don't -- I don't think it's necessary, but I will defer to you-all if you do.

DR. MODLIN: Jon?

DR. ABRAMSON: Yeah, I think it is necessary, because I think, for instance, that people get confused between intravenous immunoglobulin and immunoglobulin. That's

just one example of where people are calling -- physicians are calling and asking us at times what do we mean. So I do think that's it helpful.

DR. MODLIN: Walt?

DR. ORENSTEIN: I've cited it in terms of definitions of vaccines and whatever certainly in talks.

DR. ATKINSON: Done.

(LAUGHTER)

DR. ATKINSON: This is a list. It's also on the cover of your -- cover of your document. Just to point out things, and you can go through this list, there's only two or three things that I would like to throw out. There's only one that actually needs, I think, substantial decision here.

The introduction, Chen Le contributed greatly to the rewritten introduction which I think is a nice change. You should just pay attention to these because these are things that are real new that you need to pay attention to.

Options for reducing the number of injections at the 12-to-15-month visit was something we just kind of

kicked around and is just a proposal. Again, you should look at this and see if this is consistent with what you would believe.

Two issues that I think don't need to be discussed at any great length: wording concerning aspiration prior to vaccine administration. There have been -- We have been doing some polls and informal sort of polling of individuals about whether or not the issue of aspirating prior to giving an injection or not. There clearly is no agreement whether it is. It's pretty much split 50/50. It's integrated and ingrained into nursing practice, and we're finding the wrath of God when we even suggest trying to take it out. I'm suggesting, based on some wise commentary from Dr. Peter, that we, in fact, change -- In fact, I've already changed this wording in the General Recommendations prior to the -- after the draft you have. The document currently says -- it basically says in 1994, like it always has, it basically -- it says de facto to aspirate. That's the way it had always been in all the General Recommendations. The Red Book,

however, says that -- has this little caveat that says, "Although most experts recommend aspiration by gently pulling back," blaa, blaa, blaa, "there are no data to document the necessity for this procedure." That may well be enough, and just in the spirit of harmony with the Red Book, we may want to basically incorporate wording like this, admitting there are no data really to say one way or another whether it's required or not. Nurses will swear on it. Other people say that there's no data, let's scrap it. I don't think that there's any way to resolve this unless somebody has strong opinions on the Committee. I would suggest we go with Red Book wording and just admit that some people recommend it and there's data to support it unless you have other thoughts, just not to create anymore conflicts with the Red Book that already are there.

DR. MODLIN: Bill, I think you're getting general agreement that --

DR. ATKINSON: Did that seem like general agreement?

DR. MODLIN: Sure.

DR. ATKINSON: Okay, yes.

DR. MODLIN: Except for Dr. Zimmerman.

DR. ZIMMERMAN: Actually, I'm in general agreement on that one. I was hoping we could go back to the second topic on your list and discuss that, the issue of --

DR. MODLIN: Why don't we finish with this, Rick, if it's okay, discussing aspiration, or actually, for those of us who participate in the vaccine listserve, there's been a considerable amount of dialogue on this issue and different viewpoints, which pretty much reflects Bill's statement that there are two sides to this issue and they both feel quite strongly about it. Dave?

DR. JOHNSON: One other difference between the Red Book and the current document is in picking a new site, in the current document we talked about tossing out that syringe and vaccine dose. The Red Book purposely does not suggest doing that if blood is aspirated into the syringe.

DR. MODLIN: John?

DR. PICKERING: (Inaudible)

DR. JOHNSON: Oh, it does. It doesn't seem to up there.

DR. MODLIN: What is the Red Book policy on this, Larry?

DR. PICKERING: The last sentence -- Larry Pickering. The last sentence after that says, "If blood appears after negative pressure, the needle should withdrawn and a new site selected."

DR. JOHNSON: A new site selected. You would use that same syringe --

DR. PICKERING: Right.

DR. JOHNSON: -- and that same dose of vaccine and select a new site?

DR. ABRAMSON: I mean, it would be hard for me to imagine why not to use the same vaccine. I guess you could make some case to changing the syringe.

DR. MODLIN: We need to be explicitly advised in that respect, say that you may use the same --

DR. ABRAMSON: I like the way ours is.

DR. MODLIN: Okay, all right.

DR. ATKINSON: The current wording is basically that

which has been carried down through the General Recommendations. So that's basically the same wording that was in 1994 and 1989.

DR. MODLIN: Bruce?

DR. WENINGER: Yes. Would you clarify whether you're going to still require the dose be thrown away with Prevnar and over 50 dollars and varicella not far behind? Is there any evidence for that old recommendation?

DR. ATKINSON: Not to my knowledge. It's one of those things that's just been in the document. I don't know where it started or why. It's just been there all along. I just -- You know, I just copied it.

DR. MODLIN: Again, I would raise the issue again. Do we explicitly state for that reason that the dose does not need to be discarded?

DR. ATKINSON: I can easily strike that. I'm flexible. So consider that phrase to be out. Is that what I hear? So not say anything about discarding the dose and make it more consistent --

DR. MODLIN: I got the sense that people felt that the

language that Georges had suggested or adopting something similar to the Red Book would be the most acceptable. Is that --

DR. ATKINSON: I like it.

DR. MODLIN: Did you have a question about this, Bonnie?

DR. WORD: I mean, personally, I like the language, but I think the reality of it is, most of the nurses are the ones administering. And as you said, that is standard teaching in -- for nurses. And if someone decides to say, what are you doing, why are you doing that, then you'll start that level of disagreement there. The nurse is the one that's doing the administering. And until we change their teaching, it'll go against everything they're taught. It just avoids another level of confusion.

DR. MODLIN: Bonnie, are you suggesting that we should advocate aspiration in the General Recs?

DR. WORD: Probably just to have left it.

DR. MODLIN: But you would prefer to leave the language as it is.

DR. WORD: I just thought he just changed the last part, you know, discard it.

UNIDENTIFIED SPEAKER: We're going with the Red Book.

DR. MODLIN: I think the consensus is to go with the Red Book language.

DR. WORD: Okay.

DR. MODLIN: Are you comfortable with that?

DR. WORD: Yeah.

DR. MODLIN: Rick, did you want to go back to --

DR. ZIMMERMAN: Page 9.

DR. MODLIN: Okay.

DR. ZIMMERMAN: It's the recommendations -- Rick Zimmerman.

It's the recommendations for what to do at the 12-to-15-month with the number of injections. And I would like to propose a slightly different tact or strategy and that would be to list the principles, and I would suggest two principles. At the 12-to-15-month visit, if the parent says no to the number of injections, then I think the first priority are to give those vaccines

which they have not had any doses before, measles and varicella as examples. And secondly, to look at the risk of what they might be exposed. Probably pertussis is more of an issue than, for instance, polio is in this country. But I prefer the principles because I think the specific strategies get into detail that we can, I think, debate -- We could spend a lot of time debating about which vaccine might, in a particular circumstance, be better or not better, and with combination vaccines, this is really going to become an ever-changing issue. So I would suggest that instead of specifics to go to principles. And particularly, for instance, one of the specifics listed is hepatitis B vaccine. We know immunogenicity is higher until the third dose is given later. So I'm not sure in a low-risk setting we have to give at that visit by 12 months of age the hepatitis B third dose. It works as well if you give it a couple of months later. I think we can get caught up in the minutia, and I would rather see us have a tact of principles. That's a little different strategy than the one that's listed.

DR. MODLIN: Okay. Walt, do you or Melinda have a response?

DR. ORENSTEIN: I think I'm okay with that. I have to think through some of the issues. I think certainly the issue of -- the first one of giving vaccines that they ever had would be very appropriate. I think there are concerns of finalizing and completing the series and losing people to drop-out, but I think it -- I think it sounds reasonable.

DR. MODLIN: Okay. Dean?

MR. MASON: Dr. Modlin, just a quick comment for this -- the complexity of issue of withdrawing the needle and considering throwing away the contents as well. You also have to factor in that some of our products are pre-packaged. So if you cannot reinsert that needle with that product, you've got to throw the whole baby away.

DR. MODLIN: Good point. Deb Wexler?

DR. WEXLER: Deborah Wexler, Immunization Action Coalition.

I have one more comment. I'm not on either side of the

aspiration issue, but not only is it standard ingrained nursing practice to aspirate, the standard ingrained nursing practice to throw away the syringe full of the vaccine, which is -- you're going to -- it's going to create a lot of friction with nursing -- the nurse population if you just say that without studying it, because that is -- it's my understanding that is not how they're trained. They're trained to throw that away and aspirate.

DR. MODLIN: I think this is something that we clearly can address with the program. There is a -- I understand now a national organization of nurse immunization practitioners, and I'm embarrassed to say I don't know the -- remember the exact name. There may be a representative from the organization here.

MS. VONTA: Lynn Vonta from Immunization National Coalition. I'm on the steering committee of this new organization. It's called the National Network of Immunization Nurses and Associates. And basically, it's a collection of nurses who work very, very specifically in the field of immunization and

consulting. And this, too, has been a subject that has been bantered back and forth in this organization.

DR. MODLIN: I would guess as such they would be just as interested in education and maintaining scientifically-appropriate practices and updating their own practices as necessary, and it may very well be that we could work with this group rather than just simply accepting the fact that something that we've been doing for however long is necessarily the right thing to do just for that reason alone.

MS. VONTA: As Chair of the Nursing Practice Committee of that, we would be very, very interested in --

DR. MODLIN: Maybe this is the opportunity to do that. Okay, Bill, let's move on.

DR. ATKINSON: The next one is the only one I anticipated any substantial discussion.

(LAUGHTER)

DR. ATKINSON: Obviously, after eight times I haven't figured this out yet. That has to do with more minutia, sorry. The General Recommendations is minutia. I don't know if you realize that or not. It

has to do with vaccines given by an incorrect route or site. The 1994 wording, for reasons that I can't recall, perhaps Dr. Katz can or someone else with a better memory, says essentially that if you give a vaccine by the wrong site or wrong route, it should be discard, period. No exceptions. If it's given by the wrong route or wrong site, it should not be counted and it should be revaccinated unless serologic testing is done. This is later, of course, to a lot of repeats of a lot of MMR vaccine given IM or perceived to have given IM. It leads to a lot of repeating vaccines that probably don't necessarily need to be repeated.

In an attempt to try to get at this, we rewrote the first part to try to get at the data that actually was there, which is not much. So, again, we're dealing with kind of thin data. Essentially what exists is that there is evidence that varicella vaccine given IM is equally immunogenic as varicella vaccine given subcu. We also know that hepatitis B given interdermally is not immunogenic. We know that hepatitis B given in the gluteus is not as immunogenic.

Beyond that, we also know that anecdoctally, they use probably intramuscular deep subcu vaccination for MMR in Europe. We also know that DTaP trials are often -- DTaP is often given deep subcutaneous, whatever that means, in Europe. And actually, Melinda pointed out to me that even some of the trials gave DTaP in the gluteus with adequate, apparently, responses. So perhaps the blank statement isn't as valid as it should be and we're giving doses over that we don't need to because it was given too deep. So to try to get at this, we basically admitted that some -- that probably giving vaccines IM that were intended or recommended to be given subcu does not affect their immunogenicity given the fact that there isn't apparently data specifically on MMR given IM, except anecdoctally, unless somebody knows about it. Apparently, the one study that did say this was an error. I'm informed by Dr. Naylen [phonetic] at Merck and, in fact, there are little, few if any, and apparently, Merck doesn't even have internal data on IM MMR.

So, basically, kind of a stretch was to try to reduce the number of doses having to be repeated because of that reason. We basically admitted that probably subcu vaccines given IM would have no effect based on the varicella data and did not have to be repeated -- So we sort of took a little bit of it -- but that other vaccines given by an inappropriate route should be. So we retained that part of the original 1994 wording. Reviewers suggested that that may not be, in fact, reality either and that this isn't, in fact, what is being recommended. So I leave it with three options about how to deal with this issue for which there are very data.

Number one, we can leave the wording as it is, admitting that IM vaccination -- yeah, administration of a subcu vaccine probably has little or no effect on immunogenicity based on varicella data. We probably -- and then leave the wording -- and then repeat doses of other vaccines given by the wrong route. We can basically

accept -- as apparently is done in some cases, just accept

any route or site as valid and throw out all the 1994 wording, or the third option is to accept everything with the exception of the antigens for which there are actually data to indicate that seroconversion is not adequate, which essentially is hepatitis B given intradermal or in the gluteus or gluteal administration of rabies vaccine. As far as I know, and we've got a lot of collected knowledge here, there may be more than that.

So I don't know if you want to give me any guidance on this or if we should leave the wording like it is or you would rather think about it. I realize we could probably talk about this for another hour, but I just wanted to see if anybody had any strong feelings about it.

DR. MODLIN: I guess just to throw out one opinion here. To me, it seems as if option one may be the closest to reality in recognizing that we have a dearth of data in some respects. Maybe I might just ask, by asking how the Red Book has handled -- or is handling this issue at the moment. Larry, Jon? Do you want to

get --

DR. PICKERING: Just to give another opinion -- Can you put those back up, Bill, so we can remember what they were?

DR. ATKINSON: Sure. Yeah, this is the first option. The first option is accept subcu vaccines given IM but do not accept IM vaccines given by any other route. That is subcu vaccines -- or it's IM vaccines given subcu or intradermal. The original -- The original wording is don't accept anything given by an inappropriate route. This is accept subcu given IM, but not IM given subcu or some permutation of that. The next option is basically count everything and don't worry about it. Or the third option is don't count anything except certain things that we know that there is data that support lowered immunogenicity.

DR. MODLIN: I think you just mischaracterized that. I think, Bill, accept all doses.

DR. ATKINSON: Yes, accept everything. Accept everything -- I'm sorry. Accept everything. The most radical is the 1994 wording that said do not accept

anything given by any route that is not recommended or accept everything given by any route.

DR. MODLIN: Larry?

DR. PICKERING: John, I think one of the things with the vaccine schedule is to keep it as simple as possible, and that would be number two. However, we do have data supporting number three, and probably vaccines in that category should not be administered by those routes. So I, personally, probably -- I can't speak for the whole committee or John -- would favor number three.

DR. MODLIN: Well, you have data for the hepatitis B part, but you don't have the data for the all other doses.

DR. ATKINSON: Except the indirect about the DTaP schedules and the administration deep subcu in Europe, et cetera. So . . .

DR. MODLIN: So, actually, there is still a big data dearth even with option three.

Let me ask Melinda. You had your hand up.

DR. WHARTON: Yeah. This is something that comes up

periodically when a state immunization program goes into a physician's office and reviews immunization practices, and the situation where there's -- that I think precipitated the revisiting of this in the General Recommendations involved a very large number of children who were vaccinated in a practice over a several-year period.

Given that DTaP vaccines have been tested in clinical trials and been found to be effective when administered by the deep subcu route, albeit with perhaps a higher incidence of local adverse reactions and, as I understand it, hib vaccine is routinely given in the U.K. by either the IM or subcutaneous route, it's not clear to me what the need is to require that those vaccines be readministered given that these aberrations in recommended immunization practice are probably far more common than any of us would want to know. And we have good evidence that our immunization program in the United States is highly effective when it comes to preventing disease in spite of the fact that practice -- administration practices are perhaps not as good as

we would like.

One thing I would like to see in this is some strong guidance that when these aberrations from recommended practices are identified that corrective action be undertaken and people be -- that people be given guidance and training on how to appropriately administer vaccines so they don't do it anymore, but I'm not sure that part of the fix needs to be readministering a bunch of doses of DTaP to a child who we already know is at increased risk of getting large local reactions with the fourth and fifth dose anyway.

DR. MODLIN: Yes?

MR. SCANDER: John Scander, CDC Vaccine Safety. I would just point out for number three, at least with regard to rabies vaccine, you know, the issue is not simply lack of immune response, but actual documented vaccines -- vaccine failure.

DR. MODLIN: Good point.

DR. ATKINSON: So I'm hearing three.

DR. MODLIN: Peggy?

DR. RENNELS: I agree with three.

DR. MODLIN: Okay. Rich? It looks like there's general agreement on number three.

DR. ATKINSON: That will be reflected in the next draft.

The next issue that I hope to not spend more than 30 seconds on that I don't think we can resolve here either is the waiting period after vaccination. The current draft -- There was nothing previously. I sort of arbitrarily said there was no need to wait in the current draft. It was pointed out by, again, reviewers that this was inconsistent with the Red Book and I proposed to, in fact, change the wording to be consistent with the Red Book. ACIP has never recommended a fixed waiting period after a dose of vaccine because of observing for allergic reaction. I would suggest -- In fact, I've already made this change, unless you feel strongly -- that we basically mimic the Red Book statement which is "some experts recommend this waiting period of allergy." This is essentially verbatim for what is in the Red Book. I don't know if anyone has strong feelings about it. I

would suggest that we not create conflict when one is necessary. Unless you feel that we don't need to argue -- even talk about a waiting period, I could drop it completely.

DR. MODLIN: Let me maybe just start by asking Natalie and Dave how perhaps others -- how this would affect the public immunization programs, if at all.

DR. SMITH: As far as I know, most of our public clinics they don't insist on any kind of waiting period. They get them in and out. I mean, often if they're doing well-child visits, they end up hanging around anyway, but I don't think they use a waiting period, in general.

DR. JOHNSON: That's my impression, as well.

DR. MODLIN: Do you think they would if we had a change in the recommendation according to "some experts suggest"?

DR. PETER: I think, John --

DR. MODLIN: Yes, Georges?

DR. PETER: The Red Book statement actually was in the '97 edition and was based upon some VAERS data, if I

remember correctly, that demonstrated syncope but primarily in adolescents. Maybe Neal Halsey remembers better than I do, but I think that's what we intended was at least in adolescents it would be reasonable to keep patients for 15 or 20 minutes in case of syncope and resulting head injuries if they weren't in a medical facility.

DR. MODLIN: That's not necessarily an allergic reaction, but --

DR. PETER: No, and that's why I think it's important to -- I think it's for a reaction.

DR. MODLIN: Okay.

DR. PETER: Isn't that correct, Neal?

DR. HALSEY: Yeah, Georges, you're absolutely right. And I don't remember who pulled together the data and shared it with us at a Red Book Committee meeting. I thought it might have been published, but there were -- there are a few serious head injuries that have occurred primarily from early adolescence, leaving, walking down stairs, and so forth. And they're not trivial. I was surprised to see those, and I think

they're in the VAERS database, but someone presented those to our committee and I'm blocking on who presented them.

UNIDENTIFIED SPEAKER: Miles Veron [phonetic] did.

DR. HALSEY: Miles Veron did, somebody is saying back here. But they should probably be shared with this committee as well, and it did make me change my mind about the need to wait because most people don't have people wait, but the syncope is a serious problem.

DR. MODLIN: Okay. So I guess the other -- again, the question -- I hate to get bogged down in semantics, but I don't think we would want to characterize this as an allergic reaction. It may be "for a possible syncopal reaction resulting in injury." Fall or injury would be a more accurate way to state the intent. Would that be fair?

