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

The verbatim transcript of the ACIP Meeting held at the Marriott Century Center in Atlanta, Georgia, commencing at 8:30 a.m. on Wednesday, February 20, 2002.

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C O N T E N T S

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

(By Group, in Alphabetical Order)

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

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

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

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Dr. Margaret Cortese
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Dr. Hal Magolis (NCID)
Mr. Dean Mason (NIP, ISD)
Dr. Martin Meltzer (NCID, OD)
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Dr. Lance Rodewald (NIP, ISD)
Dr. Jane Seward (NIP, ESD)
Dr. Vishnu Sneller (NIP, ESD)

Ms. Shannon Stokley (NIP, ISD)
Dr. Melinda Wharton (NIP, ESD)

AUDIENCE COMMENTS:

Mr. Don Beeman
Dr. Robert Chen
Dr. Michael Decker
Dr. David Fedson
Dr. Neal Halsey
Mr. Rick Haupt
Mr. Phil Hosbach
Dr. Peter Paradiso
Dr. Larry Pickering
Dr. Stan Plotkin
Dr. Ben Schwartz
Ms. Deborah Wexler

P R O C E E D I N G S

8:30 a.m.

DR. MODLIN: Good morning. Could I ask everyone to please take your seats so we can get started?

I'd like to welcome everybody to the February, 2002 meeting of the Advisory Committee on Immunization Practices and to begin with, I'm going to turn things over to Dr. Dixie Snider, who is Executive Secretary of the Committee. Dixie?

DR. SNIDER: Thank you, John. Good morning, everyone. There have been several changes to the Committee since the October, 2001 meeting. And I'm pleased especially to welcome our new members who are appointed to the ACIP by Secretary Thompson. These members are Dr. Robert Belshe, Professor of Medicine, Pediatrics and Microbiology at St. Louis University. I think Bob was not going to be able to attend this meeting. Dr. Gus Birkhead, who is Director of the Center for Community Health, New York State Department of Health; Dr. Celine Hanson, Bureau Chief, Bureau of Communicable Disease

Control, Texas Department of Health; Mr. John Salamone, who's our consumer representative from Washington, D.C.; and Dr. Richard Zimmerman, Associate Professor, Department of Family Medicine and Clinic Epidemiology at the University of Pittsburgh. So welcome to all of our new members. We're delighted to have you.

I also want to welcome our new liaison representatives. From the American Academy of Family Physicians, Dr. Richard Clover, University of Louisville School of Medicine; from the Infectious Disease Society of America representing the Guide for Adult Immunization, or the Green Book, so we have a Red Book representative and a Green Book representative now also, Dr. Bill Schaffner; and a new liaison representative -- liaison organization to ACIP serving as representative from National Coalition for Adult Immunization is Dr. David Neumann, National Foundation for Infectious Diseases. I'm pleased to welcome each new member in liaison and I thank you in advance for your willingness to contribute to

ACIP.

Not able to attend the meeting today are Dr. Bob Belshe, as I mentioned, and Celine Hanson. Also Dr. David Wilson, the AMA liaison representative.

I do want to make a comment about the policies and procedures of the Committee. I think everybody has in a purple folder. These are still dated, I think, January 2000. I just want to give you a very brief update on where we stand with regard to those policies and procedures.

We at CDC have rewritten those to take into account some of the issues that we have discussed at these meetings, as well as to reflect some of the discussions we had with the Office of Government Ethics and our own Department of Health and Human Services staff. In fact, I think it was a week ago Monday that I led a team from CDC to talk about all of CDC's advisory committees with the staff of Office of Government Ethics. To suffice it to say, they were satisfied with what we do at ACIP and other advisory committee meetings,

but they do want us to change some of the paperwork. So the waiver letters that you will be getting will be worded differently than waiver letters you had seen before, but otherwise that should be the only significant change.

For those of you who are not familiar with the logistics of the Committee, the appointed Committee members and CDC employees who serve as facilitators are seated at this table (indicating). The ex officios and liaison representatives are seated at the tables on the perimeter.

I'd like to remind everyone that the ACIP home page is located at www\cdc.gov\nip\acip, and the ACIP e-mail address is acip@cdc.gov and the home page is the best way to keep up with the latest version of the agenda and the meeting minutes.

The dates for the remaining 2002 meetings are June 19th and 20th and October 16th and 17th, and the meetings will be held here at the Marriott Century Center Hotel. And I would venture we'll probably continue to do that, given the size of this meeting, for some time, at least until the new

CDC meeting facilities are completed.

Dinner tonight will be at The Violette on Clairmont Road. You will find a pink menu in the front your notebooks. Please indicate your choice of entree and give the menu to Gloria, with the cost of dinner, no later than noon today. We do have reservations and must guarantee these reservations, so please let Gloria know if you plan to attend. And once the reservations are made, we must pay for the number that we guarantee.

The hotel restaurant, in case you haven't discovered it, is in the lobby of the hotel. You go out these doors and continue down the hall to the lobby of the hotel and the restaurant is on the left. The restaurant has assured us that those dining in the restaurant will be served efficiently.

The meeting cannot begin, of course, unless there's a quorum of members present and a quorum must be present at all times. I'd like to ask the appointed members to please return from lunch and break in a timely manner and participate fully in

the meeting. We have changed the agenda to accommodate travel schedules, and so your cooperation would be appreciated.

The ACIP charter gives me, the Executive Secretary, or my designee the authority to temporarily designate the ex officio representatives as voting members, but this only takes place, according to our policies and procedures, if there are less than eight appointed members not qualified to vote due to a financial conflict of interest. The ex officio representatives will be formally requested to vote when necessary, and if this occurs they will be asked to disclose any potential conflicts of interest.

ACIP has always held open discussions, and I think John has been especially good about recognizing people in the audience who have things to say that are pertinent to the topic at hand, but we do reserve meeting time for official public comment. At the same time the Committee has restricted time in which to conduct its business;

therefore, in some circumstances, we've scheduled a formal comment period during the deliberation of the agenda items.

Casual comments are received, of course, during the open discussions, depending on the amount of time available. But these comments need to be restricted in order to keep within the time allotted for the Committee to complete its agenda. With the added interest of some individuals who want to address the Committee, individual comments on specific items need to be requested in advance. We do ask that you sign up with Gloria so that we can arrange for a time for your comments.

Because it's important for us to hear all the comments and record the comments, we have set a microphone at each end of the Committee table for members of the audience to use when they address the Committee. I would appreciate anyone wishing to comment to step up to the microphone and be recognized by the Chair. I also want to take this opportunity to ask all the Committee members to speak clearly into the microphone, hold it up close

to you.

And I think that's all I had to say at this time, John. Thank you.

DR. MODLIN: Thanks, Dixie. I'd like to add my own personal welcome to our new members, both voting members and new liaison members.

I also want to bring everybody's attention to the fact that there are several updates and other information pieces in the back of your packets -- notebooks. There are a number of pieces here, but they include the published general recommendations, which is the statement that this Committee worked on for a very long period of time and I think will be of considerable interest to everyone. Also updates on anthrax vaccine and also this Committee has worked on since the last meeting. And also importantly, an update on pneumococcal conjugate vaccine shortages, as well.

Also in the front of your book, please note that there is a draft statement for a change to the rabies recommendation that Dennis Brooks and Chuck Rupprecht and their group have been working on.

And we don't have time on the agenda specifically to address that, but if we can find some time, Dennis, we might give you an opportunity to bring the Committee up to date on that. But I do urge all of you to take a look at this statement and to get your comments back to either Dennis or to Dr. Rupprecht within -- get them back by the end of this month, by March 1st, if possible.

There will be a meeting of the rotavirus working group this evening immediately following the end of today's meeting. I don't know where that's going to be yet, but we probably will know soon and I'm going to ask the members of the working group to touch base with Gloria Kovach by the end of the day to find the location. And my understanding, Myron -- Do you want to say anything more about that, Myron?

DR. LEVIN: It's in the Magnolia Room.

DR. MODLIN: In the Magnolia Room. Thank you. And the intent is that this will not be -- may be about an hour, hour and a half meeting of the work group -- hopefully well in time for dinner.

Dixie has already mentioned dinner this evening and the dates of the next ACIP meeting. And let me again reiterate that we need to have the voting members of the Committee back from lunch and from breaks on a timely basis so we can keep on time.

And again let me reiterate that we need to ask everybody to, number one, identify themselves, and number two, speak directly into the microphone when you have comments.

At this time I'm going to ask the voting members of the Committee to introduce themselves, and at the same time to disclose any financial conflicts of interest they may have. I'd like to remind everyone that ACIP members who may have 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 that full disclosure of potential conflict of interest has occurred. However, persons who have a direct conflict may not vote on any issue related

to the conflict. Members with financial conflicts of interest must abstain from voting on the vaccines for children resolution. Since a conflict may also appear to be present if such member is allowed to introduce or to second a vote or VFC resolution, the ACIP policy prohibits a member with financial conflicts of interest from introducing or seconding any ACIP vote or VFC resolution.

Why don't we start with Dr. Word and if you will, go around the table counter-clockwise. Bonnie?

DR. WORD: My name is Bonnie Word. I'm a pediatric infectious disease physician for New Jersey, and I have no conflicts of interest.

DR. BIRKHEAD: I direct the Center for Community Health, which includes the immunization program, at the New York State Health Department, and I have no conflicts of interest.

DR. LEVIN: Myron Levin. I'm at the University of Colorado Health Sciences Center and School of Medicine, Pediatric Infectious Diseases. I do research with Merck and with Glaxo Smith-

Kline.

DR. OFFIT: My name is Paul Offit from the Children's Hospital of Philadelphia and the University of Pennsylvania School of Medicine. I am a co-holder on a patent for a bovine-human reassortant rotavirus vaccine, and I consult with Merck on the development of that vaccine.

DR. BROOKS: My name is Dennis Brooks. I'm from Johns Hopkins Medical Institutions, Johns Hopkins University. I'm in pediatrics and I have no conflicts of interest.

DR. MODLIN: Why don't we go ahead, Tim, and then we'll continue on around.

DR. MASTRO: Tim Mastro from the National Center for HIV/STD/TB Prevention, the AIDS Division, and I have no conflicts.

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

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

DR. DESEDA: I'm Jaime Deseda from Puerto Rico. I have no conflict of interest.

DR. RENNELS: Margaret Rennels, University of Maryland Center for Vaccine Development and I do vaccine evaluation studies with Wyeth, Merck, Aventis and Glaxo.

MR. SALAMONE: John Salamone. I'm a founder of a VAPP organization for families infected with live vaccine associated with polio and I have no conflicts of interest.

DR. TOMPKINS: I'm Lucy Tompkins from Stanford University Medical School. I'm in adult infectious diseases. No conflicts of interest.

DR. ZIMMERMAN: Rick Zimmerman from the University of Pittsburgh School of Medicine and graduate School of Public Health, no conflicts.

DR. SMITH: Natalie Smith, California Department of Health Services. I have no conflicts of interest.

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

I'm going to ask our ex officio and liaison members to introduce themselves, as well, and the

organizations that they represent. I think we'll start with Dr. Evans to my right.

DR. EVANS: Geoff Evans, National Vaccine Injury Compensation Program person.

DR. MIDTHUN: Karen Midthun, Food and Drug Administration.

DR. MYERS: Martin Myers, the National Vaccine Program office.

DR. HEILMAN: Carole Heilman, National Institutes of Health.

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

MR. GRAYDON: Randy Graydon, Centers for Medicare and Medicaid Services.

DR. NICHOL: Kristin Nichol, Department of Veterans Affairs.

DR. GALL: Stan Gall, representing the American College of Obstetricians and Gynecologists.

DR. CLOVER: Rick Clover, the American Academy of Family Physicians.

MR. MAHONEY: Martin Mahoney, American Academy

of Family Physicians.

DR. FRANCE: Eric France, American Association of Health Plans.

MR. REILLY: Kevin Reilly, representing vaccine manufacturers.

DR. NEUMANN: David Neumann, representing the National Coalition for Adult Immunization.

DR. ABRAMSON: Jon Abramson, representing the American Academy of Pediatrics.

DR. OVERTURF: Gary Overturf. I represent the American Academy of Pediatrics.

DR. FOSTER: Steve Foster, representing the American Pharmaceutical Association.

DR. MARCHESSAULT: Victor Marchessault, representing the National Advisory Committee on Immunization in Canada.

DR. SIEGEL: Jane Siegel, representing the Health Care Infection Control Practices Advisory Committee.

DR. KATZ: Sam Katz, representing the Infectious Disease Society of America.

DR. SCHAFFNER: Bill Schaffner, here on behalf

of the Guide for Adult Immunization and Infectious Disease Society of America.

DR. NEUZIL: Kathy Neuzil, representing the American College of Physicians.

DR. PETER: Georges Peter, liaison from the National Vaccine Advisory Committee.

DR. MODLIN: Thanks, Georges, and thanks, everyone. The first item on our agenda will be a discussion and potentially a decision on revisions to the yellow fever vaccine statement.

Rick, are you going to lead things off for us?

DR. CLOVER: Yeah, I'll make a few introductory comments. Enclosed in your books is the revised yellow fever statement. This statement has evolved since about July of last year. I would like to draw the Committee's attention to a couple of issues that Marty will shortly review in more detail.

First of all, I want to acknowledge the yellow fever working group that was a subgroup of the adult working group, and its participation in developing the statement, and thank the efforts

provided by the Center for Disease Control, the Department of Defense and the FDA in their contributions to this document.

There are a couple of issues I want to draw the Committee's attention to. First is the name change as it relates to the adverse event associated with the vaccine that Marty will shortly review in more detail. Number two, the incidence rate for this adverse event and the variables that went into the calculations of that rate.

The other issue I just want to draw your attention to that we'll respond to if you have questions of is the revision of the statement with regard to testing after vaccination in certain populations, specifically pregnancy, and our rationale behind that.

With those brief introductory comments, I'll turn it over to Marty to give us more details as relates to those issues.

DR. CETRON: We're going to wing this a little bit since we're having some technical difficulties with the laptop, but I think that will only allow

us to move more swiftly. It's not recognizing the CD drive. It'll allow us to move more swiftly.

The first comment I want to make is to thank Tony Marfin and his colleagues at Fort Collins, who are sort of my co-workers on this effort, along with the rest of the members of the working group who have been named on a slide that we'll skip over. Unfortunately, Tony suffered an accident last week and has his jaw wired shut -- actually, the accident en route to one of the working group conference calls on the last iteration of this draft, which we've been working on now for about six months. And so he has his jaw wired shut and was advised not to fly and misses the opportunity to be present, but would like to acknowledge all the work that the folks at Fort Collins have put into this.

The topics that Rick brought up regarding the name change is something that the Committee struggled with for a while. As you know, we have been working with multi-organ system failure, which had described sort of the end-stage spectrum of

this illness that we'd seen in at least seven cases that were published in The Lancet in July, and some additional cases which were published in letters in response to the original articles, three additional cases. And what we sort of revealed as we looked further into the entity was that there's a clinical spectrum of disease, not all of which ends in multiple-organ system failure in which liver, kidney, pulmonary, heart -- all the organs ultimately sort of collapse and results in death. But there is a spectrum of the illness with more moderate specific target organ involvement, particularly liver and kidney, and not the entire picture. And we decided -- and in many of those cases with more limited target organ involvement, there's been recovery, fortunately, from the event. Three of the -- or two of the three cases I believe that were subsequently reported in Lancet letters ultimately recovered.

In keeping with the known tropism of wild type yellow fever virus, which is predominantly either viscerotropic attack in visceral organs or

neurotropic, we elected and the working group uniformly adopted and agreed with naming this yellow fever vaccine Associated Viscerotropic Disease, and that I think more accurately reflects what goes on naturally with wild type yellow fever, as well as the possibility that only selected target organs will be involved and it wouldn't end in a very non-specific multi-organ system failure, which is not very specifically linked to yellow fever virus any more so than it is to a number of other agents.

Now in addition, we've adopted a similar framework for talking about what had been previously described as post-vaccinal encephalitis, also which was a less specific event, and we referred to those instances as neurotropic disease and in keeping with what's known about the target involvement of wild type and it turns out in vaccine type, as well.

The further evidence that this is a spectrum of illness comes from a paper that's in press currently, authored by Tom Monath which is a result

of the largest clinical trial of the yellow fever vaccine, and it was an equivalence trial intended, without a placebo arm, to compare YF-VAX with Arilvax, which is used in the UK, and about 1,440 recipients of each of the vaccines -- about 740-plus in each arm -- were vaccinated and then vigorously followed, both for adverse events -- actively monitored for adverse events and had laboratory parameters monitored on a regular basis up to 30 days post-vaccination. And it was interesting to note, as one might surmise, that the frequency of elicited adverse events in a close clinical trial monitoring system are higher than what are passively reported to VAERS, so that the rates of fever in this setting were up to 15 percent and they were equivalent in both arms, as were the safety and immunogenicity profiles, I might add. But it was somewhat surprising to note that about three to four percent -- three and a half in one arm and at four percent I think in the other arm -- of the recipients had mild asymptomatic elevations of liver enzymes, usually

between day one and ten, all of which resolved and returned to normal by day 30.

It was the largest clinical trial of yellow fever vaccines to date in which these types of parameters were monitored, but at the same time, the size was small in reference to picking up rare adverse events, as the ones that we've been discussing here. Viscerotropic disease and organ system failure fortunately were not seen, but it is interesting to note that a transaminase elevation was seen. Without a placebo arm, it's difficult to know for sure how this would have compared to a non-vaccinated cohort, but it's sort of intriguing and suggests again that there may be some hepatic replication of the virus, especially in primary vaccinees. So we've elected, by name, to reflect the clinical spectrum of the disease and to more accurately focus the observation to what's seen naturally with this virus in wild type to viscerotropic disease.

And that was an easy one on which there was real uniform agreement. The more challenging area

is to try to provide a crude estimate of reported incidents for a syndrome that's being newly described or newly recognized, and in a situation where surveillance, at best, is passive, but in many cases is non-existent at all and all there is is to go on is crude numbers for vaccine doses distributed. In Brazil, for example, the setting of a vaccine campaign in which there's no registry of each individual getting vaccinated, and in the US, vaccine distributed through civilian vaccination centers. We don't really know the completeness of utilization of all of the lots, for example. And we do know that in Brazil a large number of people received multiple doses of the same vaccine during the two weeks of the campaign, and others that don't come to the vaccination center may not be vaccinated at all.

We've also known that -- and it seems increasingly apparent -- that this syndrome is really only seen in primary vaccinees. So far all the cases have been reported in primary vaccinees only and not in anyone with previous immunity or

secondary vaccination or booster vaccination. I think this is quite interesting. In some of the other papers that we cite in this document, the viremia which can been seen transiently after vaccination with vaccine type and usually up until about day seven post-vaccination, with a peak around day four, this viremia is absent regardless of the sensitive methods that can be used to detect it in people receiving a booster dose. And we suspect that the pathogenesis of this is vaccine strain, viral replication and target organ damage, and so perhaps it's not surprising that if someone had been successfully immunized in the past or previously immune would not likely to experience the viremia and the target organ damage.

So how you calculate an incidence rate for an occurrence which probably only occurs on primary vaccination in an immuno-naive setting where there's not solid surveillance is really challenging. And what we uniformly agreed is that we don't really know what the incidence rate of this event is, but we think it's quite rare. And

fortunately since passive surveillance systems like VAERS and recently a report from Canada which reviewed their VAERS equivalent don't suggest that this is occurring at any high frequency, so we decided to give it a range of reported estimates acknowledging all the limitations behind it. And for that range we've chosen to look at the VAERS data and the publication by Michael Martin and others in the EID in December, which calculated a civilian utilization, civilian clinic doses distributed through the manufacturers of about 1.5 million between 1990 and 1998, and about four of these occurrences that we've recognized between 1998 through the VAERS system, giving us sort of a crude incidence of about -- crude reported incidence of about 2.5 per million, making the assumption that in the United States the vast majority -- and there are some data to support this -- are primary vaccine recipients. And the majority of doses used at that time were single-dose vials and there was very little wastage, so that's probably one end of the upper incidence

estimate in a passively-reported system.

The other end is to look at the campaign scenario and use literature reports from Brazil and say that during the 15 months of a vaccine campaign in Brazil, around which the two index cases were reported and they were clustered in time, about six months apart. There were approximately 23 million doses and two of those events made it into the published literature, although we are aware that the Brazilians are working up other suspect and have confirmed other cases.