DR. EVANS: I was just going to add, that was the paper that was published. Miles Veron was the lead author, and it was in JAMA, I believe. It was entitled "Syncope after Immunization." And they included at least one case from the Vaccine Compensation Program.

DR. MODLIN: I can give you a personal anecdote myself having had a syncopal reaction after an immunization. So it does happen.

Yes, Peggy?

DR. RENNELS: John, I would suggest to just drop out the word "allergic."

DR. MODLIN: Okay.

DR. ATKINSON: Actually, for the record, I believe I copied this statement exactly out of the Red Book. I think the Red Book actually does say "allergic" now. I could easily drop out the word "allergic." Not a problem.

DR. MODLIN: Do people want to retain the language that says "some experts" --

DR. ATKINSON: Do you want to discuss it? Do you need it to be here? Is it going to create more problems than it's worth?

DR. MODLIN: Rich?

DR. CLOVER: I would rather we be clear on what the data is. I think it's educational and of importance to state that it's syncope that we're talking about and

it's more common in young adolescents.

DR. ATKINSON: So perhaps the way to view this is actually add some syncope wording. The Red Book has got a whole paragraph, I think, on syncope. I could put some of that in.

DR. MODLIN: Peggy?

DR. RENNELS: Anaphylactoid reactions, you know, do occur and I thought, at least when we do vaccine trials, that's why we're doing it, why we make them stay in the office. So I think that's one -- part of the reaction we are looking for.

DR. MODLIN: We could include both. Bill, a suggestion, maybe the way to do this is to spend a little bit more time on this topic and revisit it in June, but maybe try to find what information we can, present it at that time and come back with options. I think that you're getting the sense of the Committee that they would like to include some language that is similar and that maybe we can make a final decision around the revised wording at that time.

DR. ATKINSON: Okay.

DR. MODLIN: Would everybody be comfortable with that?

UNIDENTIFIED SPEAKER: Sure.

DR. ATKINSON: Last two -- three thoughts and then a time line. There has been a suggestion that we include a VAERS report form in there. I've spoken to the Vaccine Safety folks and they tell me that they plan to revise the VAERS form in about -- in two years or less. So the question is, do we want to put a VAERS form in here, since apparently it's not in the PDR anymore? Do we want to put a VAERS form, a report form in given that fact that it may well be revised before this document expires?

DR. MODLIN: Or do you want to put a web site reference?

DR. ATKINSON: Yeah. Currently, I've got a reference into the web site. I just thought out if there was any strong feelings about including that.

DR. MODLIN: I think that's the way to deal with that.

DR. ATKINSON: Okay. The next question is, one reviewer suggested we include the Vaccine Injury Table, the Vaccine Injury Table in the document itself. I

just throw that out to see if there were -- Well, currently, there's a web site reference to the Vaccine Injury Program in the document, but I would find out if there are any strong feelings about whether we should or should not. I think it's in the Red Book. It's a matter of do we want to include it in this document as well.

DR. MODLIN: Geoff, is the table published on the web site?

DR. ATKINSON: Yes.

DR. EVANS: Yes.

DR. ATKINSON: The web site is good enough? Finally, one additional question was, Table 5 is a very large table at the very end of the document that is the Guide to Contraindications and Precautions. There was a suggestion by at least one reviewer that this not necessarily be the appropriate forum of it because of the fact it tends to change over time, that perhaps this document. This table lists appropriate and inappropriate contraindications would be perhaps more appropriate to publish as an annual document in the

revised Harmonized Schedule or some other forum rather than to put it in here, given the changeability of it. I throw that out as a -- I said I would, whether or not you think it should be in here as it was last time. This is the variant of the standards table, the original children standards table that was in the General Recs in 1994. Whether we want to keep it in this document or put in some other forum.

DR. PETER: John?

DR. MODLIN: Georges?

DR. PETER: Well, I made the suggestion. I know the CDC revises the table on contraindications regularly, but it's not generally available. And given the need to ensure correct contraindications and precautions and up-to-date ones, I would urge consideration that in addition to the yearly immunization schedule, we have a yearly guide on contraindications. Those things get posted on refrigerators. Nurses see them, and I think it would be very educational.

DR. MODLIN: I think it would be appropriate to add that to the agenda for the newly-formed work group on

the Harmonized Schedule, because it's an issue not just for the CDC but for everyone, and maybe that would be the best way to address that. That's a good point. But I think for now, I guess my suggestion would be to retain it in the -- it certainly is not going to --

DR. ORENSTEIN: I think by the time this is published, we will be close to a new Harmonized Schedule. And if we decide to put in the Harmonized Schedule, which I think makes more sense, then I'm not sure we need it here.

DR. MODLIN: Okay. Why don't, again, we revisit that in June, Bill, or maybe it'll be a little bit further along, particularly with the Harmonized Schedule Work Group. Maybe they will have had an opportunity to address that.

DR. MODLIN: Jon?

DR. ABRAMSON: Jon Abramson.

We suffer over the same problem, but I do need to warn you that less than 50 percent of pediatricians ever go on computer. So if you really want the VAERS report used, you're putting it -- you're decreasing your use

of it by putting in on the web site by whatever percent are never going to get on there.

DR. MODLIN: We just learned to today that Georges has learned to use PowerPoint. I would --

(LAUGHTER)

DR. MODLIN: Georges may very well be leading that organization. I assume that we'll be able to drag the pediatricians along in some way or another. Yes?

MR. SCANDER: John Scander. I would just point out that there is an annual hard copy mailing of VAERS report forms. I believe the mailing list is 200,000 at this point. So we're -- we're cognizant of the fact that there are still lots of folks out there with neither time inclination or resources or access the internet.

DR. MODLIN: Thanks.

DR. ATKINSON: So we'll talk about that again in June, okay.

The time table as it stands now for Version 9, I would like to get comments from anyone who cares to give them to me over the next couple of months. I will prepare a

revision in April and submit it to all of you, at the very latest, with your material here and perhaps earlier. Since it is such a large document, I realize it is something of a hardship to read it all. Perhaps if we can get the revisions done, I can get you -- At the very least, you'll get it with your mailing and maybe even a little earlier. And hopefully, we can revise the final issues and finish this thing off in June and then get it published sometime this summer.

DR. MODLIN: Again, unfortunately, Lucy is not here, but I -- it may very well be that getting the General Recs Work Group together by phone to review a final -- take a final look at it. Then if there are any issues in any respects may be considered to be -- need to be discussed or controversial, at least we'll have a focus from the work group.

Bill?

DR. SCHAFFNER: Schaffner. Just to prolong Bill's pleasure, these are general recommendations on immunization and I must say I hadn't re-read the document recently, but it's just been brought to my

attention that in the Table of Contents on page 45 -- It's really page 42 -- there are standards for pediatric immunization practices noted. Is there a -- Obviously, this document has as its major focus pediatric immunization, but is there a place where we ought to reference also the standards for adult immunization? And as I've begun to think about that kind of issue in relationship to this document, for example, the vaccination of internationally-adopted children is important, but a question that I get with some frequency is how about immunizing people who are adults who are born abroad. There may be other issues embedded in here that relate to immunization practice in adults, either issues of comission or perhaps omission. I raise this as a thought for you-all.

DR. ATKINSON: Both the pediatric and adult standards are mentioned. There is a section specifically on pediatric, mainly because that section existed in the prior iteration of the document. So it was really not comission. It was omission. I could have easily put -- It does admit that they are both under revision and I

am advised by Dr. Peter that they probably will not be ready to summarize very well in this document at this time table.

DR. PETER: I actually think the time schedule now may be about the same. We hope to publish the new standards in October. So I think you would want to list them, at the very least, as in press. Otherwise, people will be looking at the 1992-93 standards on adults and children.

DR. MODLIN: Thanks. Bill, thanks once again for bearing with us. Again, I have a very firm intent of finishing and taking a vote on this document in June. Let me reiterate or ask for anyone who has comments on the draft, it would be very important to get them to him sometime within the next month. We'll ask the General Recs Work Group to take a look at it and, obviously, all of us will have a chance to review it in detail before the June meeting.

Is Hal Margolis here yet?

DR. MARGOLIS: Yes, I am.

DR. MODLIN: Hal, are you ready to go?

The next item on the agenda will be pertinent to the hep B statement that, as I mentioned yesterday, we also hope to wrap up in June. Today we're going to focus specifically on some new information on safety with hep B vaccine, particularly with some recently published information.

DR. MARGOLIS: What I wanted to do and use a few minutes and actually this may catch you up on your schedule. Recently, there were two papers and one editorial published in the *New England Journal* related to multiple sclerosis and hepatitis B immunization and Dr. Schaffner, who is one of the authors of the editorial, is here and I presume will add very much to the discussion. I do not intend to go through the papers. I assume most everybody has seen them. They were fairly newsworthy, but I felt it was worth at least looking at the nested case-control study which was derived from the Nurses Health Study that looked at, basically, two large groups as pointed out here, one recruited beginning in 1976 and the other in 1989. And with the ascertainment of the diagnosis of MS,

actually by questionnaire and then with physician ascertainment, actually it turned out that in overall about 86 percent of these women had a positive MRI and actually in the second recruitment group in the Nurses Health Study, too, the ascertainment was around 96 percent with positive findings.

Hepatitis B vaccination was ascertained by both questionnaire and then a validation of the medical record, and that validation found that it was only ascertainable in about 64 percent. About 35 percent were -- could not find a record of the immunization, just either because of employer or other lack of record-keeping. And the controls were both healthy women and a breast cancer control group.

The cases amounted to 190 women with 534 controls and 111 cancer -- breast cancer patient controls. What I've done to summarize some overall data, which were in looking at the vaccinated to the unvaccinated using the healthy controls, the age-adjusted relative risk was 0.9 with a confidence interval crossing one. And the similar one using the breast cancer control group, the

risk was 1.2 -- Sorry, I've got an extra zero in there -- with a 95 confidence interval of 0.5 to 2.9.

It was also then looked at the group who had a later onset of MS, this trying to focus more on the recombinant vaccine group. Again, showing no increased risk and again no evidence of association.

They did a number of analyses trying to look at the issue of recall bias of vaccination and, in fact, when one just used history of vaccination, the relative risk went up to 1.0, but again with statistical association. And again, this has been discussed in -- to this committee some of the other case-control studies that were done in Europe. Most of the -- In fact, none of those actually looked at documented vaccination history. So I just put this together and I figure this is going to be the discussion point at this point, is that their conclusions were there's no evidence of increased risk of MS among women vaccinated against hepatitis B. I think one can characterize this study as being robust in that they did a number of things to mitigate against some of the problems in these studies,

which was the nest case-control design, very high rates of participation, use of documentation of vaccination through vaccination records, and also use of a wide disease onset history in using two-year onset to minimize error from self-reported dates of onset. And these data now -- I mean, here come again some of the comparisons, is that recently there is what I guess would describe as an ecologic study from Canada, from Vancouver, that showed no increase in MS in population-based surveillance in a population that's had adolescent, as well as adult immunization going on for a number of years, but it does contradict what have been and I again discussed with this committee the nonsignificant increases seen in the two studies reported by the French and the one, the U.K. study which was the database retrieval study.

So I think with that, the other study that was reported was that of a vaccination study, and I'm not going to display the data because, again, I kind of figured we were going -- hepatitis B is -- much like Bill. I guess maybe I am learning that don't put too much out

there because this will generate discussion, but this was a vaccination study of patients with MS and, in fact, showed no evidence of short-term exacerbation of their disease and actually parallels another study that had been done, not with hepatitis B vaccine. This one had three vaccines, previous ones, that had been done with influenza vaccine that had shown a similar result and was thought to be representative of immunization issues in general.

So I guess with that, I would put it open for discussion and Dr. Schaffner might want to comment with, I think, a very eloquent editorial in terms of a hot issue.

DR. SCHAFFNER: I think you've summarized it very well, Hal. Perhaps Bruce Galen, do you want to make -- my colleague in writing the editorial? We thought, as did you, that the -- both studies were done using very rigorous methodology and provided at the end, bottom line, a great deal of reassurance to people who are receiving hepatitis B vaccine to people who had multiple sclerosis and to the physicians who care for

such folks.

DR. MODLIN: Bill or Hal, was a separate analysis done on the basis of immunization -- women who said that they were immunized with hep B but what you could not confirm with an immunization record? In other words --

DR. MARGOLIS: Yes. And that was -- Their analysis would show that the relative risk moved up a little bit and, you know, then they -- I think a very discussion of the issue of ascertainment bias and -- but, yes, and they presented those data in the text.

DR. MODLIN: I obviously haven't read it. Paul?

DR. OFFIT: Hal, this question is either for you or for Glenn Nowak, if he's still in the room.

ABC did a special on 20/20, which I'm sure you were on it, where they implied that the hepatitis B vaccine was associated with multiple sclerosis in a causal way. This study goes a long way to disproving that. Do you or does the CDC have any interest in calling back ABC and having them do a follow-up study, follow-up report, since I know that their main interest is in getting it right, not in just selling advertising?

(LAUGHTER)

DR. MARGOLIS: Maybe Glenn -- AP did call and, you know, I think all of us are using these data to help arm practitioners with facts. I doubt if this is going to get aired anywhere.

DR. NOWAK: Glenn Nowak.

I think it's a good suggestion, Paul, but I wouldn't hold my breath.

(LAUGHTER)

DR. MODLIN: Bob?

DR. CHEN: I guess Hal and I didn't get a chance to discuss before his presentation. I think I would agree that these are studies that are very strong in terms of showing there's no association. We have another study, case-control study, going on in the Vaccine Safety Datalink and which we'll be presenting at the European Society of Pediatric Infectious Disease next month, which also show no association.

The one bit of caveat is that if you read the papers, they are a bit unusual in that they go -- describe the two other studies in great detail because the two other

studies, even though they have been conducted by very reputable pharmaco-epidemiologists and independently funded by the French Ministry of Health, has not been able to be published. I think it remains to be seen in terms of sorting out the methods to try to better understand if, in fact, the ascertainment bias is the true issue here. I think the other bit in which the -- at least the U.K., Marian Sturkinbaum [phonetic] in the U.K. study, and the French suggest that they may be dealing with a slightly atypical demyelination disease which may not be classical MS, and that is -- in order to sort that out, the -- you would, in fact, need more of the medical records available than the traditional record linkage studies based on an ICD-type diagnosis have available.

So I think that -- just so we don't jump too far, I think, in general, the evidence, especially these two studies, are very, very powerful and definitely put the weight in terms of the negative as does the additional VSD study, but I think it's probably too soon to base basically dismiss this whole issue.

DR. MODLIN: Stan?

DR. PLOTKIN: Well, my comment somewhat takes off from Bob's.

I would recommend that CDC, if it hasn't already done this, ask a group of statisticians to look at all of studies and to give their judgment as to the statistical accuracy of the conclusions. The reason I say this is because the -- essentially the Director of Health and the statistician in France have published an article or letter in the -- in Lamond [phonetic] contesting the results of the studies published in the *New England Journal* and that there will probably be a letter written to the *New England Journal* also contesting the results. Now, this, of course, this is another example of the French exception and, you know, we have to take that with some understanding. But my serious point is that I think one should be prepared for these objections and I think also there should be some insistence, as Bob referred to, on the publication of those initial studies which, in fact, the French are using to claim that there is something and yet have

been unable to publish them.

DR. MODLIN: Thanks, Stan. Dr. Severyn?

DR. SEVERYN: Dr. Kristine Severyn, Vaccine Policy Institute.

Dr. Chen touched on one of the comments that I have, is that there are -- there could be other demyelinating diseases that are not classified as MS, and there have been people that are -- have developed demyelinating diseases after -- some of them quite crippling after hepatitis B vaccine. So I agree with Dr. Chen in that we should not prematurely dismiss this issue.

And secondly, these studies were funded by pharmaceutical companies and that might -- may or may not have some bearing.

Thank you.

DR. MODLIN: Thanks, Dr. Severyn. Thank you.

DR. MARGOLIS: Thanks.

DR. MODLIN: We'll move on. I appreciate it very much.

DR. SMITH: John --

DR. MODLIN: Yes?

DR. SMITH: -- just to reiterate, so we're going to

review the hepatitis B statement at -- what's --

DR. MODLIN: We certainly hope to -- We've had some discussion. I've spoken with Hal and with some others, and we do hope to be moving it along and to have a statement to get out to the Committee prior to the June meeting and to take a final vote.

DR. SMITH: Okay.

DR. MODLIN: Okay. The next item on the agenda is a review of the report on the Immunization Safety Review Committee of the Institute of Medicine. It's Dr. McCormick. She's here to bring us up-to-date on that review. Welcome.

DR. McCORMICK: Good morning. In January, the Institute of Medicine convened a committee at the request of CDC and NIH to examine emerging immunization safety concerns. The planning for this study was initiated over a year ago when the Public Health Service decided that it needed ongoing assistance in addressing the increasing number of vaccine safety hypotheses.

The project was developed in response to a number of

contextual factors, including an increase in the number of hypotheses linking vaccines to adverse events, encompassing a wide range of medical conditions with varying levels of scientific data, and an increasingly polarized climate for addressing these concerns.

The intent of this committee is to provide a mechanism for timely, objective, and expert review of vaccine safety issues.

It is not the typical IOM committee. Typical IOM committees are convened to study a particular issue over the course of 18 or 24 months and usually will report at the end of that period. In contrast, this study has been -- has a standing committee that will meet approximately three times per year over the three-year study period. At each meeting, the committee will examine specific safety vaccines and possibly two or more that may be closely related and then issue a brief focused report on each of these hypotheses within 60 to 90 days of the meeting.

Another key of this study is that report findings will be widely disseminated to policy-makers, providers, and

the public. Both a scientific report and a brief two- to three-page lay summary will be issued on each hypothesis. Although the committee is operating quite differently from many IOM committees, we are subject, and I want to emphasize this, to the same usual NAS review. And at least for the Institute of Medicine, that means it gets reviewed first by the executives of the Institute and then goes to the traditional blinded NAS review.

The hypotheses to be addressed by the committee will be selected and prioritized by the interagency group on vaccines. The IAG has identified the topics for the committee's first three meetings and, not surprisingly, the first one will focus on the link between MMR vaccine and autism. The IAG has indicated the committee's second and third meetings will focus on the punitive link between thimerosal and autism and the hypothesis linking exposure to multiple antigens and adverse events. The IAG may also change the order of issues that come before the committee.

The committee is comprised of 15 members with expertise

in a range of disciplines, including pediatrics, neurology, immunology, internal medicine, infectious disease, genetics, epidemiology, biostatistics, risk perception and communication, decision analysis, public health, nursing, and ethics. In addition, Dr. Richard Johnston, who has chaired the previous IOM safety studies, is serving as a liaison for the IOM's oversight Board on Health Promotion and Disease Prevention. And I would say that Dr. Johnston is taking a very, very active role. He is not only providing continuity with previous IOM reports, he also has a very strong oversight rule. The IOM's Board on Health Promotion and Disease Prevention, which I just got off, really is one of the largest boards at the IOM and really takes its oversight role very, very seriously and has been active in defining that. So Dr. Johnston will play and continue to play a very significant role in these activities.

Given the unique nature of this project, the IOM leadership develop strict criteria for committee membership, including no financial ties with vaccine

manufacturers or their parent companies; no past or present service on major vaccine advisory committees; no expert testimony or publications on issue of vaccine safety; and no current or recent funding from CDC.

The rationale for these criteria was two-fold. First, given the controversy surrounding vaccine safety, the IOM felt it was important to have an objective and independent committee that would not be subject to criticisms of conflict of interest. And second, given the uncertainty surrounding the hypotheses that would come before the committee in the future, the IOM wanted to ensure consistency in the committee membership and avoid having committee members to recuse themselves from the deliberations because they had participated in the development of a vaccine or research on vaccine safety.

The charge to the committee, the first organizational meeting was held, as I mentioned in January. The committee heard presentations from the sponsors, CDC and NIH, and other stakeholders, including Congressional Representatives Waxman, Weldon, and

Burton, the National Vaccine Information Center, and the American Academy of Pediatrics regarding their perspectives on vaccine safety. The committee also heard a series of presentations to assist in developing a conceptual framework for approaching the charge. The charge of the committee, as outlined by the sponsor, has three components: a plausibility assessment, including the evaluation of the causality evidence, biologic plausibility, and strength of competing hypotheses. We are also asked to make a significance assessment, taking into account the number of persons affected, the serious of, and the treatability of the adverse event and natural disease. And guidance, based on these two assessments, the committee was asked to provide guidance on potential future activities such as research, surveillance, communication, and policy review.

What we will not do. We will not make public policy. That is the responsibility of the federal agencies and their associated advisory committees. For example, the committee would never recommend that a vaccine be

pulled from the market or that the schedule be changed. However, the committee might conclude that the adverse event threat is serious enough to warrant PHS convening its advisory bodies to review its evidence and policies.

The committee will agree that it will primarily on peer review literature. However, we also will be considering case reports from VAERS and other sources. The committee chose to rely on methodology established by previous IOM committees on safety -- IOM vaccine safety committees, particularly as it relates to causality assessment.

The next meeting will be held March 8th through 10th in Washington and will focus, as I mentioned earlier, on the punitive relationship between MMR vaccine and autism. The March 8th meeting will be open to the public and we have a schedule of that -- a draft schedule of that meeting available, while the March 9th and 10th meetings will be closed for committee discussion and deliberation. The public meeting on March 8th will held in the lecture room at the National

Academy of Sciences from 8:30 and adjourn at 4:30 p.m. We have the draft of that meeting.

The public meeting will be organized into two sessions. The first session will focus on questions regarding the etiology, assessment, and classification and epidemiology of autism, and the second session will focus primarily on Dr. Wakefield's hypothesis linking the MMR vaccine, inflammatory bowel disease, and autism. Dr. Wakefield and his colleagues will be presenting their hypotheses and their most recent data. We will also hear presentations on recent epidemiologic studies of the hypothesized link between MMR, IBD, and autism. For both sessions, there will be a panel of discussants who will comment on and react to the presentations and ask questions of the presenters and we will conclude the meeting with a brief public comment period.

The committee would really welcome an opportunity to present its findings to ACIP and other advisory committees. We would also encourage you to send the committee any materials or comments that might be

helpful in addressing the hypotheses and we would certainly look for and appreciate comments and suggestions about help with dissemination.

Thank you.

DR. MODLIN: Thanks, Dr. McCormick. Are there questions for Dr. McCormick, comments? Joel Ward?

DR. WARD: I was wondering if you could comment about IOM experience over the decades. I recall many years ago being removed from the committee because I had done a drug study and now I see that doing federal NIH or CDC studies or perhaps even being a researcher in the area disqualifies one. I do commend the committee on a really superb committee selection. But I'm just wondering, as the pendulum swings, if any career involvement or acknowledgement or involvement in research in vaccines now disqualifies you from assessing safety and whether there's some precedent in other medical or non-medical assessments in the process.

DR. McCORMICK: First of all, we don't believe this is the model for studying vaccine safety and we shouldn't

-- don't think this should be generalized. This model -- It is -- This model is very different, particularly because of the specific issues that are being addressed. Clearly, issues that are dealing much more technically with vaccine safety should have people who know what they're -- I won't say we don't know what we're talking about --

(LAUGHTER)

DR. McCORMICK: -- but people who are invested with the direct day-to-day data. I think that the more broad general expertise on this committee is appropriate for these level of questions, but we absolutely have stated publicly that we don't think that this is the model for future vaccine safety committees.

DR. MODLIN: Larry?

DR. PICKERING: Thank you for the update. I have a couple of questions.

One is, what criteria were used or will be used for the topic selections that you've chosen, both now and in the future? There are a lot of vaccine accusations, some of which some data to support them and some of

which don't. So could you inform us on how these selections were made and how selections in the future will be made.

DR. McCORMICK: That comes from our sponsors, from the interagency group on vaccine safety. So we don't select it ourselves. We are given the topics, and this one -- the MMR/autism one was very high on everybody's list.

DR. MODLIN: I believe I also heard you say the interagency group not only selects your agenda but can change the agenda --

DR. McCORMICK: Yes.

DR. MODLIN: -- along the way if it is felt -- Marty?

DR. MYERS: And specifically to mention this. Georges mentioned this in his comments, that the National Vaccine Advisory Committee's subcommittee on safety and communications will be a forum by which we can have public input into the interagency's vaccine groups deliberations.

DR. MODLIN: Neal?

DR. HALSEY: Neal Halsey.
I wonder if -- I want to ask two questions. The first has to do with if the IOM has ever gone back or would consider going back over some of the previous decisions and statements that they made with regard to perhaps some factual errors that took place in the consideration. And I would refer specifically to the decision that there was a biologic plausibility for hepatitis B vaccine to be associated with multiple sclerosis. I think as we've seen today, the data don't support that, and in fact, others who have reviewed that, which was based upon rabbit studies and rabbit myelon basic protein, which was not the case with humans, there was no evidence of any cross-reactivity. And I would encourage you, as your process continues, to go back over some of the things that you've said before, which might need updating with additional information.
The second has to do with your process. You said you're going to follow the same methodology that has been used before. I think it's not been helpful at

times to have those various categories of the likelihood of something being causally related or not because you came up with so many where the evidence is inadequate to accept or reject when, in fact, the evidence was so weak that it really didn't offer - it didn't offer anything. And I think there needs to be a greater burden of evidence on people who are alleging new adverse events. We're facing an increasing number, and I actually think that some of the IOM review process, leaving people with many more doubts, has helped contribute to making it possible to throw out new hypotheses where there isn't evidence one way or other or even evidence to support.

DR. McCORMICK: First, again, if the IAG suggests reviewing -- revisiting some of these complications -- I know that one was also on the list of about 30 that we were given at our first meeting -- then I think we would do that. But, again, the initiative isn't on our part. It's coming from our sponsors in terms of what conditions they feel are most important for us to review at any given time.

With regard to the second, I think that we are cognizant of the fact that we are probably going to be most of the time in the middle where we say there is not very strong evidence one way or another and very weak evidence and very spotty evidence, and I think that the committee has taken that very seriously and is working towards trying to develop some alternatives in terms of suggestions to move beyond simply saying "yeah" or "nah," and this is an emerging process at this point.

DR. MODLIN: Yes, Larry?

DR. PICKERING: One more question. The Medical Research Council of the U.K., as you know, has reviewed the first topic that you've selected. Will their deliberations and reports be part of your considerations?

DR. McCORMICK: Yes.

DR. MODLIN: Bob Chen?

DR. CHEN: Just to address Joel Ward's question about other arenas may try to deal with this question of staffing these investigations where these perceived

conflicts of interest are somehow managed in the appropriate way, and the one model that I looked into a little bit is the National Transportation Safety Board and their investigations. And what happens is that in, let's say, an airplane crash, they deputize the safety expert from the appropriate airplane manufacturer, as well as the airline, but the overall investigation is still led by the NTSB so that it's a way in which the appropriate expertise could be brought in, but the very clear oversight is still done by the independent body. So that's just one thing that we might look at in the future.

DR. MODLIN: Thanks, Bob. Further questions or comments?

(NO RESPONSE)

DR. MODLIN: Dr. McCormick, thank you very much. We certainly appreciate your willingness to come down and bring us up-to-date on the IOM process.

The last item on the agenda before lunch will be an informational item on discontinuation of manufacture and marketing of both cholera and typhoid vaccines, and

the presentation will be by Dr. Mintz from the National Center for Infectious Disease.

DR. MINTZ: Good morning. It's a pleasure to be here this morning and be the speaker. I'm honored to be the last one before lunch. I'll try and keep my remarks brief.

Today I'm going to speak to you about two life-threatening vaccine-preventable diseases, cholera and typhoid fever, which are major public health problems in many parts of the world but which are rarely discussed in this forum. The reason that they're on today's agenda is to bring to your attention the decision by Wyeth-Lederle to halt production and U.S. distribution of their vaccines for cholera and typhoid fever in June of last year. Representatives from Wyeth-Lederle have assured me that at this time there is no vaccine -- none of either vaccine on the market which has not already exceeded its expiration date.

I'd like to consider each vaccine separately and begin with cholera. The last ACIP recommendations regarding cholera vaccine were made in 1988. I apologize for an

error on the handout where it says 1998. And cholera vaccine at that time was recommended, and I quote, "only to satisfy entry requirements for persons who anticipate travel to countries that require it and for special high-risk groups that work and live in highly-endemic areas under less than sanitary conditions." Now, for nearly the past decade, no country has officially required evidence of cholera vaccination for entry and this is in keeping with recommendations by CDC and WHO that travelers not be vaccinated for cholera.

The Wyeth-Lederle cholera vaccine was never considered a very good vaccine. It was only 50 percent effective against clinical illness and a duration of protection of approximately three to six months. However, there are no other cholera vaccines licensed in the U.S. Now, two other more recently-developed oral cholera vaccines are available in Europe and elsewhere. However, neither of them is licensed here.

The demand for cholera vaccine is limited. We have not been overwhelmed with calls from travel clinics,

although there have been a few inquiring about this situation. We see approximately ten cases of cholera diagnosed in the U.S. each year and approximately two-thirds of those are among travelers, so persons who might consider vaccination or might have been protected by vaccination. So an average of about six persons per year.

I'd like to continue with typhoid vaccine and then take questions on both of them at the end, if that's all right.

For typhoid fever immunization, the last recommendations by ACIP were made in 1994. And I quote from those, "Immunization against typhoid fever is recommended for travelers to areas where there is a recognized risk of exposure to salmonella typhi, counties in Latin America, Asia, and Africa, who have prolonged exposure to potentially contaminated food or drink, also for persons with intimate exposure, that is household contact to a documented salmonella typhi carrier, and for microbiology laboratorians who work frequently with salmonella typhi."

The typhoid vaccine manufactured by Wyeth-Lederle ranged in efficacy according to various studies from about 51 to 77 percent. I saw another analysis today that put it somewhere between 63 and 80 percent. There are two other typhoid vaccines that are licensed in the U.S. However, only the Wyeth vaccine was licensed for children between the ages of six months and two years of age.

In this age category, there are cases of typhoid fever and in the six-year period from 1994 through 1999, 33 cases occurred in children between six and 23 months of age in the U.S. Now, I don't know how many of those cases were children who had travelled, but for most of our typhoid cases, the average was about 80 percent. That is, we have 20 percent acquired here in the U.S. and the remainder acquired overseas.

We have had some calls from -- generally from travel clinics, occasionally from pediatricians regarding this, and our response has been until newer vaccines are developed and licensed for children younger than two years of age, it's important to emphasize to

parents who travel with their young children the importance of attention to food and drink through which typhoid fever may be acquired.

That's pretty much the end of the presentation. I would be glad for any comments or questions.

DR. MODLIN: Questions for Dr. Mintz? Comments?

(NO RESPONSE)

DR. MINTZ: I take it from that that you're all either hungry, sleepy, or perhaps both?

DR. MODLIN: Except for Dr. Pickering. Larry?

DR. PICKERING: Are there vaccines in other countries that are utilized for children down to the six-month-of-age limit?

DR. MINTZ: Not that I'm aware of. I spoke with several people, including Phil Hosbach from Pasteur Aventis, regarding a conjugated VI capsular polysaccharide vaccine that's developed by John Robins at NIH and that's been looked at in Vietnam, primarily. It appears to be very effective in children two years of age and older, and there's some preliminary studies that it at least produces antibody responses in younger

children. There's also a liquid formulation of the oral TY21-A typhoid vaccine that has been tried in younger children in the past. I don't believe it's licensed or used there for that age group, but there have been trials and effectiveness was a little difficult to gauge because there were small numbers. However, the children did take the syrup well.

DR. MODLIN: Dr. Deseda?

DR. DESEDA: I want to know if there's any application for licensure for any of the other cholera vaccines?

DR. MINTZ: I know that several years ago the vaccine manufactured by the Swiss Serum Institute in Berna, Oracol [phonetic], was considered by the FDA or presented to the committee at FDA for licensure and was not licensed. Perhaps someone here from FDA could comment more on that. I don't know if they plan to reapply for licensure.

DR. MIDTHUN: Is this on? There was -- is a license application, as you indicated, which was presented to our Vaccines Advisory Committee approximately two years ago and I really can't comment any further on that.

DR. MODLIN: Thanks, Karen. Stan?

DR. PLOTKIN: There is the Homegran [phonetic] vaccine --

DR. MINTZ: Yes.

DR. PLOTKIN: -- which I understood -- I hope I'm not speaking out of turn, but I understood that SmithKline was developing that vaccine, at least in Europe. I don't know whether they plan to bring it into the States.

DR. MINTZ: I think you're referring to the vaccine that we call the whole cell beta subunit, WCBS vaccine. It's a killed oral vaccine developed in Sweden, and that is licensed and sold primarily to travelers in several countries in Europe. I don't believe that's ever been brought before FDA to apply for licensure in the U.S., but I don't know that and I don't know if there are plans to do so.

DR. MODLIN: Other comments or questions? Dr. Mintz, Alison, this means that we have existing recommendations for a vaccine that will not exist within a short period of time. So it sounds like we

may have at least some housekeeping to do with respect to the cholera statement -- Is that fair? -- and perhaps the typhoid statement as well, even though it's a bit more recent.

Other questions or comments?

(NO RESPONSE)

DR. MODLIN: Dr. Mintz, thank you very much.

DR. MINTZ: Thank you.

DR. MODLIN: We'll start up again at 1:00.

(LUNCH RECESS FROM 11:53 A.M. TO 1:05 P.M.)

DR. MODLIN: We'll begin -- Dr. Snider has an announcement that he would like to make before we begin. Dixie?

DR. SNIDER: Yes. I just wanted to explain the situation with regard to a quorum. I said that there was a quorum of eight and that people may have noticed, there are only 12 members. The situation is that we have gotten the Charter approved for 15 members, which means that the quorum is eight. The three nominees have not yet been signed off on. So we have three people who we expect to come on who are not yet

officially designated. So that's the reason for -- the reason we had to increase the official quorum, and I wanted to encourage everyone to stay. I know there's travel problems, but I wanted to encourage everyone to stay so that we can have an official meeting.

The other thing, Gloria asked me to tell you, as members of the -- voting members of the Committee, just to remind you that when you come to these meetings, you are government employees and that you have to follow the travel rules. Therefore, if you make -- or if you plan to make any changes in your travel or in your accommodations for this evening, you really need to talk to Gloria and make sure that the appropriate paperwork gets done. We would hate to have members have to pay money out of their own pocket for executing something they thought was okay but actually didn't follow the rules.

DR. MODLIN: Dixie, thank you. The first item on the agenda for this afternoon will be in some respects a sequel to a very nice presentation that Joel Ward gave to us in October, just at the time or just a week or

two prior to the time that they were getting ready to break the code on the adolescent and adult pertussis vaccine trial.

Joel, I assume the code has been broken, and we are going to hear these data presented to us this afternoon.

DR. WARD: (Inaudible)

DR. MODLIN: My understanding is that no, that you're first up. We can provide some alternative entertainment if it's going to take a few minutes.

UNIDENTIFIED SPEAKER: I've heard you sing, John.

(LAUGHTER)

DR. MODLIN: Unfortunately, Chuck Helms has left.

DR. WARD: Okay. I think most of the people here are familiar with the APERT trial. This is an NIH-initiated multi-center trial that has been in evolution and conduct for about four years. It had two major objectives, and that was to define the epidemiology of pertussis in adolescents and adults in a prospective manner using very intensive microbiologic and other epidemiologic surveillance techniques, and it was also

a randomized double-blind trial with hepatitis A and acellular pertussis vaccine.

Although NIH initiated this, once an independent committee selected the vaccine, there was some major support provided by the Glaxo SmithKline Company. The eight study sites are listed here throughout the country. These are mainly the VTEU sites of NIH with two additions and these are the principle investigators at each of the sites. UCLA Center for Vaccine Research was acting as the coordinating center and the reference laboratory.

You-all are familiar with the proposition or the prospect of the hypothesis. Clearly, pertussis cough illnesses are, as I mentioned at my last meeting, probably the major infectious disease of older individuals as we think of otitis being in children, perhaps. They are extraordinarily frequent. At least one out of two people have a cough illness lasting five days or longer every year which represents enormous morbidity and mortality, and what wasn't known was whether pertussis might represent a preventable and

perhaps a significant proportion of those cough illnesses.

We know that pertussis occurs in adolescents and adults and immunity wanes. We know those symptoms can range from being totally asymptomatic to mild to moderate disease or even classical whooping cough. We know that early treatment can be effective in mitigating disease but it's almost never entertained or considered or diagnosed. And we know that for most epidemiologic studies that over half of the cases in children can usually be traced to an earlier case in an adolescent or adult in the household or in the environment. It brings the prospect that the ultimate control of pertussis may require something more than the routine immunization of infants.

Now, the difficulties of diagnosing pertussis in adolescents and adults is well-known to clinicians. It is a diagnosis that -- and a disease almost unknown to the internist. Cultures are rarely obtained and sent and usually what is known from the literature comes out of family contact studies, often from Europe and other

studies where there was a focus on pertussis and they found cough illness as part of an epidemic investigation in children or day care centers or as part of a vaccine trial in older members in that household.

Unfortunately, cultures are not very sensitive because they're usually obtained late after somebody has been coughing for quite a while and they do require careful preparation in media and knowledge of growth and identification of pertussis.

The serology I could go into for at least an hour. It is very complicated. There's nine different routine assays run. It approaches the complexity of EB virus interpretations, I think, or CMV.