So if you look at that outside range of what's published and what's used and reported in their paper, you get an accrued estimated incidence somewhere around .09 per million. So we report a range in here from .09 to 2.5. It's a very crude estimate and it would best be defined by some prospective attempts to study, but those are limited by the large numbers that would be needed to detect this type of event. And that's sort of where we stand on that factor.

So the name in the reported incident rate for

this phenomenon are two of the big issues that the Committee worked over for a while.

The third issue has to do with some revisions around recommendations or approaches to the use in pregnancy and altered immune states. I think there's been, in the decade since the last ACIP statement was published on this topic, a number of new references and studies that have gone into this statement which suggest a couple of things. One, that there is more apparent safety in using this vaccine in certain settings, at least in areas where there's large HIV-infected populations, and there are in similar experiences in terms of pregnancy. But in addition, there's probably a diminished response to the vaccine in some of these populations, as well.

Ideally, if we had testing available widely throughout the United States, one would like to confirm the take of vaccination by getting a neutralizing antibody test to the immunization in these populations with compromised immunity, if and when they were to be used. Unfortunately right

now, this assay is limited availability at CDC and perhaps one or two academic centers in the United States. And we felt to make a strong recommendation that post-vaccination antibody testing would occur in the absence of the capacity to do that would be problematic. And so what you see in the statement on this topic is consultation is recommended -- these should be considered and consultation is recommended with the CDC Lab folks at Fort Collins and an individual decision based on criteria there would be used to determine the availability and the timing and the ability to do that in real time relevant to the person's departure.

I think those were the major topics, Rick. If I missed anything, if any members of the working group are --

DR. CLOVER: Thank you very much. You covered it very well, and I really want to thank Marty for his hard work on this. There were multiple hours, multiple conference phone calls in putting this document together and I just want to thank Marty

and Tony for their hard work.

DR. MODLIN: Rick, shall we open it up at this time for questions or comments for the work group or for Dr. Cetron?

DR. SNIDER: Just -- This is Dixie Snider. Marty, it might be useful since we do have new Committee members here -- hopefully they've read the document, but just in terms of giving what the bottom line recommendation is about the use of the vaccine.

DR. CETRON: Sure. The -- So the bottom line is there's really not a change in indications for the vaccine from the previous 1990 statement, and that is persons traveling to or living in -- expatriates living in risk areas where yellow fever virus transmission is either endemic or epidemic should be vaccinated with this vaccine, albeit the recognition of some new, rare viscerotropic adverse events. What we do caution, however, is that we know from lots of work that the vaccine is both under-utilized -- that is, not being used in people going to areas of risk -- and consequently we've

had four or five imported cases of yellow fever into the developed world in unvaccinated travelers, and over-utilized, to the extent that some -- and many of the adverse events occurred in people who were not at risk at all in the areas of travel. And so what we try to caution in this is the more appropriate targeted use of the vaccine to those at risk, rather than perhaps a generous over-utilization or a misguided under-utilization. I think that really sums it up.

DR. MODLIN: Terrific. Let's open this up for questions or comments. Maybe I could lead off by asking about the data regarding immunogenicity in pregnant women. Is this largely women in their second and third trimester? Do we have any data based on length of pregnancy?

DR. CETRON: From what I understand, and there are others who reviewed this literature more directly, but from what I understand, these are data that come from developing country settings and which are confounded by malnutrition, and I think that's an important point. And the proportion of

women immunized in pregnancy that had a full response, I believe it may be cited in the document, I'm not recalling it off-hand, but it's certainly less than the 90-plus -- between 90 and 95 percent that one might expect. And I think these come from settings in Nigeria.

DR. MODLIN: Marty?

DR. MYERS: Just in follow-up with that question, outcomes of pregnancy --

DR. CETRON: One -- I believe -- and this also is in the statement, I believe one of 80 -- there were 81 immunized and followed. I believe one of 81 had congenital anomaly that was not necessarily -- or perhaps it was vaccine type virus isolated from guanine and it was not necessarily linked, so small -- a small data set and smaller numbers to really guide us.

DR. MODLIN: Bonnie, did you have a question?

DR. WORD: I think I'm jumping back -- going ahead. There was one statement when you were talking about concomitant use for malaria prophylaxis and what I was just -- I didn't know if

you had any comments about Methloquin. I might be wrong. I didn't have a chance to check, but something told me that there was --

DR. CETRON: Chloroquine was the -- where some of the previous work was done and not felt to significantly interfere with protection and the -- I'm not sure -- I'm not familiar with data regarding Methloquin specifically.

DR. WORD: Only reason why I bought that up because Methloquin is --

UNIDENTIFIED SPEAKER: Could you speak a little louder?

DR. WORD: Oh, I'm sorry -- because Methloquin is a preferred agent now for prophylaxis as opposed to --

DR. CETRON: Right, I don't believe there are new data looking at Methloquin in --

DR. MODLIN: Yes, Dr. Birkhead?

DR. BIRKHEAD: Gus Birkhead. Marty, in the discussion of vaccinating HIV-positive individuals, there's mention of symptomatic or asymptomatic status as being the determinate, but there's not

really any mention about viral load CD4 or whether patients are on heart therapy and I just wondered whether there was any discussion of that?

DR. CETRON: There is. There has been some discussion of that. There is a paper which appeared not too long ago in the literature posing a somewhat arbitrary cutoff of CD4 counts at 200, 200 and above being reasonable and below being more cautious, but I don't think there are enough sufficient data and certainly not viral load data for us to come down on a firm line on the topic.

DR. BIRKHEAD: Are there data on the question of symptomatic versus asymptomatic?

DR. CETRON: Well, there was a bit of data that it turns out that only one or two members of the working group were familiar with, and we thought it had appeared in published literature. It was a master's thesis from some work in Africa. And because we could never track down the reference -- and it basically argued on the side of safety, but because we couldn't really definitively track down either the thesis itself or find any further

reference to it, we elected to cut that sentence out uniformly, so --

DR. BIRKHEAD: I realize there are probably no data on this, but in general with HIV, if patients are on hard with suppressed viral load, adequate CD4, it's at least an indication they may be immunocompetent to respond to vaccine, so it's just a suggestion that that -- those factors. If the patient's under the care of an HIV-experienced physician, that would be another factor to figure into the discussion.

DR. MODLIN: Myron?

DR. LEVIN: Myron Levin. Just following up on that, I noticed that you used the dose of prednisone that -- prescribed use of the yellow fever vaccine was 10 milligrams, which seems to deviate from what we have in almost every other document. I wondered how you came to that and indeed I wondered how we came to 20 for other documents.

DR. CETRON: That's an interesting point. That was not a topic that was actively discussed

and I think that just got transferred over from the previous version, so I'd be willing to find out what that -- if there's a new standard for that question.

DR. MODLIN: Dixie?

DR. SNIDER: Well, I think Myron brings up a good point. That number that we use -- which I believe is 20, rather than 10, isn't it?

DR. LEVIN: It's two milligrams per kilo, but a maximum of 20.

DR. SNIDER: Right. And that came up a long time ago in talking about the use of live virus vaccines and BCG. I mean this goes back 20 years, I think when I first made my first presentation to the ACIP. And as far as I'm concerned, it really is sort of mythology in many ways. There was some data indicating that at a level somewhere around that, you might get some suppression of immune -- delayed type immune responses, but I think the data are pretty soft and it's rather arbitrary, and it would be nice to see some better data somewhere along the line to help guide us.

DR. MODLIN: Yeah. Myron?

DR. LEVIN: We at least should be consistent, I guess.

DR. MODLIN: I certainly would argue for consistency, I agree, and I think we all recognize the basis. We've had these discussions around measles and around other vaccines over the past few years.

I would point out, though, that we're dealing with a vaccine here where we do have a recognized, albeit very rare, but serious complication that occurs in presumably normal hosts, although we don't know for certain that they're normal. And therefore I think we have to pay a whole lot of attention to the possibility of -- the possibility -- of an increased risk for someone that's even slightly immunocompromised, even somebody maybe on heart therapy, so it's not an easy issue here.

Jon and then Mike and then Bob.

DR. ABRAMSON: Yeah, Jon Abramson. The way it's written right now for age, it provides the rationale for not giving the vaccine in four months

and under. But then it makes the leap of faith that you have to be hesitant between four and nine months, without any data. I think there are some data, if I remember way, way back. But I think it's important because you're asking a physician to make a judgment between four and nine months of age. They need the data in there to make that judgment on what the risk is.

DR. CETRON: And the data, I think -- the challenge is that the settings vary. For example, in endemic areas in Brazil and in other places where there are efforts to integrate yellow fever vaccine into childhood immunization schedule, but certainly in risk areas in Brazil. In the Amazon, for example, children are quite safely immunized at six months of age. And I say that in the absence of necessarily the best surveillance for adverse events. Yet at the same time, early on in the forties when the early trials were going on, I think that the post-vaccinal encephalitis or the neurotropic profile occurred in ages most frequently under four months, but there were still

cases -- there were still cases in the sort of four to nine-month range. So I think the data are somewhat conflicting and the decision has to be weighed by the risk of yellow fever. If you're in an area where there's an outbreak going on, the attack rate's going to be as high as 30 percent. And clearly the argument weighs in favor of vaccinating a five-month-old or a six-month-old. If you are traveling and it's elective, you know, it becomes a different issue. And it also depends exactly where you're going within the country. We tend to think of the travel by country boundaries, but actually it's a very focal disease and transmission is seasonal as well as sporadic, epizootic as well as endemic, and so the risks vary tremendously. As well as the phenomenon of epidemiologic silence where there are just no good surveillance data. So I think it's a big challenging and, you know, we would say if the option exists not to immunize under nine months, that's good. But there are clearly situations where vaccinating between four and nine months is

reasonable. And in endemic areas in Africa, as well as South America, that's been safely applied.

DR. MODLIN: Dr. Decker?

DR. DECKER: Michael Decker, Aventis Pasteur. As Marty and Rich know, I'd like to request -- before the Committee votes -- a change in language in one section, lines 114 to 116 of -- which appear on page four, and that's a paragraph that prescribes the indication for laboratory personnel.

The proposed language differs from the existing language by adding into that sentence the phrase, the 17D vaccine strain. And to do so, as it is here, would cause a profound and I think inappropriate change in our employee health practices inside the factory.

This isn't vaccinia, and I can't think of any reason why we would want to deliberately inject a half-cc. of the final product into somebody who might come in contact with a bench that might have come in contact with trace quantities of the final product. It makes no sense.

So what I would propose instead is that in

front of the phrase, the 17D vaccine strain, you add the words, concentrated preparations of, which would then make this language consistent with what our practices are. If you don't make that change, we're going to be in a position of having to immunize hundreds of people, where right now we immunize about six people in the factory.

DR. SNIDER: Michael, could you say what line that is again?

DR. DECKER: That would be line 115, and the proposal would be that after the second word in line 115, which is presently the word or, we insert the phrase, to concentrated preparations of. And then we'd be proposing it not for merely final product that could have a trace of it on the outside of the vial, but for people working with something special that might pose a hazard.

DR. MODLIN: Okay. The comments regarding Dr. Decker's suggestion? Marty or Rick?

DR. CETRON: No, I have no problems with that. I think that was the intent, as this topic was raised and discussed by the working group. It

didn't intend to be secondary, you know, trivial, remote contact with vaccine-strain virus.

DR. MODLIN: Thank you. Dr. Chen?

DR. CHEN: Also I wanted to second the wonderful work that Marty and the work group has done on this. Unfortunately I missed the last conference call where the discussion about how to express the risk best was discussed, and I wanted to suggest on line 315 also a friendly amendment. The range of reported frequencies is currently reported out. The high range of 2.5 per -- is .09 to 2.5 per million doses. Essentially what this is describing is describing the passive surveillance systems available out there, so the 2.5 per million, as Marty indicated, comes from VAERS. We know that the VAERS, even under the best setting, has a degree of under-reporting. With the rotavirus intussusception, even with the MMWR article that came out, our capture/recapture now suggests only about half of the real cases out there were reported to VAERS. So that from some of the unpublished data that Marty has shared earlier

that the real incidence is likely to be let's say one order of magnitude more frequent at the end of the day, once we've done more studies. And given that the ACIP regs for the US population, most of the yellow fever vaccines will be given electively to travelers, while it's accurate that we describe the document, it's a reported incidence. I think most readers will actually miss that nuance. So what I would suggest is that we add major limitation to these estimates were presented previously, comma, however the real incidence is likely to be higher. So that at least, you know, gives the reader that sense that these ranges in fact are not the ones necessary to make their decisions on, so that would be my recommendation.

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

DR. CETRON: I think Bob is absolutely right about that. The harder you look, the more often these kinds of things come up.

DR. MODLIN: Bob, do you want to suggest how much higher they may be in this sentence, so as to add some clarity here?

DR. CHEN: That's the part that you engender a lot of controversy. I think we are only working with the Department of Defense to do a large-link database study of their population. They're -- You know, at one level that's perhaps not quite representative of the US, population's a little bit younger, a bit healthier, and we'll be hopefully getting a better estimate. I think at the moment I can just live -- You know, I'm happy with higher. I think once we start to venture a number, we may start to get into difficulty.

DR. MODLIN: Jon?

DR. SNIDER: This is Dixie. Just in follow-up to that, I think Rick, Marty, it would be good -- even though we don't hold everybody to the hard standard of following our format for recommendations, I think this is one where we have -- the last item for our recommended format is recommended surveillance, research, education and program evaluation activities. It seems to me this is one of those documents that would benefit from pulling out from the document the things we don't

know that we really do need to know and add a section there. I think a lot of it is already in the document, and much of it in an implied manner, but it could be useful for efforts of the nature Bob is talking about to research organizations to have the ACIP making those kinds of recommendations.

DR. MODLIN: That's a good point. Walt?

DR. ORENSTEIN: I just want to endorse what Bob said, and also not to try and quantitate our imprecision. I think that what we have seen with other adverse events there's quite a bit of variability in reporting efficiency and I think that we ought to stick with what we know, which is -- I think with Bob's modification would be reasonable.

DR. MODLIN: Fair enough. Rick?

DR. ZIMMERMAN: Dixie had -- and I share a similar idea. I think it's a very well-written document, but I think it would benefit from a research section. I think in addition to the adverse events research, there is also the

possibilities of some other things, including simultaneous vaccination with other vaccines -- influenza, mumps, rubella, as examples, Methloquin, and so there would be several other things that could be added.

DR. MODLIN: Other comments? Yes, Sam.

DR. KATZ: Not a comment, but a question. Lines 148 to 151 talk about boosters, and I wondered where do the International Health Regulations come from that require boosters every ten years?

DR. MODLIN: Where -- what do you mean by where?

DR. KATZ: Who makes the International Health Regulations?

DR. CETRON: Well, it's this -- the IHRs tend to be drafted in Geneva by working groups in consensus, and then they're signed on by member countries who either sign on to the whole or can sign on with reservation about selected parts. So this -- it's generally where that goes. They don't tend to be revised all that often, although they're

actively undergoing a revision process currently. To my knowledge, this issue is not one that's under debate. It had been raised maybe a decade or so earlier about revising this boost for ten years based on some data in the US looking at the duration of protective immunity, but that was turned down, saying the setting in which it was studied in the US represented an ideal circumstance that may not apply in developing county areas and they were more comfortable with the ten-year booster.

DR. KATZ: When you think of all the problems of injectable vaccines in the developing nations and in sub-Saharan Africa, South America, Asia where yellow fever may be a problem, imposing a ten-year requirement for boosters is really far from realistic. But I accept that we have no control over that. Thank you.

DR. MODLIN: Yes, Dr. Deseda?

DR. DESEDA: I just wanted to ask, after what Dr. Katz was asking, why is yellow fever vaccine handled so differently from all other vaccines in

the sense that we need a special certificate and, you know, you could say the same for rabies or other vaccines. Why specifically nobody ever addressed this, to my knowledge, anyway?

DR. CETRON: It evolves from historical circumstances and flows into the IHR issue because of the large numbers of outbreaks of yellow fever that occurred during resettlement and colonialization. The idea of having a way to protect entry or importation of yellow fever virus by requiring proof of vaccination really originates with that. And there was a period of time in which that may have seemed -- where vector-control was strong and the number of cases was not climbing -- reported cases to WHO and so on is not climbing. That may have seemed superfluous. But in the current climate, with the resurgence of yellow fever and the risk of re-urbanization in Latin America, I think several countries have felt strongly that this needs to stay in place, and it is planned to continue as part of the new IHR revision process. And in addition, there are very

strong feelings on the part of Asian countries, which are receptive for the introduction of yellow fever virus into their *Aedes aegypti* mosquito pool that are adamant about not admitting people without proof of immunization.

DR. MODLIN: Rick?

DR. CLOVER: If I could, I would like to summarize what I've heard for the --

DR. MODLIN: One second, before we get there, Dr. Midthun has a comment.

DR. MIDTHUN: I know everyone really worked hard on -- to name this entity and what you all came up with was a vaccine associated with viscerotropic disease. I guess the question I have about that is that it really would seem that with the Brazilian and the Australian cases that there was a lot of evidence that really suggested a causal link. In those particular situations there was a lot of histologic type information, virologic information. With the US cases there was much less in the way of tissue specimens and it was overwhelming disease, but it wasn't -- certain

pieces of information were missing. So I guess what I'm struggling with a little bit is where we talk of where -- the section where you describe the US cases and you say that because of lack of tissue specimens, you can't really -- you can't definitely say that there was a causal relationship between these events, but you're calling these events vaccine-associated viscerotropic disease, which by definition means that there's tropism of the virus with the organ, so I guess I'm just struggling a little bit with, you know, what one calls this entity.

DR. MODLIN: Do you have a better suggestion?

DR. MIDTHUN: No. I mean clearly in all of these cases it was a systemic disease that occurred. It was a vaccine-associated systemic disease that certainly in the key cases involved multiple organs, and that's why you all had initially come up with the multiple organ system failure. But then as you looked at additional cases that had been reported, it wasn't really multiple organ system failure that you necessarily

saw. You saw involvement perhaps of the liver or of the kidneys or of both, but not necessarily associated with organ failure. In some cases clearly -- you know, I guess --

DR. MODLIN: Don't you think with the data that Dr. Cetron's quoted from Dr. Monath's unpublished study that suggests the vaccine virus is viscerotropic, even to a proportion of asymptomatic individuals, that --

DR. MIDTHUN: I'm not saying that it's not. And again, I come back to the Brazilian and Australian cases. I think they're -- clearly the evidence is compelling that it is a vaccine-associated viscerotropic illness that led to foment an outcome in these. I guess what I'm struggling with a little bit more are some of these other instances where yes, perhaps some of these manifestations were indeed the result of viscerotropism by the virus, but we don't definitively know that. The connection really hasn't been made in some of these instances. And so I'm just raising a point that it -- I don't know

how you make the link, how you say on the one hand this is a viscerotropic disease, and then say but we're not sure it's causally linked. That seems to me not totally consistent.

DR. MODLIN: Okay. Marty, then we need to wrap this up.

DR. MYERS: Yellow fever is both viscerotropic and neurotropic, so I guess the Committee must have -- or the work group must have struggled with another expression, so maybe you can explain why you don't call it vaccine-associated yellow fever, parentheses viscerotropic, parentheses neurotropic, because that's really --

DR. CETRON: That was one of the things on the table, and I think viscerotropic disease was sort of the compromise. Some -- the full spectrum, as Karen points out and Marty just pointed out, for wild type is exactly what we're seeing in this, from asymptomatic infection to foment a multi-organ system failure to isolated hepatic involvement with full recovery. I mean this is actually what yellow fever virus does. And I think the Committee

firmly believes this is what vaccine type virus does. There's little to -- reason to -- there's little difference. There's 99 percent sequence homology between the strain that's used in Brazil, for example, and there's virtual identity -- to the extent that that's possible with quasi-species -- with the Australian 17D 204. So there's -- the Committee doesn't really have any reason to believe there's something different necessarily going on. And several members proposed vaccine-associated yellow fever for exactly that reason, and there were others that objected that well, this isn't really yellow fever the way they understood it. But it is -- yellow fever is in fact a spectrum like this, so --

DR. MODLIN: Karen, there seems to be a lot of angst these days over what to term vaccine adverse events, as you know, and it seems like this is kind of the same exercise. I get the sense that the majority of the members of the Committee are at least comfortable that this is as close as we can get to a reasonable definition.

One more comment and then we need to vote. Bob?