One of the conclusions of our study was to evaluate PCR, which ultimately proved not to be very -- add much more diagnostic sensitivity. And of course, the infections and illnesses that occur, since they're not diagnosed are rarely reported.

So, again, we had several objectives: primarily epidemiology of infection and disease; the efficacy of

vaccine; of course, vaccine safety; and a lot of adjacent studies to look at immune response, not only to the vaccine but to naturally-occurring infection and illness; to look at variability; and to see if we could assess something about correlates and protections. An ambitious agenda for one trial.

This was prospective, control, randomized, double-blind, eight sites, two years, 2,781 subjects, two vaccine groups, a three-component vaccine with PT, FHA, and Protactin. There was very active surveillance with phone calls every two weeks. Anyone with a cough illness of five days or greater was brought in for microbiologic and clinical evaluations and this was carried out for two years at eight sites.

PCR was employed. A great amount of work went into maximizing serologic capabilities and all illnesses were evaluated with acute and convalescent sero as most of the published literature has sero that are obtained weeks after a cough illness. So this was trying to get acute and convalescent. Since all of this had been exposure to pertussis, either by virtue of having been

immunized as children and through natural infection, interpreting antibody responses can be very tricky. This was the essential study design. There was just one dose of vaccine given at entry into the trial. Blood specimens were obtained from all subjects three to six times as part of routine serological surveillance so that we could look at periodic changes in paired sero over time periods in the study, but in addition to that, every time there was a cough illness, there was an additional pair obtained at day five, early -- relatively early in the cough illness, not necessarily early in the time of infection because we don't know when that might have occurred, and then one month later -- This totalled many thousands of bloods collected, and I'll show you a slide on that -- and of course, careful safety evaluations.

This showed the representations in the number of blood specimens obtained. There are more than 13,881 and if you multiply that times nine different assays, you have some idea of the volume of serologic work that's required.

This is the enrollment of subjects who were recruited rather quickly in the summer of '97. This was the dropout rate which was very insignificant until this period when we extended the trial for a six-month period to try and ascertain more cases, and there were competing studies going on at several of the sites. This is the age distribution of the subjects. They ranged from 15 to 65 years of age. Since these two cohorts are half of these decades, it's a pretty good representation by age across the eight study sites. There was some variation between different study sites in their distributions, but the mean age was 34.8 years and it did include an adequate number of adolescents, I believe.

This is a comparability of study groups. This is after the breaking of the codes and the randomization of the AP and hepatitis A groups, the number of person months, drop-out, sex. Interestingly, two-thirds of the subjects were female in this recruit/volunteer, intensively studied population. A predominance of caucasians, 70 percent, no difference. In fact, there

were no significant differences in these factors. I would just point out that the study consisted of about a third health care workers, a third students, and a third community-acquired volunteers. It varied a little bit between different study sites. They reported we didn't have independent validation of prior vaccine in essentially a majority of the subjects and smoking, which is a variable for coughing illness, was prevalent at 17 percent and quite variable between study sites, with California being the lowest.

I had some interesting safety data, which was just analyzed in part by virtue of the IOM in the last 12 hours. So let me present this to you.

Usually a mundane subject, and these would be adverse reactions in the first 14 days after immunization, but this was a blinded trial and this was analyzed sometime after the event from a multi-center study done at a coordinating center. This just looks at fevers, and there were almost no fevers in either the hepatitis A or in the pertussis vaccine group, which is reassuring.

We further looked at this by sex and by vaccine group

and this is an expanded scale. So you can see this is .4 percent. So fevers are very rare. And there is no difference really between males and females or between the two vaccine groups.

This is looking at decreased activity and this is general malaise, systemic, over a 14-day interval. This was obtained by diary card where it was very complete and careful education of the subjects and then a 14-day phone call and follow-up of the diary information. Again, no differences in general malaise between the study groups and no real dramatic differences by sex, males and females. You have to focus on the solid lines of the pertussis group. And the dotted lines here are the male and female of the hepatitis A group. There is a significance here with more malaise in females, but this difference is the difference between one and two and a half percent. So it's not a very important difference.

However, this difference is quite different. This looks at the appearance of muscle lumps at the injection site and the occurrence in time after

immunization. The hepatitis A in red. So there is some lumps being reported and a rather somewhat biphasic reporting, both initially but of a much greater magnitude, a range of six percent compared to two percent in hepatitis A group, and then a delayed appearance of lumps around day seven or eight. But the interesting analysis to this is looking at it by sex, and essentially all of these lumps are reported in the female segment of the -- of the pertussis study group with really no meaningful significant differences between the males in the group and the hepatitis A group, which may shed some light on previous reports in children.

Swelling, which is probably related to the lumps, is likewise significantly higher in the pertussis group, but not of a high magnitude, two to five percent. Again, biphasic and higher than the hepatitis A, significantly so. Again, all of that is due to reports from females, not males.

This analysis came about, I think, because of the focus on the anthrax and the sexual difference and reported

reactions. And they asked us to look at this in the APERT trial, and that's what I'm sharing with you today.

Redness, likewise, another measure. Not very high. I don't think any of these are in the range of real worrisome. None of these were severe. None of them required medical follow-up, hospitalization, or treatment, but they clearly are a significant finding and different than hepatitis A. Again, all of that redness was in the female group, not to the males.

Soreness at the injection site, likewise, and again, that proportion was almost -- almost -- there's a little blimp here, but it's essentially all in the female segment.

But here muscle aches, and this is -- this is generalized muscle aches, really not a difference between the study groups and not a difference by sex.

So there were some reported differences, but the local reactions appeared to be very sexually dominant.

There were no serious adverse reactions attributable to the vaccine and the distribution between the two groups

were essentially the same, and there were no adverse outcomes in the 60 pregnancies that occurred to study subjects, in spite of screening and admonitions.

This is the incidence of cough illness. I think I shared this slide with you earlier. Again, just to reinforce for the Committee and for the public health practitioners how important cough illness is, and you may hear me cough today, but it's not pertussis. It's in the range of four to five percent per month in some of these subjects. It certainly has a seasonality occurrence to it.

There was some variability. These are cough illnesses at five days or longer. So this excludes all cough illnesses lasting one to four days, presumably to try and filter out the viral etiologies or some proportion of them. But overall, this would be .6 episodes per year per person.

Now, half of the study subjects had no cough illnesses over the two-year period, but the other half had more than one, this proportion, fifteen percent having two, eight or nine percent having three, et cetera.

And this is the distribution, a slight trend towards increasing incidence of prolonged cough illness in older individuals, but clearly present across the age range in all age groups.

And the duration of these coughs are really quite significant. So this is five to ten days, ten to 15 days, 15 to 20, et cetera, on out to greater than 60 days of cough. And you can see that this is five percent here. The median here is 15 to 20 days of cough. These are not insignificant illnesses in the distribution. And this, of course, excludes all cough which I'm sure would be off the chart here, those less than five days.

And this was to look at the fact of smoking. This looks at the percentage of individuals by frequency of their cough, and those that tend to have more frequent coughs significantly have a much higher proportion of smokers, 39 percent. So there is a confounder in the coughing analysis, obviously, and there was a geographic difference as well.

Okay. The important issue is did hepatitis, in

comparison of the pertussis-vaccinated versus hepatitis A control vaccinated, was there a difference in the incidence of cough illness? And I must tell you this is the biggest reason why I went into this study and, following true to form, there was no difference in the overall incidence of cough illness between the study groups. That's not to say that it didn't prevent pertussis and not to say it didn't prevent disease, but the overall burden of cough illness could not be measured and I will show you a slide explaining the reason for that when I tell you what the proportion of pertussis was in this population.

And this now looks at that same data in the pertussis-immunized versus control subjects. No significance here, stratified by duration of cough. So if you know look at coughs greater than one week, two weeks, three weeks, or greater, you still see no significant difference. And this is due to the fact that the proportion of pertussis is smaller -- is relatively small. It's between one and seven percent, and the study is not powered to detect a difference with a

proportion that small.
Now, the important primary case definition was there. There were individuals with a cough illness detected prospectively and evaluated at one of the study sites. It required a positive culture or a positive PCR or a positive serologic change in the acute to convalescent. This is a much different case definition than has been used in the literature, which is generally a high convalescent, which you can't tell really what the (inaudible) was before that or whether the rise was related to the illness or not related to the illness. So these are paired within 28 days. We had tight time windows for this. And we used our committee, oversight committee, which was chaired by Neal Halsey, and Bill Schaffner was the safety monitor for this study. It had PT alone or it required two independent antibody rises of two-fold or greater and there was considerable amount of validation to show that a two-fold or greater provided almost no chance of a random occurrence of a false positive.
This shows the categorization serologically. The

culture and PCR are relatively clear-cut, but the primary case definition included serologic cases that had a PT or two other antibody rises between acute and convalescent, and this was the primary case definition. We then had five other categories of less stringent, presumably more sensitive but less specific case definitions. And basically what these did is since we had from each individual sometimes as many as ten sero over two years, we were able to look at paired sero prior to the onset of cough. Let's say a month earlier or two months earlier. So we called that an early specimen. So the primary case definition depended on acute to convalescent.

This category two looked at one within six months of the illness. Another category looked at any antibody rise not requiring two independent antibody. A fourth category looked at early to convalescent, looking at any antibodies. And the latter two categories are the standard literature kinds of looks that looked at high acutes. It's a very complicated area and I'm not going to present it in any detail today except in the control

group because of the confounding of immunized subjects having higher titers than controls. There will be a detailed analysis of antibody decay since we have an antibody profile in all subjects to look at those latter two categories, but it will take some time. These categories are useful in getting at our primary objectives, one of our primary objectives, which was our assessment of disease incidence using different criteria.

Now, these are the results of the study. I spent many hours trying to make it as simple as I can, but it's hard. The primary case definition are the first two rows, hepatitis A control group cases and the acellular pertussis. This is unblinded, broken codes. There were five cases in the hepatitis A group that were culture of PCR-positive and one case in the AP group. This case is a very interesting case because it was PCR-negative, culture-positive, and careful serologic showed absolutely no antibody change to any of the nine antibodies before or after. The committee questioned whether this was really a case or not. It was a small

number of colonies identified on the plate and may have been a contaminant in the lab, but that couldn't be confirmed one way or the other. But technically, it did meet our primary case definition. So I've indicated with an asterisk.

Serologically, there were an additional two cases in the AP group and nine cases -- excuse me, an additional one case in four. What's shown on the lower -- in the denominator here is a cumulative tally. So this is this plus this. We had no additional cases in category two serologic cases. We had three and one, actually suggesting nonefficacy here, but the -- And category four -- And what I've just shown for the single high titer, again what's in the literature, I've just shown the data for the hepatitis control groups and I only show you this not to estimate efficacy, but it is used in our incidence estimates.

The point estimate of efficacy was 77 to 88. With these lower categories, it drops to 49 to 45. None of these are significant. If you include the one case, they just overlap zero, but there's obviously a strong

trend to protection. But they are significant if you eliminate that one case.

Now, looking at the incidence, same table, but looking at the incidence, looking at the primary case definition, the other categories and high -- single high titer -- Again, there's no data that I'm showing you for AP group here. Let's forget the AP group because they are somewhat protected and focus on the control group. And you can see that our estimate of incidence, depending on case definition, is fairly tight. It's between 3.7 and 8.6 cases per 1,000 person years. That contrasts with two orders of magnitude higher incidence of cough illness or -- and I've projected these taking the U.S. population of 15- to 65-year-olds, using these incidence rates, as to how many cases of pertussis occurred, not in children, but in individuals 15 years of age and older, an additional disease burden, and that somewhere between 674,000 and 1,500,000 cases per year in the United States. I didn't present all the morbidity, but all of these cases had a prolonged cough and significant morbidity

associated with them.
Obviously, one of our limitations was number of cases, but I do think we were able to estimate incidence and at least trend on efficacy. This is an important slide. This is the same slide you've seen before, but now looking at the proportion of individuals with primary case definition -- It would be a little bit higher if I used the probable or suspect cases, but overall, looking at stratification of duration of cough, it varies from about one percent to six percent of those cough illnesses are due to pertussis. That would be the fraction that might be prevented with acellular pertussis vaccine.
Now, we have a number of analyses that are pending, particularly the single high titer, which will take us some time both for incidence and estimating efficacy. However, from the data I've seen on the probable cases, they tend to dilute the finding that they -- they tend to show less efficacy rather than more efficacy.
There's a number of other issues relating to the serologic criteria, para-pertussis PCR on the specimens

we've collected; some CMI studies; doing survival analysis of efficacy; and importantly, I should present to this group the studies that are currently being conducted under company sponsorship of disease burden in cough illness which might be relevant to your decision. It seems to the investigators in the APERT trial that there's three general approaches that one can take probably for. The first option would be to do nothing and just continue an infant immunization program. Another option would be to routinely immunize adolescents at their middle school entry, at 10 to 12 years of age, by incorporating AP into the small DTP recommended booster. Another approach would be to do that in addition to routine boosters in adults. And the third approach would be some combination of high-risk implementation. These would be older individuals that would have potentially some risk, either to themselves or to young children in their households. And one that's particularly interesting would be to immunize parents to protect their children, which has a number of connotations and implications to the ACIP.

Not only children and older siblings but perhaps grandparents or aunts or other members in the family where there are young infants that might be incompletely protected from pertussis. Similar thinking with day care center teachers and staff or medical personnel, nurses and doctors. I think one could justify, given the significance of the clinical and cost data, considering asthma, CF, and other cardiopulmonary or immunocompromising conditions and outbreak control.

I think the key variables that are needed to complete this analysis -- and there is an international group of economists working on this -- is, of course, the incidence of pertussis in older individuals, and I do believe that the APERT study has come up with the best estimate prospectively of the incidence of disease and the proportion of cough illness due to pertussis. APERT did not assess secondary risk, but there's a considerable amount of data in the literature looking at secondary transmission. We do have data on morbidity, duration of illness, and costs associated

with medical care and loss of work and other indirect costs. Although the efficacy was not significant, including the primary case definition, there's a very strong trend and the point estimates are consistent with the data in young children. And I can think of no reason why the efficacy would be any less in an adult than it would be in an unprimed child, but we cannot say anything about duration of protection.

Obviously, there's issues of cost of implementation and practicality and whether the public would accept such an issue. I just listed on this slide some of the considerations in this multi-national cost-benefit team that Glaxo SmithKline has put together to try and address these in a model that are being assessed from visits to indirect costs to secondary transmission issues, presupposing certain transmission rates and secondary prevention in the community.

So, in conclusion, I really have three sets of conclusions. First, epidemiologically, the incidence of cough illness is enormous in our population, but pertussis accounts for only one to seven percent of

that. The incidence of pertussis cough illness in adolescents and adults is between four and seven cases, depending upon which case definition one uses. They're fairly tight, I think, in that incidence rate. That I think is somewhat less and quite a bit less than has been reported in the hospitalized case reviews which used less stringent study criteria and were not prospective. They were retrospective assessments. This does represent a significant disease burden if you are to project it to the whole population of close to a million cases per year.

Culture and PCR, under the best of circumstances, is relatively insensitive even in individuals at day five of cough, which implies that the infection may occur some number of days or even weeks prior to the onset of cough. And of course, we can't detect that clinically and that's a subject of a number of proposals being considered by NIH currently to do some human challenge studies to evaluate the natural path of physiology of pertussis, which is really not completely understood. I haven't gone into a lot of data on serologic

responses. It is complex because adults and adolescents are primed. They're not virgin to these antigens, and interpreting what is a specific and a nonspecific response is a little tricky and that has some implications diagnostically.

Now, with regards to safety and efficacy of the vaccine, I do believe this vaccine is safe for adolescents and adults. There were no serious AE's, and although we did find significant differences by sex and between the two study groups, I think they're all in a range of five, eight, ten percent, and none of them were severe in nature.

I think the trivalent AP vaccine reduces disease incidence, although our point estimate is not very precise. I have no reason to believe that this data is not totally compatible with the data in children, larger trials, and we have no doubt on duration of protection, nor do we have any data on secondary transmission.

Lastly, the implications that this committee will have to consider is the comparability of this data, which I

think is about the best that one can get from a clinical prospective trial -- I'm not sure what other types of trials could add much to this, but I think it's compatible, comparable, perhaps absolutely identical to the data in the seven infant trials that have been conducted previously. Immunizing adolescents and adults might not require much incremental costs. If it meant adding one antigen to a pre-existing vaccine, obviously it depends on the price of that vaccine. There is a detail cost-benefit analysis being done by economists in Europe, Canada, and the U.S. that has been pulled together by one of the companies, and there are several approaches that you could consider. First of all, I think there's -- if the marginal costs are small, I think routine adolescent immunization with a DTaP would be relatively easy and provide some significant benefit. Immunizing older family contacts of infants is something that might be very useful and could be justified to protect young infants who might contribute the majority of significant morbidity, hospitalization, and death.

And I think another target population of asthmatics, EF, immunocompromised, or other collections of -- is another strategy or some combination of these four. That's it. Thank you.

DR. MODLIN: Joel, thanks. Let's open this up for questions and comments from anyone. Walt?

DR. ORENSTEIN: Joel, from looking at your age distribution, you had quite a few patients that were fairly old. I am concerned that this illness has always been looking at younger groups. When you look at your nine cases, for example, in the hepatitis A group, what proportion of them would have been under 20, or are they fairly evenly spread through the whole age spectrum?

DR. WARD: Well, in our primary analysis, it was nine and two, and they're fairly evenly spread, Walt. I would have to look at it. It was at my desk. I don't have a slide of it. They weren't all in the older -- I can --

DR. ORENSTEIN: Or younger, is what I was wondering about.

DR. WARD: There were cases in all of the age ranges. I don't know if nine or 11 cases -- There clearly wasn't occurring in just the adolescent or just in the mid-range or just in the elderly. There were cases in all three.

DR. MODLIN: Dr. France?

DR. FRANCE: Along those same lines, was there any lumping between the health care workers versus community workers, versus your third group, I think? So did more of the cases fall among health care workers than people who were enrolled from the community?

DR. WARD: I don't believe that there were. They were in all three groups also.

DR. MODLIN: Paul?

DR. OFFIT: Joel, would you -- do you have any data or do you care venture a guess on how long you think immunity, protective immunity, would last following a boost in adulthood or adolescence? If it were said another way, how many booster doses do you think would be required?

DR. WARD: Well, the data that we are collecting, and

it isn't fully analyzed yet, is we do have two years of data after immunization. So we have a good estimate over two years on the decay rate for each of the significant antigens by class, at least Gm -- Ga, and we are doing M now. So I will have that. There is a significant decay over a year in the data I've seen. You know, it's less than half, probably more in the range of 20 percent, and there is a difference by antigen. Some of the antigens decay much faster than others, but I need to pull that together and I don't have it today. But that would just be over a two-year period. I wouldn't have a ten-year period.

DR. MODLIN: Marty?

DR. MYERS: Two questions, Joel.

Did both vaccines contain alum adjuvant?

DR. WARD: Yes. And they were monovalent. They weren't -- It wasn't an aPDT. It was a monovalent -- It was a trivalent aP product.

DR. MYERS: The second thing is a separate question. I know you excluded pregnant women from the study, but you also had 60 women who --

DR. WARD: Right. But --

DR. MYERS: -- had pregnancies. I was wondering, did you have a chance to look at cord sera?

DR. WARD: No.

DR. MODLIN: Stan?

DR. PLOTKIN: Another vex question. Are you going to have any analysis --

DR. WARD: I would expect nothing less from you.

DR. PLOTKIN: Sorry?

DR. WARD: I would expect nothing less from you.

DR. PLOTKIN: Well, I'll pass over that. Are you -- Do you think you're going to have any data on correlates or protection in your cases?

DR. WARD: Only anecdotally, only anecdotally by case. I have looked at the onset of illness in time post immunization and some of the cases occurred soon and some of them occurred late. There was no pattern that the pertussis cases occurred only late in the immunized subjects. So we might have some anecdotal (inaudible), not only by level of antibody but pattern of type of antibody. And what we're trying to do and the reason

this will take another year is, obviously, there's 125,000 assays required to draw a pedigrees, a decay pattern over two years for every subject and then look at the occurrence of cough illnesses, for example, in relation to that, as well as the pertussis cases by each of the six different diagnostic criteria. But statistically and epidemiologically and what we had hoped for, we had -- the study was designed with the anticipation that we would have as many as 40 cases. And even though the trial was extended an additional six months, in the primary case definition category, we really only have 11.

DR. MODLIN: Joel, you cast your net pretty widely by using a case ascertainment definition of cough for five days. I'm sure you well know some of the earlier studies say in emergency room settings and so on have used cough illness for two weeks as a -- not a case definition, but for screening purposes, for identifying cases. I guess the question is, for those that had a positive confirmed diagnosis, clinically, were they any different than -- did they tend to have longer duration

of cough? What I'm getting at is if you were to tighten up the case definition where it would make any difference in terms of outcome -- I suspect that it probably would not, but --

DR. WARD: It's hard to do what you're saying with only 11 primary cases. But there is a tendency for these cases to be quite ill. I remember one 65 days of cough, another 45 days of cough, another 35 days of cough. Almost all of them were more than 14 to 21 days of cough. I was impressed with the duration of cough, the number of times that they went in for medical care, and some of them were treated. Actually, I don't have it off the top of my head, but I suspect at least half of them were treated with erythromycin or chlorythromycin. So these would be aborted cases. I think it is a significant illness, and that's something that will be looked at by this cost-benefit group to try and cost out and look at that, as well as data from the literature.

I guess I went into this trial not having been an exhaustive pertussis researcher, although I've always

enjoyed the topic. It's an issue of dogma, and dogma drives so much of our science and case definitions, and we try to attack that, both serologically as well as clinically, and I felt that the need for prospective evaluation, rather than fulfilling a presupposed idea that pertussis is x disease when there's almost no data anywhere in the literature and there's plenty of anecdotal data from trials where people are carrying the organism asymptomatically and people don't know what proportion -- In fact, years ago, you know, it was thought -- there was no such thing as an asymptomatic carrier, but that's clearly not true. I thought -- And a lot of my dogma was rejected. I thought for sure the PCR, which was highly maximized for sensitivity, cross-checked with labs in Europe, would pick up a higher proportion of cases and it didn't.

DR. MODLIN: Yes, Natalie?

DR. SMITH: Joel, one question. Just what you said on PCR, without limiting the number of cases, could you comment on how much we can generalize that to public health practice? A lot of areas are moving to PCR only

and a lot of areas don't do serology at all.

DR. WARD: Well, nearly all -- except for that one case, all of the cultural-positive were PCR-positive. So it did detect the cases and there were no false positive PCR's in that there were no PCR-positives that had no serologic evidence of disease.

DR. SMITH: I guess on one side it said relatively insensitive culture --

DR. WARD: Only that it didn't -- it didn't bring the iceberg down --

DR. SMITH: Okay.

DR. WARD: -- and I didn't detect an additional 50 percent more cases. That's what we were -- You have to understand that, you know, some of the literature sites 15 to 35 percent of cough illnesses lasting 14 to 21 days is due to pertussis. I personally do not believe that. And within my own investigative group, there are strong differences of opinion about this, and amongst the investigators. But our data, I think, is clear and irrefutable that it's a much smaller proportion.

DR. MODLIN: Further questions or comments? Yes, Dr.

Cheek?

DR. CHEEK: Jim Cheek.

It seems like one of the things that I'm faced with, and I think a lot of the state people working out in the field are faced with, is a community-wide-type outbreak that comes and it lasts for weeks and weeks and it may have been going for three or four months before we ever even hear of it. And this is the thing that happened -- In fact, just at lunch today, I got an e-mail about a new pertussis outbreak that's just starting in one of our reservation communities. And I'm wondering if that might be a setting that it would be useful to try this as a control measure or whether it would be possible to even measure efficacy in such a setting as that.

DR. WARD: Well, that's why I included it on this slide of targeted high-risk populations because I was aware of those occurring. I don't know how you could study that prospectively because you would have to immunize different populations with different strategies and then wait for that outbreak to occur to assess it. So

it would be a tough thing.

DR. MODLIN: Dr. Severyn?

DR. SEVERYN: Dr. Kristine Severyn, Vaccine Policy Institute.

Dr. Ward, if you tease out the smokers, do you see any difference in efficacy between the hepatitis A and the pertussis groups? Because you were talking about that the smokers confounded the results.

DR. WARD: Yes. What they confounded was the occurrence of cough, not the occurrence of pertussis.

DR. SEVERYN: Okay. And you don't have any data on what the pertussis incidence was with no vaccine, that is, no hepatitis A or --

DR. WARD: That's what I presented to you.

DR. SEVERYN: Okay.

DR. WARD: All of the data that I presented to you today was from the control group. I purposely did not show you the incidence data from the vaccinated group because it's somewhat less, and I thought since that's a blinded non-immunized group, that that would be an appropriate --

DR. SEVERYN: I guess maybe -- Please forgive me, but the control group was a group that received hepatitis A vaccine, right?

DR. WARD: And not pertussis.

DR. SEVERYN: Correct. And then one group received pertussis vaccine. You do not have a group that received no vaccine that you looked at pertussis incidence -- pertussis disease incidence?

DR. WARD: What would your thinking be about how hepatitis A might --

DR. SEVERYN: Well, we talked -- I don't want to beat a dead horse here, but we talked last meeting about the problems with running vaccine studies with actually no control groups, where you run -- the control group is actually a vaccinated group but another vaccine. So the point is, we really don't have any data on what the incidence of pertussis would have been --

DR. WARD: The reality is that most people don't want to enter into trials that they don't perceive some benefit. And we did -- we had an independent committee to pick the vaccine and to pick the control. The

investigators did not pick them and there were pilot studies doing testing of potential recruits as to what it would take to maximize recruitment, and that was a requirement. And there's certainly no scientific data that I'm aware of to think that hepatitis A would, in any way, influence the incidence of pertussis in a blinded trial.

DR. SEVERYN: Thank you.

DR. MODLIN: Bill?

DR. BRUNELL: Joel, I would like to ask one other question about your data and the periodicity of pertussis.

If you go back to the Massachusetts data in '93 and '94, they had quite a blimp in their cases. I don't want to get into their data and your data. I also want to congratulate you on doing a fabulous study. But in these communities, was there any epidemic pertussis at anytime and could you comment, in general, on how the periodicity of pertussis may impact the study? You're taking a relatively short interval of time to do your study and you may not have gotten into an epidemic

period.

DR. WARD: There were -- We were hoping for an epidemic, we prayed for an epidemic --

(LAUGHTER)

DR. WARD: -- and we had projected that an epidemic would occur based upon a three- or four-year cycle and when our study would occur and some of our communities, including California, did have an epidemic coincident with terminating this trial. We would been happy to have had more cases by virtue of an epidemic, but we didn't observe that in any of the study sites, although they were not under active surveillance. This represents the cases in time and what you can see is the date of the confirmed cases in red, and this is time and date. So you can see the cases -- This is anecdotal because we -- you have to throw out these bottom two, but you can see they're occurring at all times of the year, at least anecdoctally, and they were also looking at the interval from the time of immunization, which is in the blue, to the time of onset of disease, and here's a case about six weeks

later and then obviously here's a case two years later. So there's really no clear pattern.

So, at least in this small number of primary cases in adults, it doesn't seem to be a striking season. I don't know, but maybe you could say there's some cluster here which is between July and February. We'll look at that in some more detail.

DR. BRUNELL: Talking about periodicity, in terms of three- and four-year cycles, you happened to get in between, but what you're saying is that some of these communities actually did have --

DR. WARD: We asked the investigators to be in league with the public health officials, and actually, the rationale for extending the trial the extra six months was that Dr. Cherry and a number of other investigators were absolutely convinced that there was a going to be an epidemic in the fall because a number of studies have implied a fall peak incidence. So it was extended from August till January of that final year, but there were, as you can see, only one additional case.

DR. MODLIN: Rich, I guess the question is, what is the

next step now that we have data from the trial? It probably would be worthwhile spending a minute or two discussing that with you and the adult working group and with the other members of the Committee. Maybe I'll start with your thoughts. Joel has presented some thoughts, some options.

DR. CLOVER: Well, Joel promised me all the answers. I think there are several things. The Committee talked briefly yesterday about taking the data that Joel presented and working through it. I mean, I think there are some issues of note. One is the projected annual incidence of this disease. The Committee has interest or concern about the data that CDC has with regard to the infant cases that seems to be occurring from parents in the household, being transmitted to them, and you know, unfortunately, this study was not designed to look at transmission within -- within households, but I think that's an issue that we've got to address.

We would be interested in the cost analysis as well. But I think it's up to the Committee to digest this and

think through it before I can make any other recommendations.

DR. MODLIN: Yeah. Joel, do you think the plan cost analyses will be done in the next couple of months or -- I'm just trying to get a sense of what -- not pressing you to do them but, on the other hand, get a sense of where we should be putting this on our timetable.

DR. WARD: I've been impressed that this is an international interest. There's a group in Europe that is very focused on whether they should implement -- I think one country, Germany, had implemented routine adult or adolescent immunization. Indeed, I think Ciro is gone, but I think that there is some question about whether it should be implemented in Latin America also and the Canadians, of course, have always had a strong focus on pertussis given their disease burden in the past.

So there are groups independently that Glaxo SmithKline -- Is that right? That's a new name -- linked together and they're trying to review the literature, do some

modeling, pull data from APERT to come up with some projections and I think -- Could you comment on what the time frame of that --

DR. HOWE: I would think that -- Barb Howe from Glaxo SmithKline.

I think that we would probably have that in time for the fall meeting rather than during the summertime. So I wouldn't target before then for presentation of this data.

DR. MODLIN: Since the adult working group is meeting on a pretty regular basis, at least by phone, I think it might this is something to add to the agenda to move along, as I'm sure you're doing already. And maybe we should -- we can touch base, but whether or not we ought to have some initial thinking about this on the June agenda -- Already the October agenda is beginning to fill up, but we need to think about this a little bit more --

DR. WARD: It might be possible --

DR. MODLIN: -- but we do want to keep the issue -- Well, I'm trying to get a sense of how we keep this

issue in front of us.

DR. WARD: It might possible to not do things in series but in parallel such that the Committee -- I think Hughes Bogart [phonetic] is the coordinator for that group and you might want to contact him and see where they're going and what data is being developed. I mean, you could do your own independent assessments. I think there's just four or five key assessments. You would do those assessments and you can, I think, come up with your own answers from a non-economist saying that.

DR. MODLIN: Trudy?

DR. MURPHY: Yes. The working group may already know, but CDC is planning studies looking at the source of disease in infants and also some cost studies -- burden of disease.

DR. MODLIN: Okay. Melinda, do you have anything else to add?

DR. WHARTON: No. We just wanted to make sure that the Committee was aware that we are planning studies focused on looking at the cost of disease, primarily

for pertussis generally, but with the hope we get some information about adolescent and adult cases, as well as to explore further the risk factors for disease among young infants. It's actually been quite difficult in the routine surveillance data to ascertain source of infection. When one can't ascertain it, it frequently is a household member or other family member. But, you know, in a fair proportion of cases, in fact, we can't identify the source of infection. So we are planning a risk factor study.

DR. MODLIN: Bob?

DR. CHEN: Joel, in the recent NIH pertussis meeting, several of the European infant AP trials managed to do some type of long-term follow-up for efficacy. Is there some way to continue monitoring for efficacy even though the trial has officially ended?

DR. WARD: No. I'm afraid it won't be possible to do that. I think it -- it was such an intensive prospective that required collection of specimens and clinical evaluations and they were really a recruit population as opposed to a captured HMO or a database

that you could monitor. I suspect one could do phone calls or track back to them, but you wouldn't have any microbiology or serology, although you might be able to collect a later blood and compare it to the last one in the study. It would be an order of magnitude difference in the quality of kind of study. So nothing -- there hasn't been any discussion about that.

DR. MODLIN: Joel, thanks very much. Let's go onto the next item on the agenda which will be an update on hep A vaccine activities. Is Dr. Bell -- There she is. She'll be leading the discussion.

Just to remind everyone that we did make a change in our hepatitis A immunization, a major change. We made a major change about a year and a half ago. And I assume, Beth, this is an update on where -- what the impact has been so far?

DR. BELL: Good afternoon.

As Dr. Modlin says, what I would like to do this afternoon is take a little bit of time to give you an update on where we are with hepatitis A vaccination and also with hepatitis A incidence and try to give you a

sense of potentially what the impact of recommendations for routine hepatitis A vaccination have been.

Just to remind everyone, our strategy has been for incremental implementation of routine hepatitis A vaccination of children, beginning with the ACIP recommendations in 1996, for a vaccination of children living in so-called high-rate communities such as, for example, the American Indian and Alaskan Native communities, and continuing in the recommendations in 1999, extending routine vaccination of children to those living in states and communities with consistently elevated of hepatitis A, with the idea eventually that we might be moving towards vaccination of infants nationwide. So what I would like to do is spend a little bit of time talking about routine vaccination of children living in high-rate communities and then routine vaccination of children living in these areas with consistently elevated rates.

As a reminder, the ACIP in 1996 recommended that children living in high-rate communities should be routinely vaccinated at or after two years of age and

that there should be catch-up vaccination with priority given for children before school entry and finishing this catch-up vaccination within five years of implementation.

Over the last year or so, we've been surveying and doing a number of studies to try and get a sense of what's been going with hepatitis A vaccination in these high-rate communities, and I'd like to show you some data from American Indian and Alaskan Native communities as an example of these high-rate communities. This was a survey that we did in 1999 in collaboration with the Indian Health Service of providers at all Indian Health Service facilities in the United States. And of the 79 facilities that responded, 92 percent reported providing vaccination to preschool-age children; 64 percent reporting providing vaccination to school-age children; and we asked the providers to estimate their coverage of preschool-age children, which they fixed at about 60 percent.

Now, this last summer, also, once against, in collaboration with the Indian Health Service, we

reviewed charts of almost 2,000 children from all the Indian Health Service facilities and a large reservation in the southwest in order to determine hepatitis A vaccination coverage of children aged four to seven years. And as you'll note here, if you first look at the first column, of the -- of the 1,900 or so charts that we reviewed, 79 percent of children had received at least one dose of hepatitis A vaccine. 53 percent had completed the series. We also looked at the proportion of children that have received their first dose of vaccine by 36 months as a sort of indicator of timeliness of vaccination, and if you look across this row, you'll notice that the younger children, in other words, the four-year-olds, 61 percent of them had received their first dose by 36 months of age, suggesting that hepatitis A vaccination is being incorporated into routine well child care in these facilities on this reservation.

Now, one of the obvious things that we are most interested in is how is this reflected in disease incidence, and I would like to show you a number of

slides of surveillance data, which addressed this question.

This is hepatitis A incidence actually in the counties that include the majority of this reservation from -- in which we just did this coverage survey which showed 80 percent coverage among four- to seven-year-olds. And you'll notice that in this community, beginning in the late 1980's, there were these two very large community-wide outbreaks with an interepidemic period of approximately five years. Should we -- If we were to assume a similar outbreak with a similar interepidemic period, we would have expected to start to see an upswing in cases here in 1999 and 2000. And in fact, we see this continued decline in the number of cases and, actually, there were only two cases reported from this entire area in 2000 using the provisional data.

Now, we wanted to look at this on a somewhat larger scale and the next couple of slides illustrate that. This is American incidence -- hepatitis A incidence among American Indians and among non-American Indians

living in 15 rural counties in the United States that include reservation communities. If you first look at this figure in the lower left-hand corner of the slide, you'll notice that in the early 1990's through the mid-1990's, American Indian cases shown by the yellow line here were significantly higher than non-American Indian cases shown in the pink line, with the difference in rates reaching many-fold during an outbreak time, but even during this time period, this is a difference of something like 70 per 100,000 compared to 10 or 12. If you now just turn your attention to the upper figure in the slide, which just takes 1996 to 2000, putting it on a different scale, you notice this precipitous decline in American Indian cases beginning in -- with 1997 and continuing through 2000 such that during these last few years, the hepatitis A incidence among American Indian in yellow has been below that of non-American Indians living in the same communities. This represents a rate of one per 100,000 compared with 14 per 100,000. This is a phenomenon that I don't think that we've observed during the time that we've been

keeping track of such things.

Similarly, we looked at incidence among American Indian and non-American Indian residents of five large urban counties that include fairly large American Indian populations and we essentially see a similar trend, which maybe is not quite as dramatic, but nonetheless is telling us the same story: much higher rates among American Indians in the early 1990's, with this precipitous decline in the late 1990's, and provisional data from 2000, rate among American Indians in these cities is three per 100,000, six for non-American Indians.

Just one more way to look at this. This is overall hepatitis A incidence in the United States and among American Indians during this same time period. The United States is in pink, once again American Indians and Alaskan Native are in yellow. And we see this drop in hepatitis A rates. And in 2000, overall, the overall rate among American Indians was lower than the average over our U.S. rate for the country.

So, in conclusion, I think that these data have shown a

dramatic decline in hepatitis A rates among American Indian and Alaskan Native populations, in fact, transforming in a certain way the epidemiology of hepatitis A in these populations. Now, clearly, we need a few more years of data to put this into context given the cyclicity and periodicity of hepatitis A incidence, but I think that some of this information is quite compelling. We've seen a decrease in both urban and rural reservation areas, although perhaps more marked in rural areas. We've seen that children using -- at least Indian Health Service facilities are getting vaccinated, although I think that there's a need for additional coverage surveys. And we certainly need better information from non-Indian Health Service facilities, realizing that 50 percent of American Indians are not cared for in Indian Health Service facilities and live in urban areas and also from other high-rate communities.