DR. CHEN: And that's really just a clarification, Karen. I think I was probably responsible for suggesting how we might try to name this based on past experience of vaccine-associated paralytic polio I think was in part the etymology of this term, and I think we were comfortable with the term association, because I think the word association, as it is used, could mean truly causal -- as definite as you can in terms of laboratory viral isolation -- but it could also mean that it suggests but you haven't quite proved it. So I think the term associated gives us both the definitive as well as the softer, and I think the US and the down-under case difference is really that the US cases were retrospectively and so we didn't have the advantage of collecting the cases on a fresh basis, whereas the down-under cases, they knew about this investigation so they could get all the viruses, et cetera, at the same time.

DR. MIDTHUN: I guess the point I'd make,

though, is that you say -- okay, vaccine-associated paralytic poliomyelitis, it's associated. I guess the difficulty I'm having with vaccine-associated viscerotropic disease is, by definition, the viscerotropic means the virus has done it. It's no longer just an association. I mean you're saying that there's causality. And again I'll come back to the Brazilian and Australian cases. I think those are vaccine-associated viscerotropic disease. You know, I think the data are there. I think for the US cases what I would say is those might be cases of vaccine-associated viscerotropic disease but we don't know in those cases whether it was actually viscerotropism of the vaccine because we just don't have that information. I guess that's the distinction I'm drawing on.

DR. CHEN: Karen, I think as we get more cases, we're happy to come up with definite probable and possible categories of this, but I think at the end of the day, we have to come up with a term that is reasonably simple, and this is our best shot at it and we're open to other

suggestions, but I think what you're saying is that down the road we do probably want to have definite probable and possible.

DR. MIDTHUN: Yeah, I mean I would say all these cases are vaccine-associate organ system disease. I think for some of them you actually have information that says there was viscerotropism involved; in the others, you don't have that. I guess that's the point.

DR. MODLIN: Fair enough. Rick, let's wrap things up, if we can. You wanted to summarize that -- there's basically three changes that I heard. Do you --

DR. CLOVER: Correct. Let me try to summarize these and I'll be glad to entertain others if I've missed them.

The first one is line 394 of the changing in the prednisone dose from ten to 20 milligrams.

The second one is line 115, the insertion of the phrase: concentrated preparations of -- in front of the 17D vaccine.

The third change is in line 315, the addition

of the -- however, the true incidence may be higher.

And the fourth one is the addition of a paragraph on research or areas that need further work.

DR. MODLIN: Okay. Is there any other aspects or parts of the statement that anyone can't live with or has a problem with? Hearing none, I'll entertain a motion that the Committee adopt the statement.

DR. ZIMMERMAN: So moved.

DR. MODLIN: So moved by Dr. Zimmerman. Seconded --

DR. LEVIN: (Indicating)

DR. MODLIN: -- by Dr. Levin. Those who are conflicted with Aventis are conflicted. The rest of you may vote. Those in favor of the motion?

Those in favor are Dr. Smith, Zimmerman, Tompkins, Mr. Salamone, Dr. Deseda, Dr. Brooks, Dr. Offit, Dr. Levin, Dr. Birkhead, Dr. Word and Dr. Modlin.

Those opposed? None. Those abstaining? Dr.

Rennels.

Thank you. And Marty, thank you very much, and Rick for all your hard work on this.

The next item on the agenda will be an update on the anthrax recommendation that will be led by Drs. Ashford and Helms. Dr. Helms of course has just very recently stepped down as a member of this Committee and has graciously continued his involvement with the work group representing the ACIP to a recent meeting of the National Academy of Sciences on anthrax and anthrax vaccine and responses to the anthrax threat. And Chuck, you're going to lead things?

DR. HELMS: I will. Thanks very much, John. Good morning, everybody. It's good to be back. What David Ashford and I are going to try to do over the next 30 minutes is to update you on where we've come since last December when the Committee forwarded some advisories to the -- to Dr. Koplan in regard to the use of anthrax vaccine and other issues related to the anthrax outbreak.

I'm going to begin by reviewing with you a

meeting that I participated in on December 15th, 2001 -- ironically, a full year after, to the day, the release of the first anthrax recommendations that we as a Committee did. That committee was called to really work on an issue which was arising in Washington, D.C. about the optimizing of post-exposure prevention of inhalation anthrax, and we were to discuss issues and options in relation to that situation that was arising. And specifically that was about the Hart Senate Office Building exposure and the thought that the intensity of that exposure in terms of numbers of spores was significantly higher than one might have expected, and would our recommendations for post-exposure prophylaxis really hold under circumstances like that.

In their introductions, D. A. Henderson and Jeffrey Koplan explained that the meeting was occasion to assist them in advising care-givers and the Secretary of HHS about appropriate options in managing individuals recently exposed to those anthrax spores. And in particular they cited the

concerns that those physicians who are managing staff up on the Hill had about what constituted optimum post-exposure prophylaxis when the spore inoculum was very high, as it appeared to be in the case of that setting.

In specific, the physicians on the Hill were wondering whether 60 days post-exposure antibiotic prophylaxis was sufficient to eradicate all the spores in their patients. They wondered whether extending antibiotic treatment or adding immunization with anthrax vaccine and a longer course of antibiotics to the currently recommended regimen might not be safer. So Drs. Henderson and Koplan called the meeting to address those issues.

Specifically, the options that were raised in terms of approaches to solutions were, one, to treat for 60 days of post-exposure antibiotics and stop. That's the current recommendation, as you're all aware. Secondly, to treat with antibiotics alone for 30 additional days. And third, to treat with 30 additional days of antibiotics and immunize with three doses of anthrax vaccine.

In the first half of the conference, several scientific papers were read or reviews presented pertinent to the subject. Much of the information had been reviewed by this Committee and by the working group on anthrax vaccine in its initial recommendations and were part and parcel of those recommendations. They were also reviewed -- some of the findings were reviewed by us later, ACIP at the time, in November and December in its advisories to Dr. Koplan.

David Ashford will comment on some of the novel information that was presented at the meetings for you in a moment, but in the remainder of my time I'd like to comment about the last half of the conference.

I had the opportunity to summarize the original ACIP recommendations related to post-exposure prevention of inhalation anthrax, as well as those updated recommendations requested and sent to Dr. Koplan this past November and December. Among those latter recommendations, the one that was most pertinent to the circumstances surrounding

the need for the conference was in relation to the use on IND of newly available anthrax vaccine adsorbed in the post-exposure setting. You'll recall in our December telephone call meeting that ACIP re-examined the post-exposure use of AVA vaccination in light of, at the time, several new pieces of relevant information. First, ongoing epidemiological investigations were suggesting that some persons might have been exposed to high doses of anthrax infectious particles in excess of those doses previously studied in animal models, and therefore the degree of effectiveness of antimicrobial prophylaxis in such individuals thus might have been less predictable than in persons exposed to fewer particles.

Secondly, in a study of over 9,000 persons who had received post-exposure antibiotics for suspected or confirmed exposures to *B. anthracis* spores, the 30-day adherence to antibiotic regimens range widely, from only 45 percent in some instances up to 94 percent. Therefore, the predictability of the effectiveness of post-

exposure prophylaxis when adherence to antibiotics was low might thus be less predictable.

Thirdly, an increased supply of AVA vaccine had become available for civilian use. The available vaccine had come from lots which were not then licensed. Moreover, AVA was not licensed by the FDA for post-exposure prevention of anthrax. Given this new information, the ACIP endorsed the CDC making anthrax vaccine available as a new investigational drug on IND to exposed persons. That was the key recommendation we made that was pertinent to the conference, I thought.

The Center for Civilian Bio-Defense Perspective from Johns Hopkins felt similarly about making anthrax vaccine available on IND. Interestingly, unlike physicians at the Hart Senate Office Building, who were pleased that vaccine might be made available, representatives of local and state health departments in states where anthrax release had occurred, were less than enthusiastic about recommending the vaccine under the current circumstances. The reasons that I

caught during the discussion related to that appeared to be related to controversy over determining who was at greatest risk and who should receive the vaccine, controversy over whether the vaccine was really necessary, and observations that those exposed outside the Hart Building setting were not likely to take the vaccine if offered, especially if offered without proof of need.

As you know from reading the newspapers -- my favorite journal these days is the New York Times or the Washington Post on this subject -- anthrax vaccine was released on IND, coupled with 30 days additional post-exposure antibiotics for post-exposure prophylaxis. And what I gather from the newspapers, consistent with the mixed response to the possibility at the conference, the demand for vaccine, from newspaper accounts, seems low. David will bring us up to date on some numbers in respect to that observation.

That concludes my report on the meeting. I've tried to be brief and succinct here. And I will turn the rest of the presentation over to Dave

Ashford, who is prepared for the fact that the slides may or may not work, but I guess they're going to work, good.

DR. ASHFORD: I'd like to thank the Committee for the opportunity to address these issues related to anthrax and our response to the bioterrorism events at the CDC. I'm going to speak specifically on a few different issues, fleshing out some of the topics that Dr. Helms brought up in his introductory remarks -- as soon as we have a computer.

I've organized this around a brief update on our activities with the Committee before 2001, and then some specific information on the CDC response -- the details of our response to the anthrax attack, with an emphasis on our post-exposure prophylaxis and on the use of vaccine in the post-exposure prophylaxis recommendations. And then I've organized some of the information related to new scientific information that I thought the Committee should be aware of in relation to those recommendations and our original recommendations

about the vaccine. And I'll follow that up with an update on the IND.

While we're waiting, I think I'll also just say that I'd like to thank Dr. Chuck Helms for the many years now -- it's been two and some-odd years -- of working together on these anthrax vaccine recommendations. We're very sorry to see him leave the working group on bio-terrorism preparedness.

As I mentioned, I'll just go through a brief time line of our previous activities prior to 2001 and then review the response with our specific emphasis on the post-exposure prophylaxis and vaccine issues. I'll touch on the new scientific insights that I think attributed to some of the decision-making as the response was progressing, and then specifically review the anthrax IND.

You'll recall that we first met in October of 1999 to discuss the possibility of moving on specific recommendations regarding anthrax vaccine. We reviewed some of the initial data regarding anthrax and we introduced the possibility of coming up with a statement. And then in February I

reviewed the science related to the vaccine and post-exposure prophylaxis in general. We came up with some initial language. And then in June of 2000 we approved the full recommendations for the use of anthrax vaccine in the US, our recommendations from the Committee, and those included specific recommendations related to the possible event of bio-terrorism in the United States.

We continued preparations at CDC and then on October 3rd, Dr. Lisa Rotz and I were notified by Steve Wertz (phonetically) of the State Epidemiologist of Florida, of the first case of inhalational anthrax caused by *B. anthracis* to be reported in the United States. This was reported at the time as a suspect case on the 3rd. A 63-year-old male photo editor employed at the AMI with onset of fever on September 30th. He had also altered mental status. He was admitted the day before with severely altered mental status and signs of meningismus and he had a lumbar puncture performed, and we can see here the results of the

gram stain of that CSF, with several bacillus -- with lots of *Bacilli anthracis* in chains and lots of neutrophils. He was positive on blood and CSF cultures, and the cultures were sent to CDC immediately for identification on that same day, 10/3, and he was confirmed as a case on the 4th.

Sadly, after a period of what appeared to be a potential improvement, he deteriorated and we lost this patient. His autopsy revealed that he had indeed been infected by the inhalational route and he was confirmed as an inhalational case on the 6th of October.

This was important in this particular case because the initial signs on the chest radiograph did not reveal mediastinal widening, and there was some question as to what the possible route of infection may have been for that index case.

Following the index case we had a report of a cutaneous -- a suspected cutaneous case from New York City on the 11th and we worked through that evening with immuno-histic chemistry to rule out or rule in the possibility that this was also an

anthrax case and confirmed that on October 12th. This led to a large investigation in New York City and the discovery of several other cases.

Then the investigation spread as we had cases and exposures appearing in Washington, D.C.; in New Jersey associated with the postal delivery of *B. anthracis*; and then ultimately a case in Oxford, Connecticut on November 20th; again across the eastern seaboard, a number of different clusters of cases associated with delivery. This is the histogram of the outbreak, and what we can see here are two different clusters of cases associated with two separate deliveries of mail, one with postmark -- one particular set of envelopes with postmark on September 18th, the other cluster of illness associated with the delivery to the Capitol with postmark on October 9th. Each of these squares is colored according to the state affected. You can see that multiple states were affected by each of the deliveries. The inhalation cases are indicated with arrows in these -- in this histogram. And then ultimately we had the final inhalational case

associated with -- that appeared on November 14th, and for that case we never did have an association of a potential vehicle discovered.

These are the letters associated with the delivery to the Capitol Hill that were determined to be contaminated with *B. anthracis* spores, and these particular envelopes and all the others -- and some others that we just have to suspect may have moved through the mail but were never confirmed -- led to the exposure of thousands of individuals.

Our immediate challenges in the response were regarding the issues surrounding post-exposure prophylaxis of those individuals exposed, and we first submitted an IND application immediately to the FDA to use the anthrax vaccine for post-exposure prophylaxis, as was recommended by the Committee following an exposure. The recommendation stated that if vaccine was available, it should be utilized in combination with antibiotics. And we also were immediately faced with the issue of the numbers of days of

antibiotic therapy which the Committee initially struggled with in its recommendations prior to December, 2000. And we originally stated in the recommendations a range of 30 to 60 days. We had to adjust that for -- primarily for logistical reasons of recommending a range of antibiotics became very difficult for management of the stockpile and other issues related to managing post-exposure prophylaxis, so we stuck with a single recommendation of 60 days of antibiotics for post-exposure prophylaxis. We reconvened the Committee and the Committee endorsed the routine use of 60 days of antibiotics for post-exposure prophylaxis.

Eventually approximately 10,000 individuals were recommended to take 60 days of antibiotic therapy. This is a humongous effort, led by both state, local and Federal health departments, and it's required a tremendous amount of cooperation to get this off the ground. We had no idea exactly how huge this effort would be.

Post-exposure prophylaxis of these individuals

were initiated between October 8th and November 25th, 2001. These are primarily occupational exposures from the media outlets or the media offices, the postal workers, from the postal facilities and Congressional staffers in the Capitol Hill exposure.

I just wanted to revisit the primary complicating factor for post-exposure prophylaxis for *Bacillus anthracis* and that is the fact that the spores remain in the lung, apparently viable for long periods of time. And this was first -- not first, but primarily indicated by a paper by Henderson in 1956 among macaques. Macaques were exposed to an estimated dose of 400,000 spores and here we have the table that shows the numbers or percentage of spores of those original 400,000 that were recovered at different days after exposure. There's a steady decay of recoverable spores after exposure, but at 50 days, two percent of spores were still recoverable.

The difficulty with this data, and something that we have to struggle with, is that the exact

risk translation of the source spore survival with the disease threat is not known. These animals were sacrificed at these times. They did not die of *Bacillus anthracis*.

There is additional data that helps with the possible for -- from human exposures from the exposures that assist with this assessment of how does the survival of spores translate to risk of disease, in that there's a single case with an extension of incubation period out to 43 days. So this assists us in trying to ascertain exactly how does this decay translate to risk. There's only a single human case at 43 days. That's the longest incubation that's reported for humans.

This is the same data presented in another format here on a log scale, with the percent of retention on the Y axis and days after exposure on the X axis, and basically this shows -- with these few data points -- that survive -- that at 60 days there's a two-log decrease in spore concentration in the lung tissue.

That survival information of the spores,

combined with what was new information released during the investigation, raised additional concerns regarding the potential need for added post-exposure prophylaxis. And in the case -- specifically in February to April of 2001, the Defence Research Establishment Suffield conducted a study of the release of a beakal BGI simulant from envelopes, and this simulant acts similarly to *B. anthracis* spores. They conducted this experiment because of hundreds of threat letters that were being delivered in the late nineties, and they decided to specifically study what exactly happens under these conditions. They mimicked the opening of envelopes in a chamber that they constructed, 18 by 10 by 10 feet, approximately, a room-sized -- small room, and then they established an extensive and sophisticated system of aerosol sampling as an individual was in the room in full protection gear opening the envelope, and evaluated what happened with those spores -- where they moved and what was the exposure to the individual sitting in the room. He also had personal sampling systems on him, as

well as the plates set up through the room.

Based on this experiment, the estimated exposure in this environment would be 500 to 3,000 LD50s in a ten-minute exposure, and that compares to the macaque studies that are the basis for a lot of the -- the basis for the post-exposure prophylaxis recommendations that we've made are in those macaque studies the exposures were anywhere from eight to 20 LD50s, and occasionally up higher, but primarily at a lower level. So our concern increased when we learned that the exposure potentially to put people in those environments was very high.

Additional considerations for vaccination also that we were and continue to be investigating further are the risk of re-aerosolization following primary release. In the December, 2000 statement, we all addressed this particular issue of re-aerosolization, and the risk was considered negligible based on DOD experience, publications from DOD and our conversations with our Department of Defense colleagues. However, those were

experiences based on different environments, probably, and that may explain what the differences that we have seen in the first instance of bio-terrorism in the United States, the first opportunity to potentially understand what happens under these conditions.

We have certain preliminary data generated during the response that suggests re-aerosolization is a concern under certain circumstances, and particularly in the Capitol Hill evaluation there was an investigation lead by EPA and DOD that suggested that those moving into that environment -- it's a particularly unique environment in that the air circulation systems were shut down at a half an hour after the initial release, so there was no opportunity for dilution effect or pulling the spores out of that room -- or those rooms. And those particular studies suggested that normal activities in that environment might create re-aerosolization. They initiated a -- not a similar study, but air sampling while their workers were in that environment and detected spores in the air.

Another consideration that Dr. Helms mentioned earlier was post-exposure prophylaxis adherence and our initial data -- this is some initial data. These data are subject to changes. They're again preliminary, but we've seen adherence ranging from 40 percent to 98 percent, suggesting that individuals are making their own decisions about the need -- their risk, the need to continue, and they have other factors to consider and the need to take antibiotic prophylaxis, and perhaps there's an additional benefit that could be gleaned from vaccination in these situations, despite the fact this adherence -- potentially low adherence is despite the fact that there are -- they were all considered to be exposed and they were all advised to take 60 days of antibiotics.

And then as time went by, the 217,000 doses of anthrax vaccine were obtained by DHHS from DOD and the Committee encouraged the provision of this vaccine under an IND to the exposed persons, those 10,000 individuals. This is the IND protocol that's in effect. After informed consent, the

regimen is for three subcu anthrax vaccine adsorbed doses at zero, two, four weeks and 40 additional days of antibiotics. For children we had a contingency in case children should be brought into the IND, and that was for three IM AVA doses at zero, two, four weeks and 40 additional days of antibiotics, switching to amoxicillin once susceptibility results are known and we knew some information about these particular isolates.

The eligible population were all the individuals known to be exposed to *B. anthracis* who were originally recommended to receive 60 days of antibiotic prophylaxis.

Thanks to another extremely great effort on the part of multiple personnel at CDC, led by Dr. Nancy Rosenstein, but including Dr. Michael McNeal from NIP, Dr. Stacy Martin from NIP and many others, the IND has been implemented at all affected sites. At Washington, D.C. the sites are the Brentwood mail facility, what is called the State Department mail branch or SA-32 at the Hart Building, the AMI building exposure, all those

individuals at that site were offered -- the New Jersey site, New York City and Connecticut postal facilities.

The number educated about the program -- that is of the approximately 10,000 people originally exposed, the number that have been reached and educated are now at 5,420. The number enrolled is 1,740 or 32 percent of those individuals. Those that chose antibiotics only are the majority, with 1,548 and only 192, but that is still a considerable number, chose vaccine. The initial results on the adverse events we have to report are only the number of serious adverse events as defined by the FDA, and that is one. That serious adverse event was an acute renal failure in one individual that did not receive vaccine, but had received Ciprofloxacin and had continued on Ciprofloxacin and had a renal biopsy with histopath consistent with Ciprofloxacin toxicity. Thank you very much.

DR. MODLIN: Thanks Dr. Ashford, and to Chuck, as well. We put this item on the agenda largely

for informational purposes this morning, but of course I'm sure this will generate some questions and queries. As both Chuck and David mentioned, the ACIP did meet by conference call and discuss this issue specifically in December, and what you've heard is basically a summary of the outcome of that call.

Stan?

DR. PLOTKIN: Yeah, Dixie knows about this complaint that I and other members of the DSMB has raised and I'd like to have Dr. Ashford's comments on this. The acceptance of the vaccine was of course, as you have there on the slide, extremely low. I reckon it was something like 1.4 percent of those eligible. Now aside from the -- what shall I say -- the lack of confidence expressed in the vaccine, despite a recommendation from two expert committees, there was also the issue of the consent form, which in my judgment was unfairly written, such that I doubt that I myself would have taken the vaccine had I been offered the consent form.

Now I understand that the process of writing

that consent form was a rather laborious one, but for the future I think it may be of interest for you to tell us how that happened because, again, we may face the situation in the future and the question of who writes the consent form, who describes the risks and benefits -- and I underline benefits, the possible benefits of vaccination, who that or what that body will be.

DR. ASHFORD: So the question is how did the consent form come to be, I believe. This was a consent form which was generated originally at the CDC, went through multiple human subjects review at multiple agencies within the Executive Branch, and it developed to its form. Dr. Snider, did you want to add anything else?

DR. SNIDER: Sure, David. I mean I think Stan's view is certainly one view that I'm sure many other people share with regard to how the consent form presented the vaccine option. Clearly this is an unprecedented event, I mean a very high profile event, and without naming names, I can say that people who were very much engaged in exactly

what that consent form said were high level people at FDA, the Office of Human Research Protections at the Department of Health and Human Services, the National Institutes of Health and in the end there was a person at the White House who passed off on what the consent form said. And I think John Livingood, who is my deputy who had to lead those discussions since he's responsible for human subject protections issues at CDC, did an extraordinary job of trying to incorporate a lot of disparate points of view and get this done. And while I think the form is not ideal in the view of some, given the time pressures and the level of involvement, and the points of view of some of those officials in the department in the government, I compliment the program and John and all the people who were involved in actually getting it done.

I think that it is an important question about how these consent forms should be developed, who should have input. And hopefully as we move to develop a smallpox consent form, which is what

we're doing right now -- I don't think there's any secret about the fact that we're preparing -- that we can explore other options and not do things in such a compressed time frame and perhaps make a better product in the end.

DR. MODLIN: Peggy?

DR. RENNELS: Should there be another exposure, I'm concerned about just recommending it for children. To my knowledge, there are no data whatsoever on the use of this vaccine in children, and children can become interpreted as a two-week-old. So I think the working group at least needs to discuss that more.

DR. MODLIN: Good point. Yes, Natalie?

DR. SMITH: Yeah, just a couple of questions. I realize we will have ongoing discussions in the B2 working group, but I wondered what your opinion was in the event that we had a highly concentrated event again, would we more swiftly move to vaccination this time? And then just the second question is we've been talking about pre-event vaccination for laboratorians, especially in

government labs that deal with -- dealt with hundreds of powder exposures and how is that process going forward?

DR. ASHFORD: The issue related to whether we would immunize earlier is related to supply of the vaccine, and we -- I just wanted to update on supply issues. The lower half of this slide addresses that lots that are now available through the DHHS/DOD agreement, and we have about 220,000 doses available, and that's about -- that's sufficient for 73,000 people for post-exposure prophylaxis, so there is vaccine available for post-exposure prophylaxis and the recommendations will stand as utilizing the vaccine in combination with antibiotics as early as possible.

In relation to your second question --

DR. SNIDER: Yeah, and I think as the person at CDC who's sort of been designated as the negotiator with the Department on pre-exposure prophylaxis -- as David said, we have these doses. One of the things that is somewhat problematic with regard to pre-exposure is that although FDA

believes that all of these doses are safe and effective, there are -- the largest subset of vaccine we have available is not licensable. There is -- There are a certain number of doses that are now licensed, but they're a limited number of doses and we've had some disagreements with the Department on whether to deploy those doses that we have that are licensed for pre-exposure or not, or whether to keep them in reserve in case of an event. Hopefully that situation will get resolved in the fairly near future, either by further discussions with the Department or hopefully increased vaccine available of -- made available for the civilian sector through negotiations with DOD and increased production from BioPort, but these are -- have very difficult issues to deal with in the setting of a short supply of licensed vaccine.

DR. MODLIN: Dr. Chen?

DR. CHEN: David, I was wondering if you could say some more about the choice to go the subcu route for the adult three dose. As you know, much

of the concern about the safety in part may be due to the administration of this heavily alum hydraventive (phonetically) vaccine subcu rather than IM, and there's a kind of a trial underway to assess that. Since this was given under IND under a situation where there's a lot of public concern anyways, I was just curious why you guys chose to go the subcu route rather than the IM route.

DR. ASHFORD: So the preliminary data from one pilot study suggests that local reactivity may be much lower by the IM route, but that data was insufficient to test statistically for the -- for FDA's concerns regarding the change in route and we submitted a larger IND for our human protocol to evaluate that exact question. This did come up in discussions with FDA as to whether we could offer the vaccine by intramuscular route for adults as well as children, and there were differing opinions at differing stages of those discussions, but generally speaking, the consensus was that this would be administered by subcutaneous route for adults. That's all I can say, Dr. Chen.

DR. MODLIN: Myron, did you have a --

DR. LEVIN: Yes, following up on Stan's comments, it strikes me that one of the reasons for the low use of the vaccine is the terrible press that the vaccine had gotten before, during and after this outbreak. And I'm wondering what -- how we're going to respond in terms of education, if it has to be used again.

DR. ASHFORD: I think one of the -- this bears on the previous question about whether the consent form influenced people to not choose the vaccine and is worthy of study among those that did not participate. What exactly was it that influenced people to not participate in the program is a question that should be evaluated further so we can discuss that. But certainly possibly the negative media had a strong influence with those individuals. I can't say with certainty. But again, the ongoing communications are improving the public's knowledge of the safety of this vaccine.

DR. SNIDER: And just to supplement what David said, I think that was one of the reasons why we

insisted that our staff make the presentation and not Postal Service or anyone else, and so we had our own staff go out and make the presentation and show the video and tried to present a balanced point of view with regard to this vaccine. But it is a challenge because of all the press.

DR. MODLIN: Dr. Birkhead?

DR. BIRKHEAD: Gus Birkhead. Could you just clarify whether the need for the consent form arises because of the licensure status of the vaccine or because of lack of data of post-exposure --

DR. SNIDER: It's being used under IND for post-exposure because it's not licensed --

DR. BIRKHEAD: So are we ever going to get out of the need for a consent form in post-exposure setting for this vaccine? Is there a --

DR. SNIDER: My guess is in a way we would say we hope not. We would hope we never get out of that situation --

DR. BIRKHEAD: I agree.

DR. SNIDER: -- because we would never be able

to get the kind of study information from humans to do it, but the bottom line is -- I think Karen should probably respond to this, but I think the pre-licensure issue is going to be easier to take care of as it relates to the vaccine. And it may be that, you know, with appropriate animal studies we can move out of the IND situation, but Karen --

DR. BIRKHEAD: Well, just a comment from a practical point of view of trying to deal with a public health emergency, to have to administer consent forms and say what you're doing is experimental, basically you're going to end up with this result I think. The smallpox scenario is also pretty concerning in that regard. It's the same vaccine but packaged differently, and if we're going to have to administer a consent form in the midst of a smallpox episode incident --

DR. MODLIN: It sounds like a message and lesson that's been a well-received experience. Let's just a couple more comments and then --

DR. SNIDER: Karen --

DR. MODLIN: Yeah, we wanted -- then we need

to wrap this up. Karen.

DR. MIDTHUN: Yeah, I would agree with what Dixie just said, it was used under IND because the product itself had not been released for licensure, plus it was being used for an indication that the vaccine did not have. And as Dixie has said, certainly there could -- the FDA has something called the Animal Rule that is currently sort of in its final stages so that we hope that it'll actually be finalized shortly and that's actually a mechanism that would allow indications for some products to be based on -- significantly on animal data. And so for example if one could then develop an indication for this product using animal data to show that it worked in a post-exposure setting, I mean one could then concede that one would then be able to have an indication for that and then you would not have to use it under an IND.

DR. MODLIN: Lucy, last comment.

DR. TOMPKINS: I was just -- Lucy Tompkins. I was just going to make a comment or query to Dave, which was don't you think the disconnect between

the state health departments and the Feds was also strongly associated with the concern that people had about taking the vaccine? I mean it just seems to me that since there were two sets of quotes, experts advising two different things, that it was impossible for the lay person to really make a decision about that.

DR. ASHFORD: I'm sure that led to the issue related to participation and also -- not only at that level, but at the management versus union level or certain employees, and then the social networks around the other individuals may have influenced very much their decision-making, so it's worthy of further study.

DR. SNIDER: This is Dixie Snider. I would just add one more thing and that is that each of these situations is different. I mean the Daschle situation is different than Brentwood and so forth, and so there are actually scientific reasons to have a different point of view about risk and therefore about the need for vaccine. The problem is that the meeting that Chuck attended and so

forth, you know, you could talk about a gradation, but it was hard to talk about drawing the line. And again, we decided that all the 10,000 people had to be judged to be eligible. There were a lot of missing data points in terms of what was the exposure at the time the letter went through.

DR. MODLIN: Thanks, Dixie. Chuck, thank you very much. David, thank you.

DR. ASHFORD: Thank you very much.

DR. MODLIN: Appreciate it. We will take our break now and return at 10:45 on the dot to begin the influenza session.

(Whereupon, a recess was taken.)

10:45 a.m.

DR. MODLIN: We will devote the rest of the morning and into the noon hour on the influenza recommendation for next influenza season, the 2002/2003 season. There are a number of important changes or options for change for next year's statement. The influenza working group has been working very assiduously on this and this has been led by Dr. Bonnie Word. Bonnie, you and Keiji will

be the point people today, so I'll turn things over to you for this morning.

DR. WORD: Well, I think you can see from your agenda that there are a number of issues to cover in discussions for the ones the Committee would like -- or should I say the working group would like to make at this time.

As always, there's an update of the current influenza recommendations -- or should I say the current influenza season and the 2002 vaccine. That information will be presented by Lynette Brammer, and she's going to be kind enough to do that for us. Afterwards, Dennis O'Mara actually is going to briefly review the current vaccine supply issues.

Also, since it's February, I think most of you know it's that time of year where historically the new influenza vaccine recommendations are discussed and approved. This will be the last time that'll be done this time in February, hopefully. I know there's a lot of people in the flu branch who are probably having a sigh of relief, because the goal

is to try to transition it into June and not have it done in February anymore, so this is the last time we'll be doing it this time. For them it's a lot of hard work to crush it all in at one time. Hopefully it'll give a little more time to have it prepared by in the June meeting.

In terms of just trying to prepare this particular update, there were a lot of key issues that the working group had to address, and one -- the biggest one was the language for use, particularly for use in healthy children. You'll see that there are two options that will be presented. I think everybody was in agreement that it was time we were heading in the direction of expanding the use of vaccine in this group. However, every -- many people felt it would be too premature just to make a definitive recommendation without trying to overcome a couple of obstacles that we've identified.

One, we wanted to avoid establishing the two-tier system of vaccine delivery until the formal recommendations could be made. And also issues

such as feasibility of administering the vaccine, as well as looking at the economics of vaccine administration to an additional group of individuals needed to be addressed. That will be addressed in this session. Marika Iwane is actually going to present an update on the Rochester feasibility study today, and subsequently Kathy Neuzil and Martin Meltzer have prepared a discussion that reviews the economics of vaccinating young children.

The next question is okay, how does this affect the Vaccine for Children's program, so Lance Rodewald actually is going to provide some insight on the implications specifically of how expanding the use of this vaccine into other children and what role VFC will play, how it was going to affect -- he'll be able to address that and probably answer some of the issues that some of the Committee or the working group members themselves raise, and some of you may have some other questions.

Keiji is probably going to summarize this a

lot better, probably not as haphazardly as I am right now, since he's used to speaking up there, ultimately after they finish all these presentations.

And then finally Carolyn Bridges, she's going to go over the 2002 recommendations, and at that time she's going to direct you to a couple of key points to look at. One is looking at that new language. There's going to be language that suggests that prioritization and timing of how vaccine is administered, and that's really based on the risk group of the individual; i.e., should there be staggered immunizations. But that's a discussion that she'll lead us through.

Another issue which had been addressed was whether to preferentially recommend thimerosal-free or reduced vaccine to certain groups of recipients at that time. And finally, after -- you know, before all this is done, I understand -- I know that there are some manufacturers -- at least one, and forgive me, I forgot your name -- not your name, but I guess right now it's escaped me -- that

just want to -- they do have some comments and will probably be able to help us, particularly when it comes -- when we start thinking in terms of vaccine supplies.

So I think, without further ado, it's probably time to turn this over to Marika.

DR. FUKUDA: No, actually I think Lynette --

DR. WORD: Oh, I'm sorry, Lynette is first. That's why this is a tag team. Thank you, Keiji.

DR. MODLIN: Ms. Brammer.

MS. BRAMMER: This morning I'd like to provide you with a brief summary of the current season's influenza activity, and a quick update on where we are with vaccine strain selection for next season.

Influenza activity in the United States this season has been relatively mild. You can see from this chart of our biologic surveillance data that Influenza type A viruses have predominated this season, and of those that have been subtyped, the Influenza AH3 and 2 viruses have been most commonly identified, and you can see those in red on this slide.

Influenza B isolates shown on this slide in green have been isolated less frequently, and the Influenza AH1 viruses have been isolated only rarely.

You can see from the black line which shows the percentage of specimens tested for influenza that were positive each week that we've seen a gradual increase of activity since December. That last -- the drop that we saw last week may actually be due to a -- the fact that this is partial data rather than a true decline in influenza activity. We'll have to see as more data comes in, though.

This slide shows influenza-like illness as reported by our sentinel physicians. The red line shows the percentage of patient visits for influenza-like illness for this season, and you can see this, compared to the previous two seasons -- shown as the black and the blue lines -- that this season at this point has been -- the percentage of influenza-like illness is lower and the peak is definitely going to be later than in the previous two years.

This slide shows data from the 122 cities' mortality reporting system and the percentage of deaths due to influenza -- pneumonia or influenza is shown as the red jagged line. And you can see this has not exceeded the epidemic threshold yet this season, which is represented by the upper black smooth line.

Right now I'd sort of like to step back and look at worldwide influenza activity because there's been several interesting things going on with influenza viruses recently. Worldwide, or at least in the northern hemisphere this season, Influenza AH3 and 2 viruses have predominated overall, but Influenza B viruses have also been commonly isolated and have actually been the predominant strain in several European countries.

The interesting thing about the Influenza B viruses this year is that although Influenza B viruses cannot be subtyped like Influenza A viruses are, there are two antigenically distinct lineages of B viruses, known as the B/Victoria lineage and the B/Yamagata lineage. The Influenza B strain in

the current vaccine belongs to the B/Yamagata lineage, and this lineage of viruses has circulated widely since 1990, whereas the B/Victoria-like viruses have circulated only in Asia since 1991. But Influenza B viruses recently have begun to spread out of Asia.

This map shows countries where Influenza B/Victoria-like viruses have been identified. Those countries are shown in the tan color, and you can see that these viruses, in addition to being identified in Asia, have now been identified in Europe and North America. During the summer Hawaii reported several B/Victoria-like viruses, but in the continental US we had seen only the Yamagata lineage viruses until this week. This week B/Victoria-like virus was identified from a specimen taken from a child in New York at the end of last month. Canada, in contrast, the majority of the Influenza B viruses that they have tested have been from the B/Victoria lineage.

The other interesting thing that's been going on with the influenza viruses is that a new

influenza virus, A(H1N2), was reported this month. This appears to have resulted from the reassortment of genes from the currently circulating A(H1N1) virus and A(H3N2) viruses. The hemagglutinin on the new virus is similar to that seen on the currently circulating H1 virus and the neuraminidase is similar to that on the H3N2 virus. Because of this, and because both of these proteins are found in the current influenza vaccine, there should be good coverage against the new virus, in addition to the other viruses. Also while the A(H1N2)s have been getting a lot of attention, the A(H1N1) viruses also continue to circulate. As you can see from this map of the distribution of H1N2 viruses, these viruses so far have been reported from Asia, Africa, Europe and North America.

Antigenic characterization of the US influenza isolates that we've seen so far, both the A(H1N1), A(H1N2) and A(H3N2) viruses are well matched to the current vaccine strains, the A/New Caledonia and the A/Panama viruses.

The Influenza B viruses, however, many of the

Yamagata lineage viruses are now showing reduced titers against the B vaccine strains. And as I said earlier, we now have identified one B/Victoria lineage virus in the continental US.

On January 30th the FDA's Vaccine Advisory Committee met and voted to retain both the A/New Caledonia H1N1 and A/Moscow-like H3N2 viruses. The US vaccine manufacturers use for the Moscow-like virus the A/Panama virus that we discussed earlier.

WHO held their vaccine strain selection meeting on February 4th through 6th, and in addition to voting to retain the H1 and H3 components, they recommended that the Influenza B component be updated to a B/Hong Kong/330/2001-like virus, and this virus is a virus from the B/Victoria lineage.

On March 6th the FDA's Vaccine Advisory Committee will meet again and will at that time finalize the strain selection for the US vaccine.

At this point I'd be happy to take any questions anyone has.

DR. MODLIN: Questions or comments? Yes, Sam.

DR. KATZ: In the discussion of global influenza, it seems to me the newspaper was reporting again recently slaughtering of thousands of chickens in Hong Kong. Can you tell us anything about what's being isolated there now?

MS. BRAMMER: They have recently isolated Influenza A(H5N1) -- I believe it's N1 -- viruses in Hong Kong from chickens and did carry out the slaughter of quite a few chickens.

DR. KATZ: Any human cases?

MS. BRAMMER: No, there are no human cases, thank goodness. Anyone else?

DR. MODLIN: Other questions or comments for Ms. Brammer? If not, you -- are you continuing?

MS. BRAMMER: No, I'll turn it over to someone else.

DR. MODLIN: Keiji, who's next?

DR. FUKUDA: Dennis O'Mara is next.

MR. O'MARA: Good morning. I'm Dennis O'Mara. I'm the Associate Director for Adult Immunization in the Immunization Services Division at the National Immunization Program, and I want to take

about five minutes, hopefully no more, to provide you with a brief update on this past season's influenza vaccine supply and a couple of other points as we go along, just to put this into some perspective.

Here are estimates of the numbers of individuals in the various risk and target groups that this Committee recommends receive influenza vaccine annually. It totals up to 152 million.

Here are estimated numbers of doses of influenza vaccine produced by the manufacturers in aggregate during the past three seasons. Of course in '99 there were four manufacturers and in 2000/2001 only three. As you can see in 2001 the three companies together produced 87.7 million doses of influenza vaccine for the US market.

Here's a graph we've shown several times here before this Committee, and the past couple of times the data for 2001, which is depicted in dark blue, have been projections, but now we have the final estimates on there. And as we have said, as was projected earlier and as we now see actually

happened, the distribution for 2001 tracked partway between what we observed in 1999 and 2000. Of course 2000 we had a substantial delay in distribution of the vaccine supply that year, and you can see that in 2001, if we use '99 as a bench mark, we also had a delay in distribution of at least a part of the vaccine supply. For the end of October, 43 million doses had been distributed compared to 26.6 in the year 2000, far short of the pace that the manufacturers -- at which the manufacturers distributed in 1999. You can see, though, that by the end of November of 2001 distribution was almost equal at that point cumulatively to what we experienced in 1999, and with some additional distribution in December of 2001 the total distribution for that year exceeded '99 and far exceeded 2000. But nevertheless, again, there was a delay in distribution of at least a part of the supply.

I'm going to just pop right past, in the interest of time, these two slides which are simply a list of some of the issues that we faced during

the past season. Some of it is an overstatement of the obvious, but the bottom line is that we did experience this delay in distribution. The question is what impact did this have on coverage, and of course for 2001 it's too soon to know.

We don't have data yet to be able to say much about that, but we do have some data from the National Health interview survey for -- that may help us understand a little bit about the impact during -- of the delay in distribution during 2000. And what we've done here is plot the data that were collected from the first calendar quarter of each of the years depicted, 1997 through 2001, for each of these three age groupings. The top line in sort of lime green is the 65 and over age group. The middle line in yellow is for those 50 to 64, and the bottom line there in dark blue, 18 to 49.

We put the point estimates up for these data and what -- so for example, if we look at the top line, see the first data point for 1997, 65 percent. What we're suggesting is that those data are a good surrogate possibly for coverage during

the previous fall and into and through December since the question posed to the respondents is did you receive a dose of influenza vaccine during the past 12 months. So as you can see, for each of the curves actually, there's a slight upward trend during the period '97 through 2000.

And then the 2000 data point, you look particularly at the top line, drops off somewhat to 63.3 percent, even though the confidence limits -- intervals overlap, nevertheless this may give us some glimpse of what may have happened as a result of the delays in distribution of vaccine during the 2000 flu season.

I'll just conclude by looking ahead to the coming influenza season. We've had conversations recently with all three of the manufacturers and their early projections suggest that they are going to make for the US market this coming year anywhere from 88 million to 93 million doses of influenza vaccine.