Now I would like to turn our attention to the second phase of this incremental implementation of routine hepatitis A vaccination of children and just review the

epidemiologic foundation of this strategy, which was based on our observation that specific states and counties could be identified that had consistently elevated rates of hepatitis A and that disease from these areas accounted for the majority of reported disease and that our surveillance data indicated that these elevated rates persisted over time.

On this county-based map of hepatitis A incidence here, what we have done is calculate the number of years during this period of 1987 to 1997 when the rate in the county exceeded the U.S. average of approximately ten cases per 100,000 population. And these sort of data formed the basis for the ACIP recommendations in 1999. You can see that the areas with these elevated rates are clustered in the western and southwestern part of the country.

So by way of review, the 1999 recommendations called for routine vaccination of children in states and communities where the average annual hepatitis A rate during this time period was at least twice the national average and for consideration of this routine

vaccination in areas where the rate was above the national average but less than 20.

The other point actually to be made here is that these recommendations were approved for use of vaccines for children in the VFC program in 1999 and that was what I was going to show on the next slide, data that were provided by the National Immunization Program. It shows the number of pediatric hepatitis A vaccine doses purchased through the National Immunization Program by year from 1996 to 2000, and you'll note this large increase in the number of doses in 1999 coincident with the extension of the children for whom VFC vaccine could be used and an even larger increase in the number of doses purchased in 2000. This is almost three million doses of hepatitis A vaccine purchased from the National Immunization Program in 2000. The vast majority of this vaccine was purchased through the Vaccines for Children program.

Now, the 1999 recommendations on the statement did have a few things to say about implementation, and I wanted to review those with you for a moment. The statement

suggested that in states with rates at least twice the national average that there should be routine vaccination of children statewide, that in the states with rates less than twice the national average, there needed to be some discussion of what the most feasible way to implement routine vaccination of children might be in view of the epidemiology. And the statement was quite permissive in terms of the types of strategies that might be used to implement routine vaccination, including vaccination of children or adolescents, one or more single-age cohorts vaccination in selected settings such as day cares, or just vaccination of children when they appeared for routine health care. On this map is shown the states that fell into these various categories. Shown in red are the 11 states with rates at least twice the national average during this time period; and shown in blue are the additional six states with rates that fall within this 10-to-20-per-100,000 category. And I was going to show those data about vaccine doses purchased according to these 11 states and then these 17 states, keeping in mind

that the VFC program will cover routine vaccination of children living in these areas.

As I say, these are the same data, and the message here essentially is that there is large increase in the number of vaccine doses purchased in 2000 and that essentially all of the vaccine that's -- pediatric vaccine that's being purchased is being used by these 17 states covered by the recommendations. The rest of the United States, this is 150,000 doses or less.

Last summer, we surveyed all the state health departments to ask them what they were doing about hepatitis A vaccination. I've summarized some of the information from the 17 states that were included in the '99 recommendations on this slide. You'll note that 15 of the 17 states were making provisions for providing hepatitis A vaccine for routine vaccination of children in some fashion or another in their state. And this was primarily what the states reported, that they were making it available to VFC providers through the VFC program. In nine of these states, vaccine was available through the VFC program statewide. In the

other states, there were various methods being used for focusing these efforts primarily related to identifying counties or other geographic areas with rates that were above the rest of the state.

Five of the states reported that they were specifically targeting a particular age group and this primarily involved children two to five years of age or children in day care. And in three areas, there were some other methods mentioned particularly targeting areas with large American Indian populations. There were four areas that reported a requirement for hepatitis A vaccination. This includes the state of Oklahoma, the state of Alaska, and a day care requirement in one area, and a requirement limited to certain counties in another state.

So what has been going on with hepatitis A incidence in the country in the face of the amount of hepatitis A vaccination that's been going on in these 17 states in response to the 1999 recommendations? Well, this is one way to look at this. This left-hand figure here shows hepatitis A incidence starting a very long time

ago. And you notice there are these periodic outbreaks occurring the 1950's, '60's, and early 1970's. I've taken the incidence from 1980 to 2000 and put it on this upper slide to make clear that's been going on with the different scale. You notice there is this peak in 1989 and then another smaller peak in 1995 to 1997. And since then, we've seen this precipitous drop in hepatitis A incidence to levels that are well below historic averages. The 1999 rate was 6.2 per 100,000 and the provisional rate for the year 2000 is 4.5. The lowest rate ever reported in the United States previously was a rate of 9.1 in 1992.

Looking at this a little bit more closer, I've calculated the average hepatitis A incidence rate in the 11 states in which routine vaccination of children was recommended statewide, and we see more or less a similar story here, peak in 1989, smaller increase in the early to mid-1990's, and this sort of fairly marked downward trend beginning in 1998 with a rate of 8 point -- I don't remember -- 2 or 3 in 1998, and falling to a rate of five in the year 2000 in these 11 states. And

this difference is even more remarkable. This rate of five should be contrasted with the previous low in these 11 states of approximately 20 per 100,000.

I wanted to just spend a couple of moments on a demonstration project which gives us a little bit of a snapshot into what we might expect in the next few years. This is a demonstration project which provides us with the longest period of follow-up with routine children hepatitis A vaccination. This is a demonstration project that was carried out in Butte County, California, from 1994 to '95 to 2000. In this demonstration project, we vaccinated children ages two to 12 years old which, at the time we began the demo project, was approximately 30,000 children in a county with a population of approximately 200,000. The project featured providing free vaccine to all providers in the county and available to all children regardless of whether they were VFC providers or VFC-eligible. Vaccination occurred both in provider offices and particularly at the beginning of the demonstration project in school-based clinics. The

county maintained a vaccination registry which provides a fairly accurate minimum estimate of vaccination coverage, and also the county has been conducting active surveillance, including laboratory-based surveillance for hepatitis A cases in the county. The 2000 vaccination coverage was 62 percent for the first dose and overall 40 percent vaccination coverage in this target population which aged with the demonstration project. So by 2000, it included children ages two to 17 in 2000.

Here is hepatitis A incidence in Butte County. You notice that Butte County also has periodic outbreaks, but the interepidemic period is longer than what we have seen in some American Indian communities. This interepidemic period is approximately ten years or so. The vaccination program was begun in the middle of 1994, and since 1997, we've seen this drop in the number of cases in Butte. There was one case -- no, two cases reported in 1999 in Butte County and four cases reported in 2000. This -- These rates, '98 through 2000, are the lowest rates that Butte County

has ever seen.

Now, in interpreting the meaning of these kinds of epidemiologic pattern was confounded by this fact that we don't know whether this is just the bottom of an interepidemic period or represents a true change in the epidemiology of the disease, and I don't think that we're going to be able to answer that definitively in Butte County even now. These data, however, I think are somewhat interesting in that regard. Hepatitis A incidence in Butte County -- in two contiguous counties right next to Butte, Sutter, and Yuba counties, and then over on the state of California, in 1996, a year and a half or so after initiating the demo project and then in 2000, in 2000, the rate in California was 9.2. This rate of 1.9 in Butte County in 2000 is not only the lowest rate ever reported from Butte County, but also was the lowest rate of any county in the state of California in the year 2000.

So, in summary, I think that national hepatitis A rates are at historic lows, but we need to monitor this to put it into some kind of context because of the well-

recognized cyclicity of hepatitis A incidence in the country. The ACIP recommendations are being implemented and we've seen considerable progress with areas using many strategies primarily involving voluntary measures. We certainly need continuing evaluation to see who's doing what and what's working and what's not working.

The thing challenge over the next few years is going to be to sustain ongoing vaccination in the face of falling rates. We've found, speaking to parents, speaking to health departments, speaking to providers, that one of the most important determinants of interest in hepatitis A vaccination and acceptance of it is how much disease there's been in the area in the recent past. And as the rates drop, I think this is going to become much more of a challenge.

I just wanted to take one moment to look farther, farther into the future and say one or two things about our longer-term hepatitis A prevention strategy. I think we're likely to see continuing lowering of disease incidence as we essentially interrupt household

and extended-family-setting transmission by essentially catch-up vaccination of children in adolescence. But I think we've already seen in Butte County, and actually in many other places, that transmission between adults and high-risk groups can be sustained quite happily without involving children in this transmission at all. And there's always other forms of transmission, food-borne transmission, for example. So I think that if we do get to a point where we want to further reduce incidence or even eliminate transmission, we're going to eventually have to address the issue of vaccination of adults and high-risk groups and truly implement routine vaccination of infants and young children, which is going to require us to have a vaccine that can be used in the first year or two of life.

Thanks.

DR. MODLIN: Beth, thanks very much. It's always nice to hear good news.

Let's open this up for comments and for questions. I would assume that the incidence of disease that has dropped over the last few years has been mostly in

adults, although you really didn't present any specific -- age-specific data.

DR. BELL: Yeah. Actually, the incidences dropped in all age groups.

DR. MODLIN: All age groups. Rich?

DR. CLOVER: In follow up to your question as it relates to the incidence in adults, do you have any numbers on the percent of adults who have been vaccinated either because they're in a high-risk group or just because of international travel?

DR. BELL: No. It is really hard to get a sense of that at all. I will say that in a number of outbreaks -- And we've been involved in outbreaks among adults, men who have sex with men, users of illicit drugs -- we have, in general, found vaccination coverage to be appallingly or extremely low and it's been quite difficult for communities to find strategies to improve that. So, for example, we investigated an outbreak among men who have sex with men a couple of years ago and we did a case-control study, and we asked the controls about hepatitis A vaccination and it was, you

know, maybe two percent of them that said that they had been vaccinated. It was interesting because the vast majority of them did have a provider -- did see the provider at least once a year, had even disclosed their sexual preference and said they would have been quite happy to have received hepatitis A vaccination if it had been offered to them. I think that there are a fair number of adults that are getting vaccinated in travel clinics, but I think that most of the adults that are getting vaccinated are travelers.

DR. MODLIN: Yes, Dr. France?

DR. FRANCE: You showed us an interesting slide with the reduction in the nation of hep A incidence and then the specifically the 11 states. If you looked at the 33 states where there isn't much recommendations on using them, is there also a decline?

DR. BELL: There is a small decline but, you know, in general, there isn't much disease in those areas. So there's a -- there kind of a lot more year-to-year variation. It's not very remarkable.

DR. MODLIN: Stan?

DR. PLOTKIN: This is a theoretical issue but, of course, very practical in a sense. Are you doing seroprevalence studies and modeling in terms of estimating the possible increased risk for adults as you partially vaccinate the child population? I mean, I think it's remarkable that with 60 percent coverage you seem to have more or less interrupted transmission, and that may be sufficient, but have you considered doing additional studies on that point?

DR. BELL: Well, I think first of all, maybe with 60 percent coverage I'm not sure that we have completely interrupted transmission. You know, I presented some of those data from Butte a while back and actually what we saw, particularly in '95 to '97, was a marked decrease in rates in the vaccinated age groups and not as much of a decrease in rates among adults. And actually, what we were seeing was an outbreak that was involving adult-to-adult transmission among users of illicit drugs.

So I think as I was trying to say, I don't think that we have completely interrupted transmission by this

kind of vaccination. Certainly, I think that the issue that you raise is a very important one and we have kind of ongoing national prevalence surveys certainly and have been thinking about doing some prevalence surveys in some of these areas where a lot of this vaccination has been occurring.

DR. PLOTKIN: Well, actually what you just said disturbs me more, because if you have an interrupted transmission, then the possibility of augmenting seronegativity in adults does become very concrete. And there are several ways of handling that, including perhaps trying to get the states to mandate vaccination of children so that you have further decreases.

DR. BELL: I think, you know, maybe it's important to put this a little bit on context. The prevalence of anti-HIV in the population in this country is -- I mean, the average prevalence is 31 percent according to NHANES III, and the majority of change that we see in prevalence by age group is really attributable to a cohort effect and involves infection that occurred in early children.

So I think that it's going to -- that there is a huge susceptible population of adults in this country, regardless of whether our rate is 20 or our rate is four, and I don't know that given how far down our incidence rate has fallen in this country over the last 50 years that this kind of phenomenon that you are talking about is really going to be a major issue.

DR. MODLIN: Other questions or comments? Dr. Severyn?

DR. SCHAFFNER: Do we have any more information -- Bill Schaffner.

Do we have any more information about the progress to licensure of combined hepatitis A, hepatitis B vaccine?

DR. BELL: Perhaps somebody from the industry would like to comment about that.

DR. MODLIN: Karen, I assume you're got the same comment.

DR. MIDTHUN: Yeah. I think maybe just to add some clarification earlier, when perhaps some of you don't understand perhaps some of the things I can or cannot comment on, and maybe I just give that a little bit of clarity. I'm really not able to comment on the absence

or presence of files that we're looking at. I just can't acknowledge them one or another. So when I say I can't comment in many instances, that's the reason for that. So I thought that might be helpful. And I really can't comment on this particular instance.

(LAUGHTER)

DR. MODLIN: Dr. Severyn?

DR. SEVERYN: Dr. Kristine Severyn, Vaccine Policy Institute.

Could you comment, please, on the cost-benefit ratios with regard to the use of hepatitis A vaccine? I'm recalling an article from *British Medical Journal* within the last couple of years. I don't have the date. I could share it if you're interested. But it specifically says that the use of hepatitis A vaccine in travelers is not cost -- it doesn't have a good cost-benefit ratio. In fact, you lose money giving hepatitis A vaccine to travelers. It's basically just not worth it, according to the study.

DR. BELL: Well, there have been a number of cost-effectiveness and cost-benefit analyses of hepatitis A

vaccination. Among travelers, there have been a lot of them, and I think that the message overall, if you look at the sum total of these studies among travelers in general, the conclusion has been that it is fairly cost-effective, but there are a number of determinants, including the frequency of travel, where the person is travelling to, and how often -- how long they're going to be gone for.

So, as I say, I think there have been a lot of studies on that topic. We have presented data about the cost-effectiveness of routine vaccination here and there. Actually, there is a paper that was published by Jake Jacobson and Hal Margolis and our group on that topic, and Jake actually is going to speaking shortly, and these papers have concluded that the cost-benefit profile for hepatitis A vaccination using this kind of strategy is quite favorable.

DR. SEVERYN: I'll check out the papers. Off the top of your head, do you know if it would include -- was it medical costs or was it this thing about mother staying home from work with their sick children and then

calculating in those costs -- societal costs is I guess what they call it?

DR. BELL: Yeah. I guess, you know, actually, if you want, since Jake is going to be speaking, it might be easiest to have him comment on it.

DR. SEVERYN: Okay.

DR. MODLIN: That's the perfect way to the next item on the agenda, which is cost-effectiveness studies of hep A vaccine programs.

DR. BELL: All right. So this is Jake Jacobs who is with Capitol Outcomes Research, which is a corporation. Jake has done a number of studies of cost-effectiveness of hepatitis A and other vaccines. He has collaborated with us in the past. His work is primarily, however, sponsored by industry. He has -- He is doing a number of new studies and he wanted to share some of the results with the ACIP.

DR. JACOBS: Thank you, Beth. Good afternoon. I appreciate the opportunity to present some of our work in this area. I also wish to note that the two cost-effectiveness studies that I'm going to discuss, in the

interest of disclosure, were both funded by SmithKline Beecham, or now Glaxo SmithKline. I'm also PowerPoint challenged.

In 1999 when this committee approved recommended routine childhood hepatitis A vaccination in communities with high disease rates, only, to my knowledge, preliminary cost-effectiveness data were available. We have since completed two studies which I believe provide more definitive data.

The first examined adolescent vaccination. It was initiated just before the recommendation and therefore looked at a somewhat different geographic area, specifically the ten states with the highest rates or disease rates among adolescents and adults.

The second study assessed early childhood vaccination in the 11 states covered by the recommendation. Thus far, the second, or childhood study, has been only published in abstract form. We do plan a final paper upon completion of ongoing analyses of disease transmission and quality of life, which have not yet been incorporated into the model. I'll briefly discuss

those in a few minutes. In the interest of time, I will focus my attention on the childhood vaccination study, mentioning the adolescent study only if -- if results differ substantially.

As I guess most of you know, the United States spends a lot on medical care, 1.2 trillion dollars per year, which is more than twice the rate as other industrialized countries with similar incomes or economies to ours. Despite this level of spending, our health outcomes are below average for industrialized countries. We rank 21st of 24 countries in child mortality, in infant mortality. We rank 16th in life expectancy. The only country that -- of those 24 industrialized countries that ranks the lowest on both of those measures is Turkey.

There are many reasons for this poor cost-benefit ratio. One is, I believe, that we pay drug companies too much, we pay hospitals too much, we may even pay physicians too much. But another is that we spend -- a lot of our health care spending goes towards low-yield technologies, technologies or medical interventions

that cost a lot and produce relatively little benefit. Prevention programs like a hepatitis A vaccination initiative are designed to reduce disease, not to reduce costs, and that's probably good. Because most medical interventions do not reduce costs to the health care system.

According to a review of more than 300 medical interventions, more than 90 percent increased costs to the health care system. They don't pay for themselves. From a cost-effectiveness standpoint, the requirement is not that medical interventions pay for themselves, but that their costs be reasonable, or at least in reasonable proportion to their benefits. While there's no formal consensus on the issue, the term "reasonable" is usually taken to mean that the intervention provides societal benefit over and above health care cost reduction, say, for example, including the costs of work loss due to morbidity and mortality. Those societal benefits exceeding its costs or, if not, the intervention should cost the health system more than 50,000 dollars -- That's, again, an arbitrary number --

50,000 dollars per year of life saved or per quality-adjusted life year saved.

Most childhood vaccines easily meet these standards. Polio, pertussis, varicella, hepatitis B vaccines each provide benefits or economic benefits exceeding their costs. Pneumococcal conjugate vaccine seems to be the exception, but this analysis is based on the private sector price, which has since been lowered to the public sector. Polio and pertussis vaccines, looking over the cost-per-year-of-life-saved column, are among the medical -- ten percent of U.S. medical interventions that actually pay for themselves for their -- to the health care system. And therefore, their costs are less than zero dollars per life year saved.

By comparison, we have to spend 16,000 dollars to 28,000 dollars on varicella vaccine or hepatitis B vaccine for some child, some vaccinee to live an extra year. Again, the number for pneumococcal vaccine is relatively high. It's based on the higher price. So what must be -- may be a very conservative assumption

of no protective efficacy after age five.
We sought to evaluate where hepatitis A vaccination would fall under these measures using a Markov model to examine lifetime hepatitis A outcomes with and without vaccination. We developed age-specific parameter estimates from a host of sources. Disease incidence rates were based on the CDC surveillance data that we've just seen. Duration of protective efficacy and disease outcomes were estimated based on expert panel review of published literature. Hepatitis A treatment costs were based on our own study of 250 hepatitis A patients, basically a case series where we used Medicare reimbursement rates as the surrogate for treatment costs. Vaccination program costs were based on both private and public sector costs of vaccine and the value of hepatitis A-associated work loss was based on median wages in the United States.
All costs and all benefits, including life years saved, were discounted to their present value using a three percent discount rate. Our endpoints were the ratio to societal benefits to costs, and to the health system

perspective, cost per year of life saved.
Looking briefly at this rather simple Markov model, an individual will enter each year of follow-up either immune or susceptible to hepatitis A. If immune, he may maintain immunity and repeat the process, die of an unrelated cause, or lose immunity if it was vaccine-induced. Susceptibles will most likely avoid hepatitis A infection in any given year, they may be infected in which case we calculated age-specific rates of symptoms, hospitalizations, disease, work loss, et cetera, or they may die of an unrelated cause. And this model was repeated from age two through age 100 years, at which point very few were alive at least within that model.
Nearly 950,000 children are born each year in the 11 states covered by the recommendation, and without vaccination, the upper line of our model would estimate that 4.4 percent would have symptomatic hepatitis A at sometime during their lives, about 41,000 in all. With vaccination, we estimate about a 85 percent reduction in cases to about 6,200.