I'd be happy to answer your questions.

DR. MODLIN: Thanks. Questions for Mr.

O'Mara? We will be discussing some of the language regarding the supply issues when we get to talking about the statement a little bit later on. But there are questions or comments? Yes, Mr. Reilly?

MR. REILLY: I just have one question on the interpretation of the final shot where the survey is indicating a drop in coverage, which I presume is for estimated for the 2000/2001 season, but the actual distribution numbers of vaccine are equal to the prior year. And I'm just wondering whether -- how accurate and how much confidence limits there are in this survey data?

MR. O'MARA: I'm having trouble here going back to that slide, so if we could get that up -- the data point for the year 2001 is intended to represent coverage in year 2000 when the numbers of doses of vaccine distributed were substantially lower than in either 1999 or 2001, for that matter.

MR. REILLY: I think the chart -- the table indicates they're equal.

MR. O'MARA: Is this the slide you're looking at or you want the last one?

MR. REILLY: No, I was comparing the previous slide with the equal quantity of distribution between '99 and 2000 versus the very last slide showing a dip in coverage.

MR. O'MARA: This is actually the numbers of doses produced, not distributed. This is produced (indicating). This is distributed (indicating). And so the distribution for 2000 is 70.4 million.

MR. REILLY: But my memory of the 2000/2001 season is there were very low returns that year. So -- all I'm questioning, you know, whether the interpretation and the consistency between the two sets of information --

MR. O'MARA: I think we are consistent. Again -- yes, there were few returns, and what we're trying to do here is simply show the contrast between numbers of doses needed, numbers of doses produced, and numbers of doses distributed. And so again, for 2000, some 7 to 8 million doses remained undistributed -- 77.9 we estimate were produced, but only 70.4 were actually distributed. So that would be consistent, we would believe, with a

downturn in coverage for the year 2000 -- if there was a lot less vaccine out there to begin with, number one; and number two, a lot of it came late in the season and may not have been used.

MR. REILLY: Okay.

MR. O'MARA: Have I --

MR. REILLY: Yes.

DR. MODLIN: Further question or comments for Mr. O'Mara?

Seeing none, thank you very much, and we will move on to the next section, which is an update on feasibility study for pediatric use.

DR. IWANE: I'm going to present the results of a set of studies that were conducted to assess the feasibility of implementing a recommendation to vaccinate all young children each year against influenza. The studies were done in collaboration with investigators at the University of Rochester, and the PIs there were Dr. Peter Szilagyi and Dr. Sharon Humison. This is sort of a condensed version of what Peter has already presented to the influenza working group, with some updates on some

of the numbers, and an update to the database analysis that we did.

Okay, and in the studies that we did were two surveys of pediatricians and family physicians. We did a national and a local survey, and I will discuss the national survey today. The local survey -- the results were very similar to the national, and in the surveys we asked about provider attitudes, beliefs, barriers and issues regarding the universal vaccination.

We did a time and motion study to measure the time and staff effort of current flu vaccination visits, and we did a database analysis to project the number of visits that would be needed to vaccinate under a universal recommendation. We also conducted focus groups in four practices to help plan the studies.

Okay, first the national survey. This was a mailed survey to pediatricians and family physicians in the US. It was fielded in February of 2001, with follow-up mailings, and the response rate was 58 percent. Now a cover sheet did

accompany the survey that explained why the expanded recommendation was being considered, so the cover sheet did state that the studies -- that studies have shown that young children are at risk of serious influenza complications, including hospitalizations. We also stated that we expect insurance companies and VFCs to cover the vaccination costs, as they do for other recommended vaccine -- childhood vaccines. So that information was provided to the respondents of the survey.

Okay, now I would like to go over the main results of the survey. The survey did state that a potential policy was under consideration. That is, the annual vaccination of 12 to 35-month-olds, and that they can assume that both the nasal and the injectable vaccine would be available. At the time we didn't know what age group would actually be targeted, or if the nasal vaccine would be licensed -- and it is not licensed at this time.

The survey asked the providers if implementing the recommendation would be feasible in the practice, and 76 agreed or strongly agreed that it

would be, and 17 percent were neutral. That's the graph on the left.

The providers were also asked for their overall opinion of the recommendation, and 58 percent were in favor and 23 percent were neutral.

This graph shows that 66 percent of providers disagreed that adding flu vaccine would deter or delay other vaccines, and 20 percent were neutral.

The graph on the left shows that 41 percent of providers ranked the up-front vaccine cost to be the most important barrier to them to implementing the recommendation. Thirteen percent said that inability to identify children to be vaccinated would be the main barrier. And we know from other questions on the survey that about half of the providers surveyed currently use reminder recall to bring children in for vaccination, and those would be the high risk, and about the same percentage said that they would continue to do so if there was an expanded recommendation.

Now the graph on the right shows that 31 percent of the physicians thought that the number

one barrier to the families, to the parent, would be the cost to the family and 22 percent ranked the crowded vaccine schedule as the main barrier. And then we have some others that they also listed as the main barriers.

This graph shows that a high percentage of providers would use the well child care visits, illness or follow-up visits, and vaccine-only visits as opportunities to vaccinate under universal recommendation. And as expected, most of them felt -- were more comfortable vaccinating in their practices, but 82 percent said they would consider public health clinic sites as -- under an expanded recommendation to vaccinate those children. And a lower 29 percent thought that child care centers would also be acceptable.

The survey then asked how difficult universal vaccination of 12 to 35-month-olds would be if only the injected vaccine were available. So the previous questions assumed that both would be available, and now we're specifically saying only the injected is available, and about half said that

it would be much more difficult or nearly impossible to implement such a recommendation, and 28 -- 38 percent said it would be slightly more difficult.

The survey also asked -- so this is the graph on the right -- about the feasibility of vaccinating 6 to 12-month-old children where only the injectable vaccine would be available, and if you look at the color bars, the 42 percent plus four percent agreed that it would be feasible, either they agreed or strongly agreed. And this is compared to 76 percent, which are those white bars, if only the 12 to 35-month-olds were being considered.

We also found that family physicians were more likely to oppose universal vaccination and to report barriers compared to pediatricians. And we found that physicians who oppose the recommendation were more likely to believe that flu wasn't a serious enough disease to warrant such a recommendation, that the vaccine would delay other vaccines, that some parents would object, and that

safety is a concern, and the practice would have difficulty with the extra burden to the staff.

Now I'd like to turn to the time and motion study that we did, and this study measured the practice time that was spent on flu vaccinations. And the staff self-timed the vaccination process during patient visits, from check-in to cleanup and recording of the vaccination. The study did not measure time spent recalling patients, pulling and filing charts and billing. The study was conducted December, 2000 to January, 2001 in seven primary care practices in Rochester. It was a convenience sample.

One hundred and two flu vaccination visits were timed for children who were 12 months and older, and there were three suburban practices and four inner city practices. And these were not vaccination visits that were conducted as clinics. They were just individually scheduled visits for vaccination.

These are the results. All visits that were timed were interspersed with other visit types.

The times were twice as long for the urban practices compared to the suburban. The actual time to vaccinate is short, it's about a half a minute -- one and a half minutes to two minutes, and this is also comparable to administration of the nasal spray vaccine. About 80 to 90 percent of patient time involves waiting, so that is where the bulk of the time is spent. A nurse practitioner or physician conducted an exam in only 10 percent of the visits, and we find that the timings did not vary by age, time of day or day of week. The overall median time for a vaccination visit was 16 minutes.

And now I'd like to give some examples of extrapolations that can be made from these data. The median exam room time was ten minutes, so there could be six per patients per hour per room, or 48 patients per day. Now for 100 children requiring influenza vaccine, that would translate into 16 hours of exam room time, 12 hours of additional staff nurse time, and about ten minutes of physician or nurse practitioner time.

Finally, I'd like to discuss the insurance database analysis, and we did a much more extensive analysis than this. We are still in the process of analyzing it for different scenarios, but the objective was to estimate the additional visits needed for universal vaccination of a cohort of six to 23-month-old children during the flu vaccination season, and we chose this age group because it's likely to be the one that's going to be targeted now for a recommendation -- or is under consideration.

The analysis included children who were six to 23 months of age during October to December, and there are 42,000 children in the analysis. They reside in six counties in upstate New York, in the Rochester area. The children are enrolled in Blue Cross Managed Care Plan, which covers over 70 percent of all the children in the area and over 80 percent of the Medicaid enrollees, and the data are from three separate seasons, the '98, '99 and 2000.

This is a description of the database population. They were distributed across urban,

suburban and rural settings. Eighty-five percent are covered by commercial insurance and the rest by Medicaid. Seventy-six percent are pediatric practices, 11 percent family practices, and then the rest are hospitals and neighborhood health centers and others.

Now I'm just going to present, because of the time frame, selected results of the analysis. So if we assume a universal recommendation for the six to 23-month-old age group, and no missed opportunities -- that means all the visits that are available to vaccinate are used -- then, first looking at all the well child care visits, 38 percent would need one additional visit; 33 percent would need two additional visits; the others would already be captured at existing visits. If all the visits were used for flu vaccinations -- so this is the well child care, illness visits, follow-up visits and so on -- then 33 percent would need one additional visit; 14 percent would need two additional visits. And we also have found that in this analysis that the percentage that required two

additional visits is higher for certain subgroups. It's higher for the older, the 12 to 23-year-olds (sic) when compared to the younger group. It is higher for Medicaid, for the non-pediatrics and for the urban settings.

So now I'd like to give an example of how to think about the results of these studies. If a practice has 100 patients to vaccinate -- and based on our survey, that was about the median size of the newborn cohort -- and all visit opportunities are used, then 33 patients would need one more visit, 13 would need two more visits -- and that's a total of approximately 60 extra visits per practice of that size. This translates, extrapolating from the time-motion study, into ten hours of exam room time, seven hours of additional staff nurse time and six minutes of physician or nurse practitioner time if the visits are individually scheduled. And we feel that vaccine clinic hours held within a practice could probably reduce the burden of such a recommendation on a practice. And the estimates that we have made do

not include the pulling and filing of charts and reminder and recall, which one can assume is substantial. And other studies have indicated that it does consume a considerable amount of time.

So in conclusion, we found that most physicians -- or the majority of physicians thought that a universal recommendation could be feasible. We say this with the understanding that it might be more acceptable with the availability of an intranasal spray vaccine. The survey did assume that that would be available for most of the questions.

Also, a substantial number of extra visits would be required. Although the visits are short, they usually don't involve the nurse practitioner or physician, we feel that the vaccination clinics could probably reduce the burden further to the practices. And we assume that educational activities will be needed to increase acceptance and adherence to the recommendation.

DR. MODLIN: Thanks, Dr. Iwane. Jon?

DR. ABRAMSON: Yes, did you -- This is Jon

Abramson. Did you estimate on the other side of the equation the number of visits that might be saved by vaccinating children then who did not get sick because they were protected?

DR. IWANE: No, we have not done that analysis yet.

DR. MODLIN: This is pretty much a time-motion analysis.

DR. IWANE: So we've just considered that burden -- the burden to -- during the vaccination season, not what's saved afterwards.

DR. MODLIN: Georges?

DR. PETER: A related question -- and thank you, by the way, for a very extensive, comprehensive report. Did you have any idea or assessment of the amount of time that is spent in the time-motion study in well child visits in actually discussing the risks and the benefits of the vaccine; i.e., the vaccine information statements?

DR. IWANE: The time-motion study covered the steps from check-in, waiting, administration --

where we defined administration to be everything from explaining the vaccine, obtaining, preparing, administering, cleaning up, appeasing the patient, you know, if necessary afterwards.

DR. PETER: How much time is spent in explaining?

DR. IWANE: Explaining -- yeah, I do have that.

DR. MODLIN: It can't be very much because the administration time is so short.

DR. FRANCE: This is Eric France. I'd just mention that Charlie Lebaron at CDC did --

DR. MODLIN: Eric, one second --

DR. PETER: I've still got a question pending.

DR. FRANCE: It was responding to this question about how much time it takes explaining. If you review time-motion studies in general, you'll find that docs don't spend more than 30 seconds, if that, doing them. We -- there was one done by Charlie Lebaron that was published a couple of years back and found in New York that physicians really weren't talking much about vaccines. We did

one at K-P Colorado with 250 families and found very few of them spent much time explaining vaccine safety. I think if you look at the time-motion literature you find less -- 30 seconds or less are traditionally spent in explaining safety.

DR. IWANE: Our median time was a half a minute.

DR. MODLIN: Bonnie?

DR. WORD: I was going to say, many times as people are waiting they tend to hand out the vaccine information sheets and while the families are waiting in the room, that's when they read them. Then someone comes in and says did you read this, do you have any questions, and goes through it. So it's not that people just don't review it with them, but as you said, the bulk of the time is spent waiting to be evaluated and that's what -- one of the things people do to utilize it.

DR. MODLIN: Gus, did you have --

DR. BIRKHEAD: Yeah, in the national survey you found that cost was a major barrier. Did the cover sheet say anything about -- make any

assumptions for the physicians on the cost and was it the cost of the vaccine itself or the cost of the visit that was --

DR. IWANE: No, we just made a very general statement that we expected insurance companies and VFC to cover the vaccination cost, as they do for other recommended vaccines, and that's all we said.

DR. BIRKHEAD: You did make that statement.

DR. IWANE: We did make that statement on the cover sheet.

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

DR. BROOKS: Okay, yeah. I was curious. Was there any breakdown of those practices, of the demographics of the practices that dealt with commercial patients versus Medicaid patients and their differences and their beliefs of the feasibility aspect of it all?

DR. IWANE: We have done some of those analyses. I don't have the numbers with me, but I don't think that we found big differences on the survey.

DR. MODLIN: Rick?

DR. ZIMMERMAN: One of my concerns -- and I think it was a good study and an important study, but one of my concerns is the assumption that vaccine costs are going to be covered. I think that will be -- if there's a live attenuated in VFC, but my speculation would be if a managed care or indemnity plan was offered a chance to cover inactivated flu vaccine or potentially a much more expensive live attenuated, that most economically-minded managers are going to choose to pay for the less expensive one, and so I'm not sure we can assume comparable price.

DR. IWANE: Yeah, we did choose to make that statement. In our focus group that was one of the questions, as well as why are you doing the survey, why would there be a universal vaccination anyway. And we felt to clarify the questions and the interpretability we would add that. And also we did make the assumption that it would be likely that the coverage would be approached in the same manner that it might be for other childhood

vaccines, should this Committee make a recommendation.

DR. MODLIN: Comments? If not, maybe that's a nice segue to the next discussion -- I'm sorry, I beg your pardon. Kristin?

DR. NICHOL: A quick question, and my compliments also on a fine study. Did you collect any information on why the practitioners were more negative about immunizations administered in either the public health setting or day care?

DR. IWANE: No, we did not.

DR. MODLIN: Dr. Iwane, thank you very, very much. I think the next item on the agenda I believe has to do with economics of vaccinating children. Is that right, Bonnie? Is that Dr. Meltzer? And Kathy Neuzil.

DR. NEUZIL: Thank you. So Dr. Meltzer and I will now present a collaborative study on the economics of routinely vaccinating healthy children younger than five years of age, although we will predominantly focus on children younger than two years of age. I'll review the major data sources

that were used for this economic analysis, and then Dr. Meltzer will present the economic model.

So the data set that is used for this study comes from two published studies, and it's a Tennessee Medicaid-administrated data set that included all children, both with and without high risk conditions, who were younger than 15 years of age. It was a data set that encompassed 19 consecutive influenza seasons, from 1974 through 1993. And the way the influenza seasons were defined were by active viral surveillance in the middle Tennessee region. So we assumed that there -- I don't think this is working -- if you look at the green in summer, we assumed that there were a baseline rate of acute respiratory events.

When winter season hit -- and we find this by the circulation of respiratory syncytial virus -- there was, as you would expect, an increase -- a significant increase in acute respiratory disease, hospitalizations and outpatient visits. What we looked at then is the piece of influenza virus circulation within that winter virus season right

here, and we looked at the difference between influenza season and essentially respiratory syncytial virus season (indicating). So we looked at just this -- the excess. Not all acute respiratory diseases during the season, but the excess diseases.

And the study outcomes that are incorporated into this economic model are hospitalizations or death from pneumonia, influenza, and a broader range of acute cardiopulmonary conditions, and all outpatient visits.

Now if we look at the outcomes attributable to influenza per 1,000 children, again, here are the assumptions for the economic model. If you just look at hospitalizations, you see that children with high risk conditions had higher rates than children without high risk conditions for both age groups, and that children younger than six month of age have higher hospitalization rates than children six months to 24 months of age. Again, whether they're high risk or non-high risk. And outpatient visits were high in all risk groups and all age

groups.

Now it's important to remember as Dr. Meltzer goes through the economic model that there are potential benefits of immunization that could not be included in the economic model. One addresses what Dr. Abramson just asked, which is the predictable health care utilization of vaccine versus the unpredictability of how many illnesses will occur during influenza season for any given practice, effect on antibiotic use and resistance, effects on household transmissions and preparation for pandemics. And there will also be potential risks that could not be included in this economic model, which would include new adverse events which may be non-causal; these feasibility issues of supply and delivery, the limits of our data on co-administration with other vaccines, and the issue of thimerosal.

DR. MELTZER: Thank you, Kathy. The economic model is one that economists and modelists call Monte Carlo, and that's just really a fancy term for the fact that we built in variability right

into the model, so we didn't use a given rate of outcome. We didn't just assume that the rate of hospitalizations, for example, amongst the high risk six months to 24 years (sic) old would be a set number, say 18 per 1,000. We allowed for season to season variability. The model -- oh, we also considered more than just one age group, just for the purposes of comparison. We did specifically divide the groups into high risk and non-high risk because the rates of outcome, as Kathy has already mentioned, are so notably different between those groups. And the data are presented in terms of cohorts, 1,000 per age and risk group.

The data sources and some of the assumptions Kathy has already outlined. We also assumed three different attack rates because the fact of the matter is that for any given data set regarding the rate of outcomes, very rarely do you find any concurrent measurement of the actual attack rate. And why this was important in the economics is that because there's always a number of children --

person who become ill from influenza but do not seek formal medical care. These are the people who stay at home. In my household it means the child stays at home, is feeling ill, doesn't go to school. My wife usually stays at home to look after them. The kid eats a lot of candy and watches a lot of cartoons and by 12:00 is driving my wife wild. That is a cost, however -- an important cost -- to society and should be recorded. Therefore we assumed three different attack rates to allow for different probabilities of how many of those children stay at home sick, but not seeking formal medical care.

We also allowed for the fact that influenza does cause otitis media in children, one of the most common reasons for children to visit a pediatric office, and that the use of the influenza vaccine would, and has been demonstrated in other studies to reduce the rate of influenza-related otitis media.

Here's one of the most interesting graphs, and it's rather unique. There aren't too many graphs

from a single data set that show this time line, this number of years of the number -- the rates of hospitalization for children. In this case of course we're looking at six months to just under 24 years (sic) of age, high risk and non-high risk. And the really important thing, of course, is the variation year to year in both age groups. A single number cannot possibly describe the changes in rates of hospitalization over time.

So what you do -- at least if you're a mathematician, modeler or economist -- is that you consider frequency. In this graph here, the bars, the black columns, represent the frequencies of the actual data. The red line represents the mathematically-fitted probability distribution curve. What is really important to note here is that the mean for both the actual data and the fitted distribution is about 2.2. But the standard distribution is 3.6. In other words, the variability itself -- a measure of variability is even larger than the mean.

Bottom line, ladies and gentlemen, the mean

actually hides more information than it reveals about the risk of going to hospital if you're non-high risk and age six months to two years.

The costs used in this study, we have the cost of a vaccination. We assume that the cost of vaccination isn't just the vaccine plus the administration cost, but also the fact that parents have to take time off work, they have to travel and occasionally both the doctor and the family have to deal with adverse side effects. The productivity costs of time off work for a parent looking after a sick child is valued -- what -- a term we use called the human productivity loss. In other words, what is -- how much salary or wages are you paid for the time lost. The hospitalization costs were adjusted by cost to charge ratio. This is a fairly standard procedure in economics. And here are some of the values that we used for the costs.

Pay particular attention to the indirect costs. For any one of these values here -- for example, hospitalization -- ten percent of this $3,366 includes ten percent of parent -- ten

percent of that cost includes time off for a parent to look after a sick child. Obviously when a child is sick but the parents do not take it to the -- take that child to the doctor or ends up in a hospital, the majority of that time is time spent at home looking after the child.