Looking at some other outcomes, based on the age of infection and work force participation rates at that age, the risk of hepatitis A-related work loss is predicted to decline from 2.3 percent, that is a lifetime risk of missing work due to hepatitis A infection, to 0.4 percent. The risk of being hospitalized for hepatitis A from five per 1,000 -- five and a half per 1,000 to one per 1,000, and the risk of fatal hepatitis A infection would decline from 1.6 per 10,000 to 0.4 per 10,000. To put that mortality risk in perspective, it represents just under one day

of -- well, one added day of life expectancy to each child vaccinated.

Looking at vaccination from a cost-benefit framework, vaccine would cost in a single birth cohort about 26 million dollars. Vaccine administration would cost a similar amount. So vaccination program costs are nearly 50 million dollars. In return, hepatitis A treatment costs would be reduced by about 25 million dollars. Morbidity costs, that is, work loss due to

hepatitis A morbidity would decline 28 million dollars, and mortality costs due to the relatively few fatal cases of hepatitis A would decline 52 million dollars. Therefore, for young children, we estimate benefits of $2.12 for each dollar invested in the vaccination program. By comparison, vaccination of adolescents would provide about $1.80 in value for every dollar. From the health system perspective, again, we have annual vaccination costs of 47 -- or 49.7 million dollars, offset by treatment costs of 50 million dollars. When we compare net costs of the vaccination with longevity gains, we have a ratio of 11,000 dollars per year of life saved. These data describe vaccination of two-year-olds. For adolescents, we calculated a cost-effectiveness ratio of approximately 14,000 dollars per year of life saved.

We conducted at least 30 sensitivity analyses. The few that are shown here had the greatest impact on results. At the lower vaccination costs of the public sector, VFC or government contract prices, cost-effectiveness is about 4,600 dollars per life year saved. But even

at the private sector price, 19,000 per life year saved is within the range of other vaccines.

There are competing estimates about the completeness of hepatitis A reporting. Our base case assumes that about one-third of cases are reported. Last year, Dr. Baylor, along with Dr. Armstrong of the Hepatitis Branch, presented a paper debating that the range was between one-half of cases are reported to one-fifth, and another analysis out of the L.A. County Health Department suggested that they're capturing one in every 5.2 cases.

Even if we assume that one-half of cases are reported, which I think is very optimistic, this is still within the range of an acceptable cost-effectiveness ratio.

Our estimates of long-term vaccine-protected efficacy are for cost speculation. If we accelerate the loss of protection so that none is conferred past 20 years, the cost-effectiveness ratio, again, increases to about 20,000 dollars per year of life saved. And when we substitute the incidence rates of the general U.S. population for the higher rates of these 11 states, the

cost-effectiveness ratio is still within the realm of what most people consider reasonable cost-effectiveness. So if we look forward to a possible widening of that initiative, at this point our estimate is 40,000 per life year saved.

Like any similar exercise, there are many potential sources of error in an analysis that seeks to predict health outcomes over a lifetime. We're in the process of revising -- And I'll just touch on these briefly -- three issues. At this point, we have not considered any of the benefits of reduced disease transmission. All those benefits and life years saved accrued to the vaccine use themselves. We're going to address that. We will reflect, at least in states that have not fully implemented or largely implemented hepatitis A vaccination, the more recent data, the lower infection rates over the last two or three years, and we are examining the value and quality-adjusted life year terms of preventing nonfatal hepatitis A.

The transmission issue is being conducted by summarizing the results of six studies of families with

hepatitis A. In four of those studies, the immunity status of household contacts was ascertained upon identification of an index case of hepatitis A. Susceptibles were then retested at least twice to determine whether transmission occurred. Two other studies used basically the same model, but the outcome measure was development of overt disease rather than seroconversion and the denominator included immunes as well as susceptibles. We've combined the age-specific transmission rates from these trials with census data describing household size and age composition and NHANES data indicating the proportion of members who would be susceptible to hepatitis A. And if we look at the vaccination of the 11-state birth cohort of 948,000 individuals, vaccination will prevent nearly 10,000 hepatitis A cases just among family contacts of those individuals, about 40 percent as many of for vaccinees themselves.

Again, we will, in our final paper, assess more recent hepatitis A rates, including the lower rates. As you can see, if we used more recent data, even for the

period 1998 through 2000, hepatitis A vaccination appears to meet at least conventional standards of cost-effectiveness.

And probably limiting or leaving the last or the most difficult issue for last, we're collecting the data necessary to evaluate the prevention of nonfatal hepatitis A infections in terms of quality-adjusted life years. The figure to the left displays selected utility scores, essentially a value of living at any given health state on a zero-to-one scale. Moderate acne is considered to be a whole lot worse than perfect health. Recovery from a bone marrow transplant, at least in the short-term, is considered low. There are numerous estimates for utility estimates for chronic liver disease but none for hepatitis A. We are obtaining these data through something called the time tradeoff technique, that is how much of your life expectancy, if any, would you forego to avoid hepatitis A symptoms. We've analyzed just at the time of the slide maybe 10 percent. At this point, about 20 percent of the data that we expect to get and this data

is coming from former or recent hepatitis A patients, as well as the community. We now have a utility value of 0.57 which is somewhere between the value of life with frequent migraine headaches or with -- but not quite as liver cirrhosis. Based on this estimate, our vaccination of children would cost about 7,600 dollars per quality-adjusted life year term or among the more effective of interventions assess using this type of framework.

So to wrap up, it's impossible to get economists to agree on much of anything, but it is generally accepted that medical technologies can be deemed cost-effective by meeting one of two standards: either reducing societal costs for -- to an amount greater than the cost of the intervention or costing the health system less than 50,000 dollars per life year saved. Historically, childhood vaccines have easily met the standards in states covered by the ACIP recommendation. It appears to us that hepatitis A vaccination of young childhood and adolescents meets them easily as well. Thanks very much.

DR. MODLIN: Questions for Dr. Jacobs?

(NO RESPONSE)

DR. MODLIN: I think you've encountered a group on the second day of -- the afternoon of a second day of a meeting, but we do thank you for presenting this information. I think it will be very helpful to us going forward.

The final item on the agenda will be another follow-up presentation on staphylococcal vaccine in a population of hemodialysis patients. We, about a year ago, had a preliminary presentation by Dr. Horwith on the rationale and the initial conduct of this study and Dr. Horwith has additional information for us that he's going to present now.

DR. JERNIGAN: My name is John Jernigan. I'm with the Division of Health Care Quality Promotion and the National Center for Infectious Diseases.

As you know, staph aureus continues to be a pathogen of major importance in health-care-associated infections. It's common. It continues to be one of the leading causes of health-care-associated infections, including

surgical site infections, bloodstream infections, as well as nosocomial pneumonia, and it's virulent. The attributable mortality for a catheter-related staph aureus bacteria approaches 15 to 20 percent. And to make matters worse, antimicrobial resistance continues to emerge among isolates of staphylococcal aureus. Now fully 54 percent of staph aureus isolates causing infection in American intensive care units are multi-drug resistent which results in fewer and fewer choices for effective antibiotic therapy.

So a safe and effective anti-staphylococcal vaccine has been a long-sought goal and would represent a very -- extremely important public health advance. And Dr. Gary Horwith is here from NABI to give you the follow-up data. I think last June they were here to give you the preliminary data leading to their phase III efficacy trial of their new vaccine product in preventing staphylococcal bloodstream infections in end-stage renal disease patients on hemodialysis.

DR. HORWITH: Thank you, John.

Let me just very quickly try to set the stage for the

staph vaccine. As John pointed out, staph is indeed a problem, both for hospitalized as well as community-acquired individuals. This gives you an indication of the culture-positive infections, 44 percent of which are gram-positive. Of those that are gram-positive, 35 percent of them are staph aureus. And that equates to a little over 1.2 million staph aureus infections annually.

If one looks at the bacteremias in the hospital, about 63 percent of all the bacteremias in the hospital are actually gram-positive and a majority of those are staph aureus. In the U.S., approximately nine to 11 million individuals are at risk for nosocomial infection. During 1999 -- These are all data from the literature -- about 1.3 million hospitalized patients had a culture-positive staph aureus infection, the most common nosocomial pathogen reported in the National Nosocomial Surveillance System during the six-year period from 1996. The staph-aureus-associated hospitalization results had about a two-fold increase in hospital stay, two-fold increase in deaths, as well

as a two-fold increase in medical costs. Methicillin-resistent staph aureus or the MRSA, as everybody in this audience is well aware, has become an increasing problem and it accounts for somewhat more deaths in the methicillin-sensitive isolates.

Looking at the isolates that have been gathered by a number of laboratories around the world, one sees that the majority of the isolates, about 85 to 90 percent of the isolates, are what we refer to as Type 5 or Type 8. Type 336, which I really won't go into today, is another type that we've identified at NABI, which is actually a polysaccharide that seems to present on the cell wall that is expressed or is recognized when there is a defect in a capsule or the capsule is absent.

With regard to resistance, of course, the resistance is not just limited to the United States where we have identified methicillin-resistent staph aureus of about 35 to 50 percent, but it is present in Latin America and Europe as well.

Now, we've taken a look at some of the strains that are antibiotic-resistent, and particularly the one that is

getting most of the publicity these days are the vancomycin-resistents or vancomycin-intermediate strains. We've looked at active immunization using the bivalent staph aureus vaccine in an animal model -- It's a (inaudible) model -- and then challenged with VISA strains and New Jersey strain and demonstrated that the vaccine, in fact, protects against that in an animal model. We've looked at 16 VISA strains that are clinical isolates that have been sent to us from NARSA, which is the NIH Network on Antimicrobial Resistance in Staph Aureus, and have identified that 14 of those were Type 5, one was a Type 8, and one was what we referred to as Type 336.

Just as a quick overview or reminder, the vaccine that we're talking about today is a conjugate vaccine. We take the capsule of polysaccharide that's purified from the staph aureus, either Type 5 or Type 8. We conjugate that with a detoxified protein from pseudomonas aeruginosa that is expressed in e.coli that has been detoxified so it's completely nontoxic, and through a straightforward conjugation process we have a

vaccine which is shown on the bottom.
The vaccine at this point has been very well characterized as a capsular polysaccharide vaccine. We have also very -- done a lot of characterization of the recombinant EPA or azoprotein A. from the pseudomonas and demonstrated that the vaccine is quite stable for several years now.
The preclinical data that led up to the initiation of the clinical studies really points to several facts that I'll just highlight here for the sake of time.
One is that the capsular polysaccharide is, in fact, antiphagocytic. It seems to protect the bacteria from post-immune defenses by cloaking it or hiding it from the immune system. The antibodies that are generated are very type-specific and they are responsible for the opsonophagocytosis, the mechanism by which staph aureus are cleared in animals, including ourselves.
The bivalent vaccine covers about 80 to 85 percent of the staph aureus pathogens. The conjugate that we generate is quite immunogenic and induces a very high affinity and functional antibody. I won't go through

all the data that we presented last June, but I think at this point we'll just point out that the vaccine generates an antibody that is almost all functional antibody.

There is a linear correlation between the antibodies and the opsonic activity. The conjugated vaccine has been demonstrated to be protective in several animal models, representing different types of infection modes. The antibiotic-resistent strains, including VISA strains, did not effect the protective ability of the vaccine. And finally, infection in humans that had been superimposed on low levels of antibody which previously had led people to conclude that staph aureus antibodies were not protected may be due to various factors and pre-existing antibodies such as low affinity and functionality of the normally-acquired antibodies. I should point out that all of us have about five to 15 micrograms of staph aureus -- specific capsular polysaccharide staph aureus antibodies circulating at any given time. And yet, we are, of course, always susceptible to repeat staph aureus

infections. Nevertheless, we have demonstrated, I think, in the studies that I'll present right now that the amount of antibody is inadequate, and it's not that the antibody is no good, it's just not sufficient.

In 1991, clinical trials were initiated. These were originally started at the NIH and Walter Reed, collaborative studies. Those studies demonstrated that the antibodies are long-lived in normal, health individuals.

In '93, the development of the vaccine was taken over by Univax, which subsequently became NABI, and we have conducted some phase 1 and a phase 2 study that led up to the initiation of the phase 3 study that I will go onto now in 1998.

I would just like to point out that the antibody response in normal, healthy individuals -- And these are some data from plasma donors that we vaccinated in order to generated a passive immune product called AltoStaph [phonetic]. The antibody response is really quite brisk. We see good antibody titers at about 10 to 14 days. You can see

antibody titers there of about 273, 243 to the different components, and almost all the individuals respond.

Now, among the end-stage renal disease patients, we have demonstrated a dose response. This is a compilation of a couple of studies where we administered either 25 micrograms of each of the components, 75 and 55 of the two components, or 118 and 83, which is really comparable to the material that was used in the phase 3 study. And if you take a look at the Type 5 and the Type 8 response, looking at day 42, you can see that there's a dose response.

You can't see this very well, but you can see the dose response here. We've also taken a look at the repeat vaccination. We have demonstrated that when individuals are vaccinated early on, that is, at about six weeks following the first dose, there isn't much of a boost. That's probably due to high antibody titers at the time of boosting. However, if we tried to re-vaccinate individuals at about 18 months after the first vaccination or the second vaccination, we see

that we are able to return those individuals to their pre-existing antibody levels. Importantly, there's no increase in the reactogenicity following repeat doses of the vaccine. I should point out that the vaccine does not contain any adjuvant.

So with regard to the phase 1 and phase 2 studies, we demonstrated that the vaccine was well-tolerated and was safe in about 300 individuals we administered it to. The response was demonstrated in these phase 1 and phase 2 studies consistently, and for the first time in end-stage renal disease patients, we were able to demonstrate that the vaccine was quite immunogenic against staph aureus.

Now, the phase 3 study is the first study that actually was conducted in order to assess the efficacy of the staph aureus vaccine and is the first large efficacy trial that ever has been conducted in end-stage renal disease patients.

As a quick review, this was a double-blinded multi-center study. It was conducted in northern and southern California in Kaiser Permanent, Gambro, and

TRC dialysis centers. TRC is now referred to as Davida. All the patients were end-stage renal disease patients, all on hemodialysis. They were stratified at study entry by nasal culture, being staph aureus nasal culture-positive or negative, and they were stratified by the type of dialysis access that they had. They were randomized either to receive vaccine and placebo, and the vaccine dose that was administered was 100 micrograms of each of the capsular polysaccharide components conjugated to an equal amount of REPA. Primary endpoint of this study as defined by the protocol was the number of first-time staph aureus bacteremias that occurred in the 54 weeks following vaccination. And as I'll point out, there were a number of secondary endpoints as well.

Now, why did we choose ESRD patients? First, the end-stage renal disease patient population has a high rate of infection. So it gave us the ability to use clinical endpoints because the frequency was high enough. They have frequent violations of their skin barrier for the dialysis, usually about three times a

week, and they have an indwelling piece of foreign material, usually a Gortex catheter, a graft, or some other type of material. However, they also present a bit of a challenge. End-stage renal disease patients, by and large, have reduced immune response, they have impaired neutrafil function, particularly those who are diabetic, and a large number of these folks are diabetic, the renal failure, by itself, reduces their immune function, and they're an elderly population. So our reasoning was that if we could demonstrate efficacy in this patient population, one would be able to expect that the vaccine, when administered to more immunocompetent individuals, would have no problems in terms of being effective.

The individuals are at least 18 years of age. They had to be stable on a hemodialysis program for at least eight weeks coming into the study. They had to have either a fistula or a heterologous graft. Individuals who had a temporary catheter in place were not eligible for entry. They could not have any active infection within two weeks of being vaccinated and they had to be

free of any immunosuppressive agents.
The stratification numbers coming in, the smallest cell were those individuals who had a fistula and were nasal-carriage-positive. That constituted seven and a half percent of the individuals. The largest group of these four cells were those who had a graft and were nasal-carriage-negative, about 55 percent of the folks. 73 dialysis center participated. We screened just under 2,000 individuals, and of those, 1,804 individuals went on to be vaccinated or receive placebo material. The last individual was vaccinated back in August of 1999.
Median age of the group was about 60 years. The mean was 58. The eldest individual in the group was 90 years.
The only interesting thing in terms of the demographics was that, probably because of vessel size, there were more male subjects with fistula than female, about three to one, but those with the graft, it was an equal number. 52 percent of all the subjects were diabetics, and of those who developed a bacteremia during the

course of the study, 65 percent of those were diabetic. The ethnicity range was quite representative of that seen in northern and southern California.

Of the 1,804 patients who were dosed, we evaluated 1,798. There were six individuals we could not evaluate because they either had -- were subsequently found to have an infection at the time of vaccination or within two weeks or there was other major protocol violation. So you can see there were roughly 50 percent in either of the two groups.

88 percent of the individuals responded to the Type 5 component of the vaccine. 84 percent responded to the Type 8. And response, for the purpose of the protocol, was defined as two-fold increase over the baseline as well as having an antibody titer of at least -- or a level of at least 25 micrograms per mil.

In terms of the safety, the safety profile was pretty comparable to what one would expect with an intramuscular vaccine. There was some induration, erythema, heat, pain, and malaise, and myalgia. The local reactions, which are the first six up there, were

all mild to moderate and they all abated within about two to three days. None of them -- none of the reactions required intervention.

In terms of serious adverse events, there were several in the study, as one would expect with end-stage renal disease patients. In the StaphVAX group, there were 262 serious adverse events and "serious" is the FDA definition of "serious." Those 262 serious adverse events occurred among 201 individuals in the placebo group. And there were 265 serious adverse events that occurred among 213. None of these events were considered to be related to the vaccine or placebo.

If one just looks at deaths -- And bear in mind that the study was powered to detect the difference in mortality -- there were 152 deaths in the StaphVAX group, 146 in the placebo group, and retrospectively, going back and looking at these deaths and trying to account for whether or not they were related to staph aureus bacteremia, either temporally or because there was a clear-cut clinical association, you see that there were nine and 11. This was not significant.

If one looks at the efficacy of the vaccine, bear in mind again that the pre-defined outcome of the study was efficacy at 54 weeks. If you go to that particular row, you see that there are 27 bacteremias in the StaphVAX group, 37 in the placebo group, for a 26 percent reduction in bacteremias. That was not statistically significant. However, if one looks at earlier time points, and this was consistent in all the earlier time points, there was efficacy, and the efficacy peaked at around 60 percent. I'm showing you here the efficacy at -- the interval between week two and week 40 where the efficacy was 57 percent and that is statistically significant, although this is, of course, a look at an interval that was not the predefined endpoint study.

We did not, via protocol definition, collect all the isolates, but we elected to do so after the study started. We were able to recover 71 percent of the isolates and they were then typed. Of those 71 percent of the isolates that we recovered, 80 percent of them were, in fact, Type 5 or Type 8, exactly what we had

predicted from the sero surveys that had been done previously.

Interestingly, the risk for bacteremia was highest among those who were nasal-carriage-positive and highest for those, of course, in the placebo group. So the risk for staph aureus bacteremia was 7.2 percent for individuals who were nasal-carriage-positive and received placebo; 3.2 percent for those who were nasal-carriage-positive and received the StaphVAX, which was the same for all the individuals who were nasal-carriage-negative.

Now, we looked at several post hoc analyses and, first, a bit of a disclaimer as we begin to look at these. Ordinarily, one does not like to look at post hoc analyses because, either intentionally or unintentionally, one can have a bias. We looked at post hoc analyses of two different methodologies, the permutational analysis in the cubic-spline. These two particular analyses do not subset the data, so we're not, quote, "cherry-picking" data. All the data is used.

And these methods also adjust for the statistical significance of a post hoc analysis and looking at the data numerous times.

In the permutational analysis, just as a quick way of explanation, we generated 10,000 data sets for -- from all the 1,798 subjects. That is the entire sample size. And we compare each of these data sets to the true outcome generated from the staph vaccine recipients. The outcomes are tested for contiguous efficacy for any period that we felt would be clinically relevant, that is a period of at least 180 days. In addition, we also did the same type of analysis, which is referred to a weighted efficacy analysis, adding a bonus for those individuals who remained infection-free for a longer period of time than the 180 days. You can see the results of that. The P value for the contiguous efficacy was 0.012 or 13, with fairly tight -- 95 percent confidence intervals, and the same type of P value for the weighted contiguous efficacy, P value of 0.023.

Now, without focusing on the magnitude of the curve

here, I would just like to point out that if one looks at the blue and the green curves first, these are the antibody levels following vaccination. The interval between two weeks and six weeks is broken because we did not actually measure antibody levels at that point. The first time point following vaccination was actually at 42 days or six weeks. And one can see that both the Type 8 and the Type 5 components generated very respectable antibody levels of approximately 220 or 180, close to 200, micrograms per milliliter for the two components. However, the antibody levels waned fairly rapidly. So that by around 38 weeks, 40 weeks, the antibody levels had dropped down to about 100 or 80 micrograms.

If we look at the efficacy using the cubic-spline analysis, we see that the efficacy drops off at about 40 weeks, which if one superimposes the two curves, corresponds to a protective antibody level using population-based analysis of about 80 to 100 micrograms per mil.

Now, these particular values, first off, are

extraordinarily high compared to other vaccines. Going into the study, we have absolutely no idea what a protective antibody level of the vaccine should be or what the antibody should be and we also had no idea as to the duration of protection, given even -- Setting aside the fact that we didn't know what a protective level was, we didn't know how long the vaccine would be able to mount a protective level among these individuals. So the time point that we chose of 54 weeks was, in fact, an arbitrary time point, but one that was felt to be reasonable.

If one looks at Kaplan-Meier survival-type of analysis -- but this is referring to infections, not mortality -- one can see that if you follow this out over the entire course of the study, there was no particular efficacy as at ratio .75 and P value .195. However, if we back up to the time point where we feel that we have demonstrated a protective level of antibody at approximately 40 weeks, one sees that the hazard ratio is about .43 with a P value of about .02.

So we feel that the StaphVAX at this point has

demonstrated efficacy in the ESRD patients through approximately ten months, shown by a reduction in bacteremias. These protective antibody levels of 80 to 100 micrograms correspond to that level of -- over that period of protection and the vaccine was very well tolerated.

The potential impact, if one extrapolates to the literature, again, going back to about 246,000 individuals at risk, that is 246,000 end-stage renal disease patients on dialysis, with a bacteremia incidence of about five percent, equates to about 12,300 bacteremias annually. If the StaphVAX is, in fact, 60 percent effective or 60 reduction in bacteremias, one would be left with about 4,920 bacteremias or a saving or prevention of about 7,200 or 7,300 bacteremias annually.

If the vaccine is not able to be boosted, which we certainly plan to evaluate, one would still a savings over the ten months of vaccine efficacy of about 6,150 bacteremias prevented.

In summary then, we feel that the StaphVAX provided

significant protection against staph aureus bacteremia in this immunocompromised group. It was statistically significant in affording protection for about 40 weeks. It was safe, well-tolerated, and it was the first placebo-controlled demonstration of efficacy of any bacterial vaccine in an immunocompromised population with underlying disease, in this case end-stage renal disease.

Once again, we feel that the clinical efficacy demonstrated in this group of patients, which is a worst-case at-risk population, along with immunogenicity studies that we have planned for other populations, should put this vaccine in, I think, good stead to be something that can be added to the practitioner's toolbox.

DR. MODLIN: Dr. Horwith, thank you. Questions? Natalie?

DR. SMITH: It's probably too late in the day to ask for an explanation of a cupric-spline analogy, but I'm not -- it seemed like efficacy was coming back up as time went along and --

DR. HORWITH: This is why I asked you not -- I'm showing it knowing that somebody was going to pick up on this anyway.

The dip in the curve at the end is statistically no different than zero efficacy. You did not increase the risk. The vaccine simply lost it's efficacy at approximately 40 weeks. And what you see from that point on is that the vaccinees behaved essentially the same as placebo recipients.

DR. MODLIN: Myron?

DR. LEVIN: Yes. When you -- Is there any direct side effect to this antibody on the staph or is it basically enhancing phagocytosis?

DR. HORWITH: It's an up-sizing antibody. So, you know, you know the mechanism requires the antibody up up-sizing, the [inaudible] for phagocytosis on -- and complement. This provides us the up-size in antibody. It's a highly-functional --

DR. LEVIN: So there may be a limit on how it could be used in immunocompromised people. You had a statement in there how it would be valuable in immunocompromised

people, but I guess it would depend on whether they still had sufficient phagocytic function.

DR. HORWITH: That's correct. If you were to extrapolate that to that individual who had no neutrophils, for instance, yes.

DR. LEVIN: Did it have an effect on carrier state?

DR. HORWITH: No, it did not.

DR. LEVIN: And you show that --

DR. HORWITH: Let me just clarify that.

DR. LEVIN: I mean, it would fit with what you said about phagocytosis.

DR. HORWITH: Yeah. We did not do any nasal carriages. In this particular study, we only looked at the nasal carriage for the stratification. I think in future studies, it would be interesting to see if it, in fact, would have any impact along the way, but in this particular study, we did not do repeat cultures, nasal cultures.

DR. LEVIN: You said the breakthrough bacteremias were the types that you would expect 80 percent of the time, but that was for the overall group. Was there a

difference in the vaccinated group versus the nonvaccinated group and was there a trend?

DR. HORWITH: No, there wasn't. And we didn't do specific analysis of the subtypes because we had a fair number of isolates we couldn't recover. So we really have no way of accounting for that.

DR. LEVIN: And you did mouse studies previously. You must have had some idea of what the protective level was in the mouse also?

DR. HORWITH: Yes.

DR. LEVIN: And was that, in any way, similar to what you found here?

DR. HORWITH: Yes.

DR. MODLIN: Paul? I'm sorry, Myron, are you finished?

DR. LEVIN: Yes. Thank you.

DR. OFFIT: Two quick questions.

Do you have plans for looking at hosts other than those with end-stage renal disease and do you plan to do studies of booster dosing?

DR. HORWITH: Yeah. We actually have a study planned that should begin in April to vaccinate and re-

vaccinate about 150 individuals who were vaccinees in this previous study to see whether they will go back up to their previous levels. They're now about a year to two years out from their first dose of vaccine.

We also plan to do some immunogenicity studies in other patient populations, such as cabbage [phonetic] patients, orthopedic hip surgery for prosthetic devices and so forth.

DR. MODLIN: Myron?

DR. LEVIN: Just one other question.

In the people who broke through, who had the bacteremias, did you get blood serum samples at the time they were bacteremic?

DR. HORWITH: No. We only collected serum --

DR. LEVIN: Along the way did you have them?

DR. HORWITH: We collected four specimens only during the 54-week course of the study. So it's -- it is very difficult to be able to extrapolate.

DR. LEVIN: Was there any relationship between those people who had bacteremia and having had a poor response or lower levels?

DR. HORWITH: No, not on an individual basis.

DR. MODLIN: Bob?

DR. CHEN: Is there any correlation between end-stage renal disease and the immunogenicity and then their efficacy?

DR. HORWITH: No. We didn't stage or stratify the level or the length of time somebody had been on dialysis. All individuals -- It was open to all-comers, as long as they were on a stable regimen of either fistula or [inaudible] graft axis. And we didn't -- we didn't do anything else to try to stratify that.

DR. MODLIN: Further questions? Dr. Horwith, do you want to tell us, in two sentences, up-to-date where you are with your development plans?

DR. HORWITH: As I pointed out, we are going to be doing a booster study with individuals who are vaccinated previously. We are planning for an additional phase 3 study, probably in the same patient population, but we're not sure. This is something we're still discussing with FDA, and I certainly won't

put Karen on the spot to make any comments about that, but we've had -- of course, we've had discussions with FDA and their position at this point is that since we did not reach the protocol-defined endpoint, another phase 3 study would be required. So we are making plans for that.

DR. MODLIN: Terrific.

DR. SNIDER: Dixie Snider.

In terms of planning, John, I think we should ask whether this is one of those recommendations that we would be working with HCPAC in developing -- we worked with them in the past on other recommendations, the one that I was involved in with PCG vaccine for health care workers. It seems to me that given the types of patients they're talking about testing this vaccine on that it might be appropriate to have HCPAC and ACIP work together.

DR. MODLIN: I think when the time comes, that would be a -- should be the appropriate thing to do. I agree. Thank you. We appreciate it.

We do have two people who have signed up for public

comment. The first is Ms. Lynn Redwood from Safe Minds and the second is Dr. Kristine Severyn. I'm going to ask if each of you would please try to confine your comments to five minutes or less. And then a note that Gloria has handed me to let members of the Committee and others know that flights to Baltimore, Louisville, and Philadelphia are presently running on time. That's the best information we have at the moment.

Ms. Redwood?

MS. REDWOOD: Hi. Thank you for this opportunity to speak.

Mainly, I wanted to share with you my disappointment over the issue of not giving preference to thimerosal-free vaccines and that it wasn't even addressed by the Committee during this meeting. And I guess the reason for my disappointment stems from hearings that were held this past July where Dr. Roger Bernier testified before the Government Reform Committee regarding the utilization of thimerosal in vaccines. During the hearing, Dr. Bernier committed under oath that thimerosal would be removed from infant vaccines in

early 2001. Again, this past December, U.S. House Representative Matt Collins spoke with CDC and was assured, and assured me, that at the February 2001 ACIP meeting preference would be given to thimerosal-free vaccines for infants. But yesterday I heard from Dr. Bernier that it's a moot point now.

And for the life of me, I guess I just really don't understand this. I heard yesterday, as I did June of last year, that SmithKline Beecham, the maker of Infanrix, has enough vaccine readily available to meet the needs of every infant born in this country the first six months of life.

So I don't understand why preference cannot be given to a thimerosal-free vaccine the first six months and then administer the other vaccines that contain thimerosal for the fourth and fifth doses. You may very well be in a shortage situation regardless of whether or not you would give preference to thimerosal-free vaccines.

The other comments I wanted to make is yesterday there was some information about the vaccine safety data that I felt might be little misleading. First, that

particular report was not expected to provide evidence to either support or refute the existence of a causal relationship. The data say that the implications of the study were profound. A comment was made yesterday that there was not a statistically-significant association between the incidence of autism with thimerosal-containing vaccines, but what I would like to point out is that the children that were in that study, the average age was only three and a half years, and they're much too young to have a diagnosis of autism. Autism is not typically diagnosed until an infant is six years of age.

I can tell you what you will see as a diagnosis: speech and language delays; neurodevelopmental delays; ticks; echolalia, which falls under that category. I'm met with Dr. VerStaaden when the last round of data became available and the numbers for autism had increased from 67, which was reported last year, to now 187, which is what I would expect to see as the children get older.

Concerning the Harvard Pilgrimage data, the VSD data

had 213,000, where the Harvard data only had 30,000 children. The data was nowhere near as robust or as accurate as the VSD data and it was only added in after the initial VSD data became available. So it's just my opinion that the VSD data sort of draws questions to the Harvard Pilgrimage data.

The other concerns that I have is the way that FDA analyzed the amount of thimerosal that our children have received. They took the exposures and they averaged them over a six-month period of time. And if you talk to any toxicologist, they will tell you that you can't legitimately do that. Mercury has a long half-life. Because of the inherent pharmakinetics, you cannot compare a large bolus dose to small daily doses. What the FDA is trying to assert is that giving somebody two Tylenol a day for 60 days has the same effect as giving 120 Tylenol all in one day, which we know defies common sense and sound medical practice. The fact is that any one thimerosal-containing vaccine result in daily exposures in excess of all federal safety guidelines. Mercury modeling done by myself and

also Dr. Neal Halsey clearly demonstrates mercury levels above the range of the lowest observable effect. As I mentioned yesterday, mercury toxicity is highly variable. If you remember acrodynia back in the 1950's, out of 500 children exposed to mercury in TD powders, only one would develop acrodynia. And I think this is the same type of susceptibility we're seeing in thimerosal vaccines.

We're in the midst of an autism epidemic whether we acknowledge it or not. Autism went from an incidence of two to four per 10,000 in 1970 to one in every 250 today which was found in New Jersey. If you looked at the broader -- where you included pervasive developmental disorder and [inaudible], the incidence is one in every 150. In California in Granite Bay, the incidence is one in every 132 children and in my county here in Georgia, last year in kindergarten, the incidence was one out of every 125 children with a diagnosis of autism.

I don't think we can ignore this any longer. This dramatic rise began in the late 1980's and early 1990's

and that was with the introduction of two new vaccines, hepatitis A and hib, which both contain thimerosal, which essentially triple a child's exposure to mercury the first six months of life.

I guess what I would like to know is, is it worth the risk when you can void it all together by giving preference to thimerosal-free vaccines the first six months of life? You won't be putting any jeopardy of a vaccine-preventable disease or permanent neurodevelopmental disability. So I would like to know from the Committee members if this is, in fact, a moot point now?

DR. MODLIN: Ms. Redwood, you've raised a number of issues and, obviously, we can't respond to all of them. I think perhaps I can or I'll attempt to speak for the Committee on the major issue you raise which is not wanting to express a preference for thimerosal-free DTP vaccine at this point in time. We did sit through a rather worrisome presentation yesterday on the vaccine supply, of course. And I think you probably heard a fairly extensive discussion of concern not only by the

members of the Committee but representatives of the Academy of Pediatrics and many others in the room that there is real concern that even -- even -- that we are truly having to even there make choices that we didn't want to make as to whether or not to possibly increase the exposure and the risk of young children to pertussis versus the increased risk of perhaps diphtheria and even tetanus in some children. I think that the -- even though we didn't necessarily address the issue head-on, I think the clear -- if I put things in a longer-term perspective, I think I speak for the Committee by saying that we feel at this point in time, given the information that is available to us -- that we feel that the risk of these diseases outweighs -- at the moment outweighs what we feel to be, at best, a theoretical risk from the thimerosal.

MS. REDWOOD: But we're not talking about not vaccinating.

DR. MODLIN: No. But even with that, we felt that the risk of disease would continue for these very important diseases and be very real. And I think that was the

message that came across yesterday.
I don't want to engage in an argument. Unfortunately, we don't have the time, but I did feel it was probably necessary to respond. I don't know if other members of the Committee would want to speak for themselves, but I get the sense I have from the discussions that we had yesterday.
I'm going to ask that we go on to the next individual who has asked to make a public comment, and that's Dr. Kristine Severyn.
DR. SEVERYN: Thank you.
This is a question and maybe a request, both. I was wondering if there was an ACIP statement on the use of Synogis [phonetic] for respiratory syncytial virus in premature infants. Is there an actual ACIP statement? I mean, I come to all these meetings and maybe I was sleeping, but I don't know if I saw an actual ACIP recommendation for this product.
DR. MODLIN: Certainly, the Academy of Pediatrics has a statement on the use of Synogis [phonetic] and other immunoprophylactic agents for the prevention of RSV

infection. I don't believe that the ACIP has taken that on. And when we had discussed it in a -- in sort of a peripheral sort of way or tangential sort of way, I think it's been the preference of this Committee to leave that primarily to the Academy of Pediatrics.

DR. SEVERYN: Okay. Because that was a request. Because I hear of so many families around the country whose children are taking this product, and I've been told it's 1,000 dollars a shot. And I would think that maybe the Committee -- maybe a request or a question that maybe if you could consider that in future -- because there's so many little children taking that product right now. And if -- I guess maybe another question, if -- why -- since all these other statements are made on different products, like a gentleman just came today and spoke on the staph vaccine. That's used for a small number of people. You know, I guess maybe -- not to be smart-eleky, but why not differ to the renal experts on this? Why does he have to come here? Do you see what I'm saying? So that's a similar type of thing. Could you -- So my request is, would you

consider studying the Synogis [phonetic] issue in a more public forum? It's getting hard for people to find out information about it.

DR. MODLIN: I hope people are not having any difficulty finding out information about it. I think there probably is -- there are sources where there would be --

DR. SEVERYN: Yeah, the Freedom of Information Act. That's what we're having problems with.

DR. MODLIN: It's a biologic agent that's licensed by the Food and Drug Administration. And therefore, I'm certain that there's an immense amount of information that's clearly available.

DR. SEVERYN: So ACIP would not consider this or would you consider it?

DR. MODLIN: I think that's something we need to take under advisement --

DR. SEVERYN: Okay.

DR. MODLIN: -- Dr. Severyn.

DR. SEVERYN: Thank you so much.

DR. MODLIN: Any other comments or questions?

(NO RESPONSE)

DR. MODLIN: If not, the meeting is adjourned. We'll see you in June.

(Whereupon, the meeting was adjourned at approximately 3:40 p.m.)

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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 22ND DAY OF MARCH, 2000, IN ALPHARETTA, FULTON COUNTY, GEORGIA.

PAMELA T. LENNARD, CCR, CVR

CERTIFICATE NUMBER B-1797
(CCR SEAL - NOTARY SEAL)