Vaccine effectiveness. It's a well-known fact that the vaccine is not equally effective year on year, the current existing inactivated vaccine. Nobody really has presented one coherent data set that provides a measure of year to year effectiveness, so I had to construct a probability distribution of vaccine effectiveness using but five facts.

One fact is that approximately every ten years, the vaccine is a less than good match, so about 50 percent of the time -- ten percent of the time, my apologies. Ten percent of the time the vaccine in this graph is effective at 50 percent or less. We also know that it is very rare for a vaccine, when it's used en masse in the public, to be more than 90 percent effective. So the 90th

percentile is 85, and it actually maxes out at about 95 percent.

Also, most of the studies that you read in the literature suggest that the mean median and mode occur between the 70th and 80th percentile, which is this top up here (indicating). So in the end, in summary, this curve represents the probability of a vaccine effectively preventing an influenza-related outcome such as hospitalization or outpatient visits.

Some results. These are the results, three graphs showing the net returns, once you've summed up all the costs of vaccinating and all the costs saved from preventing a case of influenza, for the three age groups under consideration. These three graphs relate only to the non-high risk. And basically the black line is the median, next present value, and the red lines are the fifth and 95th percentile. Let's just concentrate for the moment on the six months to just under 24 year -- 24 month -- year age group.

Essentially the threshold value occurs at

approximately $30 for a cost of vaccination. Threshold value, this means that society would neither gain nor lose money, just break even, if the cost of vaccination were approximately $30. Please remember that I'm talking about cost of vaccination. That's everything that it takes to get inactivated vaccine, the needle and the antigen into the child's arm and the related side effects, the time off work, the time to administer that vaccine, the time in the waiting room.

Note also that the fifth percentile is constantly below $0. In other words, there's always a probability for any of these age groups under study that mass immunization of the non-high risk group will not generate net savings.

I also want to note here that the cost of vaccination is not constant as you increase the number of children vaccinated. The Rochester study presented just before this -- our talk did mention that a lot of pediatricians and a lot of physicians didn't think it was feasible to increase the number of children vaccinated. Feasibility does not

translate into cheap, and we have to consider the fact the first 1,000 or the kid number 1,000 that is vaccinated under a mass immunization program, that cost of vaccination might be a lot less than kind number 10 million. And we don't know, ladies and gentlemen, exactly how costs will change as the number of kids vaccinated increases.

I know there's some consideration and some thought about the idea that the live attenuated vaccine that is administered in the nasal passages will be a lot cheaper to administer, and perhaps allow for mass immunizations rapidly done in say a clinic setting. This may be true, but I also note then that the cost of that vaccine is one of the new generation of vaccines and is likely to be a lot higher than the price of the existing vaccine.

Here's the same set of graphs for kids who are high risk. I want you first to concentrate on the Y axis. This runs from zero to 800. When you were looking at the non-high risk, it ran from zero to 80. In other words, as we consider the differences in the economics between the non-high risk and the

high risk, we're looking at a very different scale of economic returns. And here we see, quite frankly, that the returns to vaccinating high risk children are consistently, when we consider the median net return, above zero. In other words, ladies and gentlemen, within the range of $20 to $40 per child vaccinated, we are more likely to have a net savings to society than if we vaccinate non-high risk kids.

This graph is to emphasize the impact of valuing death upon vaccination. Now many people will tell you that death, especially amongst the non-high risk children, from influenza is a very rare event. And indeed, the data set that we used, which Kathy described a little earlier, backs that up. Death is a very, very rare event. But it's also, of course, highly valued by society. We value our children, and so we should. But if we exclude death, then -- the value of death, then the median break-even value comes to just over $20 per child vaccinated. The single most important variable, in other words, in this study is the

probability of death from influenza and the probability therefore of avoiding that death due to vaccine, not the probability of going to hospital.

My colleagues asked me the question: What happened if you considered a cohort that was mixed, mixed in terms of having high risk and non-high risk together? This graph is what you've already seen. This is the non-high risk only, and then these -- this graph here is when you consider a mixture of 95 percent non-high risk, five percent high risk, and this one has ten percent high risk (indicating). And obviously as you add in a percentage of high risk, then the net present value -- that black line -- moves up and to the right, increasing the threshold value of when vaccination would just break even.

Note, however, regardless of the mix of high risk in these three graphs, the fifth percentile is still below $0. In other words, assuming blanket immunization of both high risk and non-high risk does not automatically guarantee that society will save money. Sort of overall conclusions, large

variability in health outcomes.

I think this Committee, in its considerations of recommendations of whether to make recommendations for immunizing children under five years of age have to appreciate that mass immunization is not going to prevent a fixed number of health outcomes year on year. The number of outcomes prevented by such a recommendation will change from year to year, and that's driven purely by the fact that influenza itself, as a disease, changes from year to year. Nature beats us at this particular game.

In this particular model, the most important inputs were the rate of death, the rate of outpatient visits, and of course the cost of vaccination itself. And this little graph just illustrates that black -- the longer this black line, the greater the correlation between the final result and that particular input, and we see that rate of death and rate of outpatient visits are predominant in terms of impacting the final calculated net present value, the returns to

vaccination. And the other input which other people often focus on really have a limited impact when compared to the relative importance of death and outpatient visits.

Majority of savings will actually be due to savings from the indirect losses. In other words, time saved from parents not having to take work off to look after sick children. Even if you exclude death, that is true. This is very, very important figures, ladies and gentlemen, because this suggests that from a health care system perspective, from a health care payer perspective, they will not reap majority of savings that are potentially available with this recommendation. This might cause some problem as to who the incentive, who pays and who benefits.

Also I think we have demonstrated the very real probability that there might not be consistent savings in vaccinating large numbers of non-high risk children unless you can guarantee that vaccination -- vaccination is less than $20 per child. It is always -- always -- more efficient to

vaccinate high risk children, simply because they have such notably, three to five times, greater rates of adverse health outcomes such as outpatient visits and hospitalizations.

Even if you consider the mixed -- the idea of having a mixture of non-high risk and high risk, although the threshold might seem high, the fifth percentiles are still negative. Considering mixed populations of high risk and non-high risks will not guarantee absolutely net savings.

That's all. May I have questions?

DR. MODLIN: Dr. Meltzer, thank you very much. Let's open this up for some questions and comments on the economic model for either Dr. Meltzer or Dr. Neuzil. Myron?

DR. LEVIN: One of the points that had been raised in I think ongoing studies is that you -- that collateral infections of people that are contacts of the vaccinees will be prevented, and I know that's hard to get at, but how big a factor do you think that is, economically?

DR. MELTZER: Well, there is actually a study

out there, we've seen it, that suggests that the potential to -- from vaccinating children to prevent onward transmission to other household members might be very large. However, as an economist, I note that although the savings in actually dollars and cents may appear large, a valuation of the savings may be different. Do we want to vaccinate our children to prevent us from getting ill? Is that the main reason for vaccination? As a parent myself, I'd have to say I'm not going to get my child vaccinated to prevent me from being ill. And the valuation of that, for myself personally, is very close to zero. That is a debate in society. You can measure the number and say it's going to be this number, but it doesn't mean to say we'll value that number equally.

DR. MODLIN: Myron, also we're talking about vaccinating kids who are under two years of age here, as opposed to older kids and school age kids where the influence of flu in those groups may be much greater on a household than very young

children, so it probably doesn't give us the entire --

DR. NEUZIL: Well, could I just answer -- we did consider that in the economic model, and we ended up listing it as an intangible, predominantly for that reason, because you have a family unit that may have multiple exposures. And we're really only dealing with the six to 24-month-old in this case.

DR. MODLIN: Paul?

DR. OFFIT: I've said this before but I'll say it again. The one problem I guess I always have when we do these cost benefit analyses is that we don't or -- probably just because we can't -- put any value on human suffering. In other words, is it a value to prevent several days of high fever and intense coughing? Yes, it is. But we can never quantify that, therefore we ignore it. And I think it's too bad.

DR. MELTZER: Well --

DR. OFFIT: I wish there were a better way to add that as part of the equation.

DR. MELTZER: There are some methods, of which I think are somewhat new and I'm not so convinced that they actually really answer that kind of question. There's two things. If you are somebody -- would you -- how much are you willing to pay to have your child not be ill from flu? Today they might say $50. Tomorrow they might say $10, for whatever reason. So the valuation might be transient, change with time.

The second thing is that when you consider say the fifth percentile, it doesn't save money. That doesn't mean to say you shouldn't do it. If you turn around and society says oh, despite that fifth percentile clearly demonstrating it's not net savings, we want to do it, as an economist you have told me empirically that you think all that pain and suffering is worth at least the difference between the fifth percentile and the $0. So there is some measure of that by empirical. This is just data to suggest that if you want to move forward with the recommendation with a large reason for doing that to avert pain and suffering, I can tell

you what that aversion is going to cost you. Whether you want to do it or not is matter of public debate. Sometimes I think economists should deliberately not value or attempt to value things like pain and suffering and allow public debate and understand what the cost of averting pain and suffering is. But it should always be debated, no question.

DR. MODLIN: Jon Abramson?

DR. ABRAMSON: Jon Abramson. I think a fair comparison that we ought to have some information on is what is the cost savings in a 50 to 64-year-old, which we already approved, versus a child six months to 24? Is it much different?

DR. MELTZER: You want to get me into how much trouble, Jon? We can look at that. Do you have an answer?

DR. NEUZIL: No, we -- I don't know if Kristin might have an answer. I don't know of any economic analysis that looks at just 50 to 64-year-olds. I only know of more complete economic analyses in adults where the benefits increase as the age and

prevalence of high risk factors increases, but I can't put a dollar value on 50 to 64-year-old, no.

DR. MODLIN: David Fedson, did you have a comment?

DR. FEDSON: David Fedson. I have a question. It seems to me that the health and economic variables that were used in the analysis were derived from a period before the advent of pneumococcal conjugate vaccination, and the policy question has got to be viewed today in terms of what is the incremental increase in benefit and cost of adding influenza vaccination on top of pneumococcal conjugate vaccination, and I wonder how you've incorporated that policy question into your analysis.

DR. MELTZER: It isn't incorporated at all, simply because the recommendation is taken, as far as I view it, as separate from the pneumococcal. You raise a very good question. Perhaps we should visit that issue.

DR. MODLIN: Eric France and then Georges.

DR. FRANCE: Martin, have you done these

results where you take out the societal costs, as I've seen I think Tracy Lieu often will do from the health plan perspective and from the societal --

DR. MELTZER: At the moment, no, but it is a fairly easy step to do, and when we publish we hope to have a separate set for other prospectives, yes.

DR. MODLIN: Georges?

DR. PETER: Straightforward question that I should know the answer to, but you gave two analysis, one for five percent high risk and another for ten percent high risk. What actually is the percentage of the US population of children under two that's in the categories for which we recommend vaccine? And of course, one of the important factors in this analysis is our -- in our considerations of this issue is our inability to vaccinate high risk children with a selective recommendation.

DR. NEUZIL: We assumed that the non-high risk and ten percent high risk was probably the most accurate reflection, and that was based predominantly on asthma prevalences, which are

anywhere between five to eight percent -- if there are people in the audience that can correct me -- and then all other high risk on top of that.

DR. MODLIN: And when you consider the high risk kids, do you consider immunization of the household members, as well, in that model?

DR. MELTZER: No.

DR. MODLIN: So that would be an additional cost that was not --

DR. MELTZER: Absolutely. There is one additional point there in terms of vaccinating high risk. This set of results suggests that, compared to the non-high risk, society could afford to actually pay a premium for the health care system to target and successfully vaccinate the high risk kids. And that premium could be quite notable, in fact.

DR. MODLIN: Peter?

DR. PARADISO: Peter Paradiso. I think I actually have the same question. Just so I understand it, when you said ten percent high risk, that means you're vaccinating ten percent of the

high risk, or ten percent of the people are high risk and you're vaccinating all of them?

DR. MELTZER: And this is you're vaccinating 1,000 children, of which 100 or ten percent will be high risk and 900 or 90 percent would be non-high risk.

DR. MODLIN: Kristin?

DR. NICHOL: A question I had -- and nice work -- you mentioned that the cost of vaccination was one of the more important variables in terms of the sensitivity analysis. I'm wondering what the effect of immunization on weekends or in an untraditional setting does to the break-even costs in terms of driving down cost of vaccination.

DR. MELTZER: Well, on that we answer that question only indirectly. If you assume -- let us just say for an example -- and I'm not saying I have any data. Let us assume that at the moment, to take a child to a pediatrician's office to get a flu vaccine outside a well care visit costs shall we say somewhere around $30. I just picked $30 for illustration, not because I have data to prove

that. But let's just say we set up a clinic at some more convenient location, perhaps even at the local supermarket that runs on Saturday morning, and in between the soccer game and the Brownies meeting, the parent drops the kid off there and it's successfully vaccinated in the approved manner by a physician or a nurse practitioner. That might considerably drop the cost of administration, the cost of parent time waiting. All you do then is say, if I start off at $30 -- I'd have to make a separate study of the amount of time -- it's inside that cost of vaccination. We do not say specifically that the current cost of vaccination is this. You can do independent studies to figure out where the exact cost of vaccination under different scenarios would actually fit, including, for example, the feasibility studies out of Rochester.

DR. MODLIN: Gus?

DR. BIRKHEAD: That's a very elegant study, Martin. It seems counter-intuitive to me that the hospitalization costs were such a small proportion,

so I had a couple questions on that. I didn't follow your explanation of the graph of the distribution of risk of hospitalization and in particular how there could be negative rates of hospitalization due to flu. And secondly, your figure of $3,366 per -- for the cost of hospitalization, if you could say more about where that came from.

DR. MELTZER: First on the distribution, yes, you'll remember this graph that Kathy used in explaining the excess. Well, occasionally it turns out that when you measure the excess during what was defined by the flu season in terms of the circulating strains, that there were fewer children in hospital when the flu strains were circulating than compared to the part of that winter just prior and just afterward the flu season. In other words, flu -- when flu was circulating, there were just fewer children in hospital. So there is a -- you end up with this negative hospitalization.

What did I do in the model is that no, this wasn't a savings. Any time the distribution picked

any number that said that the rate of hospitalization was zero or less, that was $0 of excess hospitalization. The real key thing to figure here is excess hospitalization.

DR. BIRKHEAD: So you didn't attribute any savings to decreased --

DR. MELTZER: No.

DR. BIRKHEAD: Okay.

DR. MELTZER: As an economist I could perhaps argue, but I realize that wouldn't fly amongst some of my colleagues so it's $0, no savings attributed to flu.

DR. BIRKHEAD: Otherwise we'd be spreading influenza some years to benefit hospitalization.

DR. MELTZER: There are cases -- seriously, there are cases in infectious diseases where having endemic stability is the cheapest way of controlling a disease, but that's another issue and really doesn't apply in influenza.

DR. MODLIN: Thank you --

DR. MELTZER: Hospitalization costs -- sorry, you just asked about this briefly. That $3,360,

that's what we figure as the actual charge. Everybody knows if you go to hospital, the actual cost -- hospital charges are always greater. However, if you go to what Medicare and Medicaid refund, Medicare and Medicaid typically refund somewhere between 50 and 60 percent of what a hospital bills. That $3,360 incorporates the actual reimbursement rate.

DR. BIRKHEAD: And is that an average across the United States or --

DR. MELTZER: These data are taken from -- the source is actually from a paper we published on pandemic -- it comes out of a database that measures the reimbursements from people covered by large companies who have private health insurance schemes. Think of your large motor companies in Detroit and they collect all their bills and catalog them and put them in a huge database, one of the biggest databases we have, of what it costs to go to a doctor or go to a hospital.

DR. MODLIN: A final question, Mr. Reilly?

MR. REILLY: I think during the presentation

reference has been made to the cold adapted influenza vaccine that's coming along. I think we should be clear, though, that I think the vaccine parameters in this study apply to the current inactivated vaccine that is in current usage and as -- in addition there is also an economic study on the cold adapted influenza, which is -- has been presented, at least some of the people on the working committee or the full Committee, and that has a threshold -- I don't want to get into a debate about economic models here 'cause it's a dead end, but that model has a threshold of $250 per dose. So I think we need to be clear that there are significant differences between the two vaccines and that will potentially lead us in a new direction on the opportunities for influenza vaccine.

DR. MODLIN: Thanks, Mr. Reilly. If we're going to have a lunch break, we need to move on.

Bonnie, I see that we have an additional item on the agenda, influenza vaccine for at-risk children. And that's next, so that's Dr. Rodewald

-- Lance?

DR. RODEWALD: I appreciate this time on the agenda, and I will be brief. I have only six slides, and there's only five left, so we'll see what we can do here.

First I'd like to just remind the Committee the VFC currently covers for influenza vaccination, VFC-eligible children for whom ACIP says really should be vaccinated, and these are the ones that you're very familiar with because these were your decisions: chronic pulmonary conditions, cardiovascular disorders, et cetera, et cetera. One that I think is not appreciated very much is the household members of high risk individuals regardless of age. But VFC does not currently cover those who ACIP says may be vaccinated. The permissive vaccination recommendation is not currently covered. And there is some interest I think in talking about this.

There is a general feeling, I think as Dr. Peter had mentioned earlier, that targeted recommendations really don't work, and I think one

needs not look too much farther than hepatitis B before and after a universal recommendation to see that there's certainly some experience to suggest that. But it doesn't necessarily have to be the case.

VFC is a very big and very powerful program. It's enrolled 45,000 VFC sites, which would include about 100,000 physicians in the United States. The vast majority of these sites are private offices. It's mainly a private practice program. Seventy-five percent of VFC sites are private offices, 25 percent are public clinics, and that includes Federally-qualified health centers, rural health centers and hospitals in the public clinic -- public site designation.

The VFC providers collectively, these 45,000 VFC sites collectively vaccinate about 90 percent of young children, and they do this with a combination of VFC vaccine, other government-purchased vaccine and private purchase vaccine. And all of this vaccine is woven together at the provider's office and ideally targeted only at

eligible children for the VFC-purchased vaccine. It implies, though, that since there are so many sites and these sites reach so many children, that VFC does have potential as a leading edge to introduce recommendations and vaccines. And another implication of course is that VFC can be expanded by including specialists, pulmonologists and allergists, for example.

While VFC was designed to level the playing field between vulnerable children and less vulnerable children, all of these 45,000 VFC sites can serve Medicaid-enrolled children, completely uninsured children, and American Indian and Alaskan-native children. About ten percent of the VFC sites are Federally-qualified health centers or rural health centers, and these sites are also able to serve under-insured children; that is, children who have commercial insurance coverage, but the commercial insurance does not have an immunization benefit. The only place where these children can have their entitlement is at an FQHC or an RHC. And in general, roughly about a third of US

children in the population under 19 years of age receive VFC vaccine. The estimates of the eligible population, according to the states, may be a little bit higher than that, and we're going to try to nail down those estimates with the insurance module in the National Immunization Survey.

There's been a fair amount of e-mail traffic about expanding VFC coverage a way not only to include of course the should-be vaccinated group, but to also include the may-be vaccinated group. And I'd like to talk about a couple of implications.

The first one of course is that this indeed may help promote influenza vaccination. If we make this vaccine more available -- more widely available and we have a source of vaccine for vulnerable children, this may really be helpful in here. And as I mentioned earlier, it's the possibility that by promoting influenza vaccination in a larger group, this may help the program become a leading edge into -- and a stop on the way toward universal recommendation.

The precedent has been set in terms of this with pneumococcal conjugate vaccine in which a permissive group, the catch-up group, is covered through VFC, even though it's only permissive and not a should recommendation.

However, there are some implications for partner organizations. Number one, as we're always concerned about the potential for two-tiered systems where a child gets turned away for vaccine not based on their medical condition but based on their insurance classification. Of course that already exists and VFC tries to level that playing field, but in a recommendation out ahead of the ACIP recommendation, a VFC resolution ahead of the ACIP recommendation may exacerbate that.

There are some implications where the states will need to raise some coverage if they're going to prevent two-tiered systems. And private health insurance, there's a question whether private health insurance would listen to a VFC resolution or would, as more generally the case, listen to a full ACIP recommendation. And there are logistic

issues, as Marika had mentioned earlier, for immunization providers.

My last slide is a couple of next-steps. I think one of the things that we really should do is that we really should try harder to vaccinate the children that the ACIP says really should be vaccinated. Currently, if estimates are even available, the coverage rate among high risk children is very low. The estimates are around ten percent to 20 percent, and there's not really a lot of studies out there that take a look and try to answer that question. So the bar currently is very low. It seems like there's a lot of potential movement that we can make on vaccinating high risk children.

VFC coverage is already in place. A VFC provider could ask the state for influenza vaccine and the state would deliver the influenza vaccine for these children. They could do that this year.

It does imply some widespread outreach to VFC providers that this is really something that's available, that you really can order this vaccine

and you really can use it for your VFC-eligible high risk patients. The states got a raise in infrastructure funding and one possible use of that raise would be to do influenza campaigns with their VFC provider population. And I think this came out through all of the presentations this morning. This is clearly an important issue for child health. Influenza may very well be the number vaccine-preventable disease killer of children, and it certainly causes a lot of hospitalizations and morbidity.

Another logical next-step is to determine the implication of expanding VFC coverage from the should group to the may group, and I think it would be helpful to have discussions with the partner organizations, professional societies and the states, et cetera, et cetera, and also to be able to have good estimates of vaccine needs, which I think tend to revolve around these estimates of uptake. How much vaccine can really go out the door through this mechanism.

And so I'll be happy to take any questions.

DR. MODLIN: Thanks, Lance. Questions or comments on Dr. Rodewald's presentation? Marty?

DR. MYERS: I guess I have a comment and question, sort of throughout the whole discussion. That is, reimbursements for the providers are usually based on direct costs, not on societal benefits. And the feasibility study that we heard about assumed full reimbursement and it identified cost as the greatest single barrier. So I wonder if we could project the impact of projected Medicare reimbursements, which is usually what health plans reimburse on -- the impact of, for example, the new final CMS rule on the feasibility of implementing an expanded influenza recommendation. And then the reason I guess I'm directing it at you, Lance, is that if reimbursements are less than actual cost to a provider, whether you feel that this would have an impact on delivery of the other VFC vaccines, could this in fact have a negative impact on the delivery of MMR or varicella if people are not reimbursed?

DR. RODEWALD: It's an interesting question.

I think for VFC, my understanding is that Medicaid will pay for the vaccine administration for the may group, not just the should group in there, if it's a VFC recommendation that comes out of the ACIP, so I don't think --

DR. MYERS: But actual costs or --

DR. RODEWALD: Well, as you know, the Medicaid reimbursement fees are much higher in general than the Medicare payment fees to physicians. I guess if I take a step backwards, one of the things we were hoping to get out of the discussion is what you're raising or what are the issues that really should be looked at and modeled before there's an expanded recommendation. So in theory, what I should -- what I think we should do is kind of take notes about the suggestions here so that we can come back with a more informed discussion. But the final rule at CMS affects Medicare directly and there's concern that it may spill over into the child population and into private insurance. I think your point is very well taken.

DR. MODLIN: Randy Graydon, did you want to

comment on that?

MR. GRAYDON: Yeah, one thing I wanted to say about that is we did do a study, I guess about four or five years ago, about the actual cost of vaccination, and we got very poor participation from pediatricians. But the good news was that what we did get was pretty consistent across the country. The bad news is that that regulation has never gone anywhere. And I checked just this week and it's kind of just in the ether. I think it would behoove us to see if we could move that and get something out that kind of supports a better reimbursement for the Medicaid side. But in general, Marty, Medicaid does tend to pay better than Medicare because they do have the understanding that there's more input into -- more physician work in childhood immunizations than there are in adults.

DR. RODEWALD: And I think another thing that helped is that VFC really saved Medicaid agencies hundreds of millions of dollars by paying for the vaccine, and so this -- a lot of the states really

turned this Medicaid savings into higher payment rates for vaccine administration.

DR. MODLIN: Walt, did you have any comment about VFC involvement with influenza?

DR. ORENSTEIN: I was actually called out from the meeting so I came in in the middle. I think the -- the issue I think is certainly -- I think we would be prepared for the June meeting to perhaps present more detailed information that would allow the Committee to I think take a more informed decision.

DR. MODLIN: Bonnie, am I correct that what's left on the agenda is to go through the -- okay, Keiji. Did you want to go through the recommendations and options, or --

DR. FUKUDA: John, I think we have two things to cover, two main things. One is to walk through what the main options are vis-a-vis children, and then the second thing is that Carolyn needs to take the Committee through the 2002 recommendations. And part of walking that through is language, but there are some substantial issues, in addition to

children.

DR. MODLIN: I wonder if it'd be best to do that on full stomachs rather than empty stomachs. Yeah, I would suggest that we actually take our lunch break and try to come back at ten past 12:00 -- or ten past 1:00. It's 50 minutes. And see if we could finish up.

(Whereupon, a luncheon recess was taken from 12:20 to 1:10 p.m.)

DR. MODLIN: Good afternoon. We have a quorum at the table so we'll go ahead and begin. We still have a lot of work left on the agenda on influenza and have about an hour, a little less, to accomplish that. This annually represents a lot of work for the flu group and for the ACIP, and we thought that, in discussing things with Dr. Fukuda at the break, that we would -- maybe the best use of our time to spend most of the time focusing on the options that the work group will be putting before the Committee and spending less time going through the statement -- going over each of the individual changes like we have at least attempted

to do in the past. So Keiji, is that the best way to proceed --

DR. FUKUDA: Yeah, why don't --

DR. MODLIN: -- and I'll let -- I'll turn things over to you to take us through it.

DR. FUKUDA: What we're going to do is I'll walk you -- I'll walk the Committee through the main options regarding children and influenza vaccine, and then Carolyn Bridges is going to follow and then Carolyn will be walking the Committee through the rest of the major topics and some of the language issues.

Just very quickly as a brief review, as you know, this is an issue that we've been working on for the last two or three years. And over the last two or three years the Committee and the flu working group has heard and has discussed several issues related to flu vaccine in children. And basically over the last couple of years we've reviewed the impact of influenza in children. We've --

DR. MODLIN: I'm sorry, Keiji -- with the

conversation going on in the back, it's hard for us to even hear up here. Sorry, thank you.

DR. FUKUDA: We've reviewed the impact of influenza in children. We've gone over the available data on whether there are any safety concerns and then immunogenicity and effectiveness data related to trivalent inactivated vaccine and also the live attenuated vaccine. And Martin has spoken both in the past, as have others, on the economic implications of a decision to vaccinate children. And then again in the past we've gone over feasibility and implementation issues.

So basically I think there are really three main options for the Committee right now, but I will mention the fourth option.

The first option is to make no change in current recommendations. The second main option is to encourage vaccination of children six to 23 months of age, but then defer a full recommendation for some period of time, for about one to three years. This was a suggestion brought up by Rick Zimmerman at the last ACIP meeting.

The third main option is to go ahead and recommend today annual vaccination of children six to 23 months against influenza. And I'll go into the pros and cons of each of these options in a minute, but the fourth main option would be to recommend annual vaccination of children six months to some older age, and the older age could be another year or two, up to three years, or it could be a much older age, up into the teenage years, but for a variety of reasons those have not been so seriously discussed by the working group currently. And so I think that unless anyone has any questions on those, I'll just skip on to the main options.

So now option number one is to continue the current recommendation to annual vaccinate children six months and older who have high risk conditions. This is a recommendation that has been in place for many years.

Now the pros of this is that this recommendation does focus attention on children with medical conditions that place them at high risk for complications. In all age groups, when

you compare kids with high risk conditions versus healthy children, they're at substantially higher risk for hospitalization and other morbidity. It has been brought up at a number of meetings that this is a recommendation which has not been -- perhaps not been sufficiently promoted in the past, so it's been on the books for a long time, but a number of people have said that they think that maximum efforts have not been extended to promote it.

And the other pro is that if this course is continued, it really raises the fewest feasibility concerns and fewest feasibility implementation issues.

Now the major cons against this course is that despite this longstanding recommendation, vaccination coverage rates remain low, for whatever reason. And the second con is that this course would ignore the increased risk for hospitalization in young healthy children, which has been demonstrated in studies over the last couple of years.

Now the second main option is to encourage annual vaccination of children six to 23 months, but then defer full recommendation for about one to three years, and in addition there would be additional language in the text added about vaccine safety and ineffectiveness, basically to flesh out the rationale for this recommendation.

Now the main pro for this option is that it does focus attention on the risk of severe morbidity in young healthy children. It would provide all of the relevant organizations and persons with the notice of ACIP's intent. Basically ACIP would be saying this is where we intend to go in the next couple of years. And it would provide a definitive time frame for conducting all the necessary anticipatory activities such as education of pediatricians, education of parents, collection of additional data and so on.

One of the cons of this approach is that it would not focus attention on children 24 to 36 months of age. In some studies this is a group in

which the risk of hospitalization appears to be elevated. However, this increased risk is less substantial than it is for younger kids, and it's not clearly seen in all studies. And it also does not focus attention on children with high risk conditions.

The second thing is that it will -- once this recommendation is made or this movement toward it, it will increase the demand and the stress on the vaccine supply. I think this is sort of a chicken and egg situation. In the short term there would clearly be some additional stress on the vaccine supply system. In the long term it could strengthen the vaccine supply system by increasing the demand for vaccine.

And then the third major con is that if we say that ACIP will be moving to this course of action in about one to three years, it may not be enough time to implement all of the desirable preparatory activities.

And then -- oh, the fourth point I wanted to put on, which I didn't put on here, is that if this

recommendation is deferred for a couple of years then of course those kids who are in the younger age group and who are at high risk for hospitalizations may not get vaccinated.

Now the third main option is to go ahead and today recommend annual vaccination of children six to 23 months of age.

Again in the pros, healthy children in this age group have a significantly and substantially higher risk of hospitalization from influenza-related causes. And then it's a relatively conservative recommendation in that the upper age limit of the recommendation can be increased in the future, so it gives room for some movement.

Now in terms of the cons, one of the cons is similar to what I just showed, it would not focus attention on children 24 to 36 months of age, and it would not focus attention on older children who have high risk conditions. And again, this is an important group that we always have to keep in mind.

Secondly, it will more immediately increase

demand and stress on the vaccine supply system. And then third, I think that there is -- there has been considerable discussion and uncertainty whether pediatricians in the public are adequately prepared for a recommendation to be made today and implemented in the coming season.

So again, the first three options I think are really the ones on the table, and I think I'll just stop there.

DR. MODLIN: I think the best way to proceed here is to open this topic up now for general discussion. We don't have an extensive amount of time, but then to focus in and ask the voting members of the Committee to make a decision on this today.

But let's open it up for comments, questions, and opinions. Natalie?

DR. SMITH: Yeah, I certainly would like to move forward with stronger flu recommendations. We've been talking about it for a number of years. I don't think -- I think if we chose option two, I also think we could agree to put much more work

into reaching the older high risk children, as well. I don't necessarily see that as a con that it doesn't focus on higher risk children. The previous recommendation obviously has focused on high risk children. We're still doing an abysmal job in getting all those kids immunized.

DR. MODLIN: Maybe I could ask Bonnie and Keiji what the recommendation of the work group would be, just to get us focused. Bonnie?

DR. WORD: Okay, so I have a TIA again. The -- actually I think, as Natalie's pointed out, I think overall the working group got most comfortable with encouraging the vaccination of the six to 23-month-olds to begin to initiate it now, with that proviso of beginning to have some educational programs going on. We talked about doing things with the AAP, as well as the AAFP, and the CDC's education -- or their communication office also has some broadcast capabilities that they developed some tape, so I think that's where we had -- that was -- people were more comfortable with that was letting know this is the intent of

what we're going to do, but to do something.

DR. MODLIN: I would point out that we sort of gave the same level of intent with our statement last year that we'd be moving in this direction, and I guess I just -- to be the devil's advocate here -- would question what's the driver for all this activity around education, preparation and so on? Is it a recommendation or is it a signal to make a -- or intent to make a recommendation? Actually, maybe before we go on to further questions here, I'd be real curious as to -- we probably ought to get the comments from the AAP here right now. I don't know where Jon or Gary want to weigh in -- or Peggy?

DR. RENNELS: Well, I guess you should probably comment.

DR. ABRAMSON: Well, I mean Peggy's working on a technical statement and a policy statement that will be reviewed beginning of next month at our spring COIB meeting, and I think that we're probably going to go on the second recommendation, which is to encourage vaccination of children six

to 23 months, try to then educate physicians and parents about the increased risk and that these children really are high risk children, and then within a year or two come out with a universal recommendation. I mean that, to me, is what likely will happen, but I'd be interested in Peggy's comments.

DR. RENNELS: I would essentially agree. I think, in answer to your question directly, John, I think this is an intent to come out with a statement, but a discomfort at this point to do it because there are some very serious logistical issues that may prevent practitioners from being able to comply and therefore would put them in a medical legal bind. And although we've had one nice logistical study, it really -- the basic premise wasn't our current reality, and I think there -- further study needs to be done.

DR. MODLIN: Paul?

DR. OFFIT: Yeah, I think that if we deem the burden of influenza disease in the young child to be high, and we deem then prevention of disease in

that age group to be important, the question is how best to achieve that. It seems to me that varicella in a sense can be an analogy. We recommended the varicella vaccine for routine use in 1995, and uptake initially was slow. I mean it sort of was in the ten percent range, now we're at 70 percent because by setting the bar at recommendation, we drove essentially that -- the education of the physician and the parent about the value of that vaccine, and now the vaccine is used and we clearly have prevented a significant burden of that disease.

I think that by continuing to encourage without setting the bar at recommendation, we just lose time.

DR. MODLIN: Rick? We'll go around the table. I'll make certain everybody has an opportunity.

DR. ZIMMERMAN: I agree with Peggy. I think that the -- certainly there's the evidence to go ahead and move towards a recommendation. But the problem is the logistics, because we've got the issue of thimerosal is in most of the flu vaccine.

There'll be some probably thimerosal-free, but we've got that issue. We've got the issue of vaccine shortages. We've got administration issues with a number of docs in the survey. If I recall right, it was about 18 percent saying they were opposed to the policy change. And so there's a number of barriers. And when you don't have a guaranteed supply and you're going to make a recommendation, and so I would actually model this more on the IPV model where the IPV we said we're going to move towards IPV. The first step was a sequential schedule and then eventually went to the full IPV. And so I would suggest that as another model that we have used in the past where we declared an intent, we did the education, we moved -- and we definitely did move and we completed the transition. It wasn't forever and ever, but it's a different model than the varicella model.

DR. MODLIN: Why don't we get the AAFP's opinion here.

DR. MAHONEY: Thank you, Martin Mahoney. Let me just start by raising a few issues, and then

I'll give Rick Clover an opportunity here. I think -- from an organizational perspective, I think what Dr. Abramson and Dr. Rennels have suggested makes a lot of sense, and that is I think we need to do more to educate family physicians, as well as pediatricians, about what some of these disease risks really are, and who the high risk groups are. When you go back and look at some of the coverage rates, as we've heard alluded to earlier, the coverage rates in these high risk individuals remain very low. I don't disagree that this is a high risk group by virtue of incidence rates, attack rates and hospitalization rates, but at the same time I think what we hear from our members is that if you were to come out and make this a recommendation or even this permissive recommendation, that it would put them in a very difficult situation in terms of reimbursement, in terms of some of the information we've heard presented through the U of R study where it will result in an increased utilization of office visits.

And you know, while the rates -- reimbursement rates are a little bit higher from the adult flu vaccine perspective, this is a loss leader. Physicians do it as a courtesy to their patients. They don't make money on immunization -- providing flu vaccines to their adult patients.

Finally, I think the U of R study does underscore the fact that there is some disagreement among pediatricians and family physicians currently based on those results, and lack of clarity on what is best for these patients. Maybe we can address some of those disparities and disagreements through a process of education, and I think that that's where our initial efforts would probably reap the most benefits, and benefits which are of most benefit to the population that we serve.

DR. MODLIN: Thanks. Bonnie?

DR. WORD: I think Paul's comment's well taken 'cause I felt that way, too, is that let's make a decision. And one of the things that we were trying to encourage is putting some time frame behind it, because before it seemed like the

statement was always open-ended. But now since we've -- we're saying okay, we're trying to put some time period when the Committee has to come back and make a decision, but during that time period -- if we're emphasizing that we need to have teaching, et cetera -- then we've asked the different parties who are going to be involved with that to provide some type of agenda and look at a timetable. Say you know, what can you do, what's feasible, what isn't feasible, or how can you combine your effort so that you go out as a united front in terms of how you present it, but I think this way you put something out on the table that says we're going to set X, Y and -- our organization is setting this up. We plan to roll this out at this such-and-such time. Then we can come back. It doesn't stay as open-ended as -- so that another three or four years, you're still sitting here.

DR. MODLIN: John?

MR. SALAMONE: My history with this Committee goes back to the time when you were discussing the

changeover from OPV to IPV, and I noticed the look on your face when Dr. Zimmerman made this analogy, but candidly, you were incredibly, incredibly cautious during this period of time making a change from OPV that had been around so many years to IPV, and I would hope that you'd use that same caution as you're introducing this large major change, if you will, in our vaccine policy. I like the idea of phasing this in. I like the idea of giving time for education, of giving time to see increased adverse reactions and getting a bigger pool, if you will, as a result of that. And I really do feel that this is -- option number two is the proper direction for us to go.

DR. MODLIN: Walt?

DR. ORENSTEIN: I think the major reason we're considering this is the data on health burden. I think the data are quite convincing. I think the data on safety and even efficacy are less -- are less sound, in my opinion, in terms of the availability. I think by having option number two, there's an ability to collect some of that

information, which I think will help in forwarding a recommendation.

DR. MODLIN: Jane Siegel?

DR. SIEGEL: Jane Siegel. Would option two -- how would that translate into VFC coverage or commercial insurance coverage? Would that change anything if it's worded as it is in option two?

DR. MODLIN: In some respects it is and it isn't a separate item here, Jane. I wonder if probably the wise thing to do wouldn't be to consider it a separate issue and bring up VFC in just a minute. I think we probably ought to be focusing on the first issue, which is is this a good thing to do now for the health of children. Myron -- and then we'll come back to VFC --

DR. LEVIN: In my notes here I had ruled out the third bullet on practicality issues, also, and that left me basically with the second bullet. But if that's chosen, I think that this document ought to try to clarify to some extent exactly what the intent is and what kinds of things will be done to prepare for it, things like what Walt mentioned and

a recognition of the problems and that need to be solved first.

DR. MODLIN: Okay. Is there any active support for either the first or the last option here? Can we kind of -- we're really talking about option two and option three here. Okay. Dixie?

DR. SNIDER: Could I just ask for clarification from Myron? I'm interpreting that perhaps inappropriately, but perhaps appropriately, as actually having wording in here that with recommendations from ACIP to CDC and any other entities to carry out certain preparatory activities, and put those explicitly in the document.

DR. LEVIN: Well, it follows from your comments earlier in the morning about what should be in some documents about research is needed, and in some cases not research, it's practical issues. But I think we should spell them out, and I think it would relieve some of the anxiety of the caretakers if they know what's going to happen.

DR. MODLIN: Okay. Jon?

DR. ABRAMSON: You know, for a long time I also was in favor of recommendation three, but I think with the number of problems we're facing with vaccine shortages, that we -- if we have another shortage here and we fail, rather than giving us a couple of years to prepare, I think we'll have done ourselves a disservice. I think by giving people a forewarning that we will be making this recommendation in a couple of years, one to two years -- I guess, it's up there as three, but -- I think we'll -- we're setting ourselves up to much more likely succeed. And we've been at this for a long, long time and I think there are now enough compelling data, as Walt says, to make us feel like this is the right recommendation, but we need some preparatory time.

DR. MODLIN: Let me -- yes, Marty?

DR. MYERS: I'd just like to re-emphasize what Dixie and Myron and Mr. Salamone said. I think that it's essential that it spell out responsibility for obtaining vaccine safety data, for example, when we start immunizing very large

numbers of children. And that this is not a sponsor's -- sponsor's not likely to take this on as a responsibility, so it needs to be spelled out that it is our responsibility to collect it.

DR. MODLIN: Okay, let me just very -- Peter, and then we'll --

DR. PARADISO: Peter Paradiso. I just wondered whether the Committee had considered what they thought the vaccination rate would be with option number two, which seems to be proposed, and whether they think that they're going to get meaningful data from that and whether there's a target below which you would say that was not successful. Because I think that the danger here is that, since nobody is going to pay for it, there's not going to be any reimbursement, nobody's going to get immunized, and it's not -- from our perspective as a manufacturer, it's going to be difficult for us to figure out what the demand is going to be and how to adjust any supply issues on the basis of option two. Whereas option three, we would assume that the recommendation would go into

effect and it would be a very slow uptake over the next three or four years.

DR. MODLIN: Maybe I could answer for the Committee or I think what I get the sense is, and that is that I think even with option three, the uptake is likely to be relatively slow, as Paul suggested with varicella. And even here we're not talking about a school entry mandate, which may drive acceptance even more slowly than say with varicella vaccine. So I would guess that the incremental increase in -- with respect to the vaccine supply is likely to be relatively small, and maybe even inconsequential.

Let me -- Does anybody else feel any differently about that?

There are a few people who haven't expressed an opinion and I'd like to just see if we have a consensus here, whether we even need to take a vote. Lucy, do you have any strong feelings about option two?

DR. TOMPKINS: (no audible response)

DR. MODLIN: Okay. Jaime?

DR. DESEDA: (no audible response)

DR. MODLIN: Dennis?

DR. BROOKS: (no audible response)

DR. MODLIN: Okay. Gus?

DR. BIRKHEAD: Yeah, I think option two, but I agree with the comments that we -- that as concrete as we can be about what more this Committee would need to see before making a recommendation, and even -- I mean three years sounds like it's even too long to wait to make a final recommendation.

DR. MODLIN: Bonnie and Keiji, would it be reasonable to expect to put this issue on the June agenda to see what the plans are for making progress on option two with respect to education plans and getting the data that the Committee is looking for?

DR. FUKUDA: Yeah, I think we can --

DR. MODLIN: It wouldn't be long, but in the way of an informational update just so that we stay on top of what's happening.

DR. FUKUDA: Yeah, and I think we can propose what those activities might be.

DR. MODLIN: Dennis?

DR. BROOKS: I just had a quick question. With option two, which is sort of permissive, would VFC still cover that --

DR. MODLIN: We haven't made that decision, but -- Walt?

DR. ORENSTEIN: I think that we would propose coming back to the Committee in June to actually address some of the issues. You have set precedent with pneumococcal conjugate vaccine. Since you are the ones who vote a vaccine into VFC, you have the potential of coverage or non-coverage, but I think in order to do that and make, in my opinion, an informed decision, we need to offer you numbers, dollars, other issues that might go with that kind of resolution.

DR. MODLIN: And this would get at the issue that Jane was raising. They're slightly -- maybe a little bit different in that you were asking about whether if there were VFC resolution -- if we were to include this under VFC, if it would make a difference in uptake. It's kind of the reverse,

but I suggest that we do plan on revisiting this in June and that's a way to keep the issue on the table.

I think we have a consensus without necessarily having to take vote, Keiji, so why don't we move on to --

DR. FUKUDA: Okay.

DR. MODLIN: David?

DR. FEDSON: A very quick comment -- David Fedson, Aventis Pasteur, MSD. I'm just speaking for myself, not for anyone else, but if you're going to come back with some further information and suggestions in June, it would perhaps be worthwhile asking the Canadians their experience in Ontario when a largely political decision was made to drop the age of recommendation for influenza vaccine from 65 to six months of age and they have a province-wide program for vaccinating people of all ages. Ask if the feasibility was difficult, what the vaccine supply problems were, how it was received by doctors and patients, children and older children and families. I think the real

world experience of the Canadians in Ontario might inform the members of this Committee in making that decision.

DR. MODLIN: Good point. Victor --

DR. FEDSON: I think it would be invaluable.

DR. MODLIN: -- maybe you could help us with that in June.

DR. MARCHESSAULT: Sorry, I can't help you because we have no data. We've asked the province and they said we're looking at this. We don't know -- that they have not studied the data and I don't even know if they have it.

DR. MODLIN: Okay, thanks. We need to move on.

DR. BRIDGES: Okay. We'll try and make the rest of this fairly quick. First of all, Bonnie mentioned that every year this is a very short time line -- you can go to the next overhead there -- for this particular set of ACIP recommendations in order to get these to the MMWR for publication by April 25th for me to have final comments if there are concerns about wording in the next couple of

weeks. We will plan on next year to present the first draft in October so that we will have a second meeting in February if there are things that need to be revisited, to lengthen up the time line a little bit.

Keiji's talked about the vaccination of children. The other issues that we need to discuss is the wording about thimerosal in the vaccine, and the other issue is timing of vaccination. There also is some wording changes in the statement on vaccination of pregnant women. This wording was changed because the MMWR office was concerned about our use of the term experts, without defining who we meant by experts. We're not planning a change in the recommendation, just the wording. The vaccine strains will be updated. The vaccine coverage level is updated. There's also some additional information on influenza diagnostics because we had a substantial amount of interest in that because of the anthrax issue, and of course the references are updated.

To get to the thimerosal section first, as the

Committee is well aware, this has been an issue in a lot of childhood vaccines and all the currently available influenza vaccines have thimerosal. That concern was primarily directed towards infants less than six months, because they received a number of thimerosal-containing vaccines. There was no change that was made in the influenza vaccine recommendations based on the discussions of thimerosal because at the time there was no thimerosal-free or reduced vaccines, and it was thought that the benefit outweighed any potential risk.

For the coming year one vaccine manufacturer, PowderJect-Evans, will have a reduced-thimerosal content vaccine. None of the influenza vaccines have an FDA-approved indication for vaccination of pregnant women, and this particular vaccine -- the PowderJect is not approved for use in children less than three years -- sorry, less than four years of age, and only a proportion of their vaccine will be in this reduced-thimerosal form, so not their entire production.

Because of all these issues and the limited availability of this vaccine -- of the reduced thimerosal and because of the ages that it's recommended for, the working group discussed this issue and recommended that the language in the draft contain information about the availability of this reduced-thimerosal content vaccine, but there was no special encouragement or preferential use given to this reduced-thimerosal content vaccine.

So if there are any comments or questions or concerns about how this was handled in that.

DR. MODLIN: That's specifically the issue. Bonnie, do you have anything else to add about the working group recommendation here?

DR. WORD: (no audible response)

DR. MODLIN: Is there anyone on the Committee, or in the room, for that matter, that feels this is not the right way to go?

(No response)

DR. BRIDGES: Okay, great. As I mentioned, the vaccine coverage levels were updated and I think that Dennis has already covered this just to

point out not only do we have problems with covering high risk children, we also don't do a good job of vaccinating health care workers nor of high risk adults who are less than 65, and there continues to be racial disparities in our vaccine coverage for indicated groups.

Keiji has -- you can go to the next one, Lynette. We've already decided about vaccination of children. Just so the Committee is aware, we will be adding -- as was requested recently, we will be adding increased information about the effectiveness data that's available and safety data available in this age group and children in general. And the section on vaccination of children had been in the back of the vaccine section and it's now been moved forward into the document.

You can go to -- skip the next one and go to the -- that one. Okay.

There was also some concern about reimbursement that we may not have been specific enough in the way it was worded in terms of the

timing of vaccination, so a child who was not six months in October but may turn six months in January, would that child be included, or a child that turned 24 months in January. What we recommend for all the other age groups is that vaccination should continue throughout the influenza season and essentially that's what this conveys. A child that will be six through 23 months any time essentially during the flu season should be -- or encouraged for vaccination. Jon?

DR. ABRAMSON: Yeah, my -- this is Jon Abramson. My concern about that is it almost implies that after 24 months it shouldn't be offered, and I think we need to make clear that that's not what we're trying to say, where it is what we're trying to say under six months.

DR. MODLIN: Jon, does it also say at the other end of the age spectrum that we can immunize a three-month-old child in October?

DR. ABRAMSON: Yeah, and I would --

DR. MODLIN: Karen, do you have anything to say about -- specifically about this language?

DR. MIDTHUN: Well, I'm concerned because it's not clear at what particular age that would be permitted, and I think it could be construed -- what you've just said, that you could go ahead and immunize them let's say in November if they're going to turn six months old in January. I mean could that be one interpretation? I don't think that's what you intended, but --

DR. BRIDGES: Yeah, I think we can work on the specific language. That's what the second sentence was trying to get at -- again, to reinforce that vaccine can't be administered to children who are less than six months. The point we're trying to get across is that you can vaccinate a child that turns six months in January to cover them for the season of January/February.

DR. MIDTHUN: Right, you can vaccinate -- if they turn six months in January, you can vaccinate them in January.

DR. BRIDGES: Exactly.

UNIDENTIFIED SPEAKER: Right, I was just going to suggest that.

DR. MODLIN: There may need to be a little clarity.

DR. BRIDGES: We can work on that to clarify your point.

DR. SMITH: A very brief point. Just from the field we get a lot of questions. If you can only get in one dose, obviously a lot of these kids are first-time vaccinees and recommend two doses. Do you go ahead and recommend the one dose and that might need to be clarified.

DR. BRIDGES: I think from the study that Kathy Neuzil just published with Kathy Edwards, they only did use one dose and they had -- they were able to show vaccine effectiveness, so...

DR. MODLIN: Gary?

DR. OVERTURF: I would suggest that since you already have the title of six to 23 months, and it's already in the recommendations, that all you need do in this sentence is to eliminate the less than 24 months.

DR. BRIDGES: Okay.

DR. OVERTURF: That's really all that needs to

be done, so that everybody realizes there's not a limit to that. The limit here that we want to emphasize is the six-month limit.

DR. BRIDGES: That's a great suggestion. Comments? Okay.

The other issue then that comes up, if children six to 23 months are going to be encouraged to be vaccinated when feasible, then what to say about household members and care providers for those children. Obviously we recommend vaccination of household contacts of all other high risk groups and the options that have been mentioned are to go to the zero to 23-month-olds. Another option would be just to recommend it for household contacts of zero to less than six months olds since those kids are not eligible for vaccination, or the other option is not to mention contacts of these children.

DR. MODLIN: So that we'd be adding a new risk group here, in essence.

DR. BRIDGES: Be adding a new target group for contacts of high risk.

DR. MODLIN: How do others -- how do people feel about this addition? Again -- Myron?

DR. LEVIN: Well, I don't think you can peg it to the likelihood that those children who are considered high risk are actually going to be vaccinated. We just got through saying that. So if the purpose of vaccinating the contacts is to prevent those children who are going to be missed, I would keep it in as rule number one.

DR. BRIDGES: Well, we recommend vaccination of household contacts of people 65 and older, for instance, and other adults less than 65 who have high risk conditions, whether they're vaccinated or not. We don't make any stipulation in the rest of the recommendation.

DR. LEVIN: But this is for younger household contacts, as I understood it.

DR. MODLIN: This is for --

DR. BRIDGES: All household contacts and out-of-home care givers, so they would be children and adults -- adult contacts of these high risk kids of the age group of kids. Peggy?

DR. RENNELS: Just my personal opinion is although I think number three is optimal economically, that's going to have a lot bigger impact than number two. And personally I could live with number two, and those are the highest risk children. They can't be vaccinated and this is our only way to try to protect them.

DR. MODLIN: Bonnie?

DR. WORD: The difficulty that I was having with one or two is that there's no mechanism in place to assure that any of these contacts of these children out of the home are going to be vaccinated. I mean there's no way to really implement it if we tried to push for one or two. Say if the care giver at the outside home, the day care center, may be vaccinated, doesn't mean all the children in the day care center attending will be. So I'm not sure how we solve the problem with that one.

DR. MODLIN: Rick?

DR. ZIMMERMAN: I have a concern about option one, and that's just thinking of some of the

feasibility. Four million birth cohort. We figure two birth cohorts, about 8 million, so we're now talking -- if we assume these households have 1.5 adults, you're talking 12 million additional vaccinees, assuming most of these people would not -- these adults would not be 50 and over, given their childbearing age, and so that adds a substantial new group of 12 million for option one, and I'm not sure we've got the feasibility to add that size of a group at this point.

DR. MODLIN: Right, it's a substantial group. Kathy?

DR. NEUZIL: I think we have to be careful, though, to be consistent here. And I don't think, if you look at this group of following groups who should be vaccinated on the basis of transmission, you can tell me if you have data, but I would say, as an internist, these numbers are quite low, that we're rarely actually giving vaccine to these family members. And I would come across more on the mixed message side, that if young children are high risk, then they're high risk. And it doesn't

carry the same risk that Walt brought up before about actually vaccinating the young children, that's not the issue. And I think to be consistent, if they're high risk, then they fit into the category where their contacts should be immunized. We don't do it -- we do a poor job of every person in this group, so I would not exclude them on the feasibility reasons.

DR. BRIDGES: In terms of the number, if you look at household contacts of zero to 23-month-olds and you assume a 30 percent vaccination rate -- we're assuming that this, like all recommendations, would take a while to ramp up -- you're talking somewhere between 4 and 7.6 million doses of vaccine for household contacts of zero to 23-month-olds. If you just look at zero to six, it's one and a half to three million.

DR. MODLIN: Jon Abramson?

DR. ABRAMSON: I want to argue against doing number three. I think ignoring a problem is not going to get the answer, and you'll have people inundating you with questions about that who know

what they're doing. I personally can also live with number two because then what the message is we're clearly sending, we worried about these kids 23 months and younger and that we want to protect them, we're encouraging protection using these various modalities. In other words, we're encouraging immunization of those six to 23 months, and we're encouraging immunization of those in the household where we can't protect them when they're under six months.

DR. MODLIN: Can I get back to Bonnie's question, which I think is very important, and that is who's going to take ownership, who's going to take responsibility for immunizing these, for the most part, young women and young men who have very young children. Peggy?

DR. RENNELS: Well, first let me clarify that I misspoke. I meant -- when I first spoke I said I prefer number one, but given the economic and number of dose limitations, I could settle for number two. But let me respond to that in that who takes responsibility now for the contacts of high

risk people? I mean that didn't stop us before.

DR. MODLIN: Fair enough. Sam?

DR. KATZ: I think what you're getting to is almost a universal recommendation. It isn't just parents. It isn't just day care. It's grandparents. You know, it's -- if you really believe in it, you're almost saying the whole population should be immunized. And I think you have to decide whether you believe in that or not.

DR. MODLIN: Except for under six-month-olds, which maybe have the highest risk.

Other comments or questions? Georges?

DR. PETER: I favor more widespread vaccination, including vaccination of children between the ages of six and 23 months and their household contacts. But I'm impressed by this discussion that we do not have the infrastructure with which to implement these recommendations. And if we make recommendations that we can't implement, then I think this Committee loses credibility and we create problems, and I would suggest that we defer some of these discussions until we have

examined whether or not we could develop a mechanism for ensuring some way that we could give the vaccine to these high risk groups. And I think Walt has already suggested that that strategy be adopted, but to make the recommendation simply because we have a recommendation on the books already is simply to perpetuate a failed strategy, and I think the first step is infrastructure and delivery systems.

DR. ABRAMSON: Again, I think we get off-based off our previous discussion of encouragement with the idea that in one or two years we'll be at this point of a true universal recommendation for this group in the household contacts. It seems to me the most consistent thing we can do at this point, given all the issues that are raised.

DR. MODLIN: Yes, Dr. Mahoney?

DR. MAHONEY: I think it's important to emphasize that this Committee does have to pay careful attention to what their credibility is with practicing physicians. They've come out with recommendations which have made a lot of sense and

been easy to justify from a review of the literature. And when one takes that perspective, they seem to be valid recommendations.

However, over the last two years there's been a lot of back-pedaling, due to various things related to vaccine supply issues, as well as more directly with limited supply of influenza vaccine. So I think to come out with a recommendation that says do more in terms of immunizing against influenza without really having any ability to ramp up the supply raises serious concerns about credibility.

DR. SMITH: I agree. I think if we could re-look at this in June it might be helpful because it is a recommendation to vaccinate parents of young children, which is a lot of logistical issues.

DR. MODLIN: If we re-look at it in June, that means leaving it out for the next year's statement, for the most part --

DR. SMITH: Okay.

DR. MODLIN: -- true, Carolyn? So we really are making a decision about whether or not this

needs to be included in the 2002 --

DR. SMITH: And then just -- this is off the point, but just -- I think we're going to have to re-look at the language of how we use high risk and higher risk, and I can see once we communicate all this out to the field, it's getting very confusing about how we use that terminology.

DR. BIRKHEAD: I would agree with that, but I think it's a little inconsistent to encourage vaccination of six to 23 months old, but recommend it for their parents. So I think we should wait that discussion until we have the language. But the less than six months old may be something that we could act on today.

DR. MODLIN: Peggy?

DR. RENNELS: Could we at least all agree to encourage number two for parents who want to prevent their infants from developing vaccination (sic)?

UNIDENTIFIED SPEAKER: I guess if we're encouraging it for the kids, we could encourage it for their --

DR. RENNELS: That's consistent.

DR. MODLIN: In the interest of consistency, certainly -- we certainly still have some work to do. Rick?

DR. ZIMMERMAN: Well, using the word encourage, I so move option two.

DR. MODLIN: Okay. A motion has been made.

DR. BIRKHEAD: Is it stronger for the less than six-month-old or --

DR. MODLIN: It was option -- this is option two presented here with -- let me just point out --

UNIDENTIFIED SPEAKER: Encourage.

DR. MODLIN: Okay, let me just point out that option two -- I'm sorry, I'm on the wrong page here. Okay. Motion on the floor is to encourage option two with the word "encourage". Okay? Is there a second?

DR. BROOKS: I'll second that.

DR. MODLIN: Dr. Brooks has -- Dr. Zimmerman has made the motion, Dr. Brooks has seconded it. Is there further discussion?

Could we add a rider onto that that we intend,

as a Committee, to review this issue in some detail, perhaps in June or in October? It's an important issue that I think we've raised and we're grappling with, and I think it's obviously going to take some more time and effort to --

DR. BIRKHEAD: Is it the same argument that it's feasibility that's not allowing us to recommend it at this point? Is that what you're --

DR. ZIMMERMAN: Yes, somewhat different reasons, because it's not as great a -- I mean you're talking -- if I remember the projections in terms of number of doses -- about a million doses, so it's not as great a hit as 12 million doses, but it is an issue of infrastructure, how do we deliver it, who's taking responsibility?

DR. BIRKHEAD: You're referencing a group that can't be vaccinated. I'm not sure why we need -- why we can't recommend it in this group.

DR. MODLIN: Well, we do have a motion pending on the floor. Jon Abramson, I did see you nodding your head in agreement with that. Is that fair, that the Academy -- the representatives of the

Academy would support that? Dr. France?

DR. FRANCE: I just wanted to clarify, is option two then that it's encouraged for people -- for families of infants zero to six months of age?

DR. BRIDGES: That's option two.

DR. FRANCE: Is that what you're discussing? Okay, I was thinking that, to be consistent with the encouraging children six to 23 months of age, that we would encourage families of children with children zero to -- six to 23 -- or zero to 23 months.

DR. MODLIN: Zero to 23.

DR. FRANCE: I'm just not clear if the motion is for the zero to six or zero to 23. My preference would be zero to 23. I think there's probably adequate vaccine to cover the small amount of families that actually do that, given that this last year --

DR. MODLIN: What was your motion again, Rick?

DR. ZIMMERMAN: My motion was number two, which is zero to six months, with the word -- it not being a recommendation but an encouragement.

DR. MODLIN: But does not Dr. France's point -- isn't it an excellent one in that we're looking at children under 23 months as being at high risk? Why not encourage immunization of the parents of those children under 24 months of age down to zero, in order to be consistent with the direction that we're going in with our other encouragement?

DR. SMITH: It depends what level you think will be vaccinated of those zero to -- the six to 23 months old.

DR. ZIMMERMAN: The two reasons I would say for zero to six, first of all, you can't -- if you're going to follow FDA guidelines, you cannot vaccinate the zero to six months, so there's nothing else to do for them. The other concern is that if you go to 23 months, you're quadrupling the number of families involved and the amount of vaccine, and it's just a question of how big a bite to take.

DR. MODLIN: Well, you hope that you're quadrupling it. I think the likelihood is probably somewhat lower.

Okay. We've got a motion on the floor that's been seconded. Do we need to exclude those that are conflicted with each of the influenza manufacturers, Dixie --

DR. SNIDER: Yes.

DR. MODLIN: -- on this issue? Which means that those that are conflicted with Wyeth, Aventis and I hadn't heard anybody say that they were conflicted with Evans. Is that fair?

Okay, who is conflicted on this. Peggy? Terrific.

So those in favor of the motion, would they raise their hand? Those in favor? Dr. Zimmerman, Dr. Smith, Dr. Tompkins, Mr. Salamone, Dr. Brooks, Dr. Offit and Dr. Word.

Those opposed? Those opposed are Dr. Deseda, Dr. Levin, Dr. Birkhead and Dr. Modlin.

The motion passes.

DR. BRIDGES: All right, the last section -- I don't know if anyone had questions or concerns about the way the section on vaccination of pregnant women was reworded. Again, it's not a

change in the recommendation, just some -- mostly wordsmithing.

Okay, I see none. The last big issue is timing of vaccination, and as you know, the last two years have been supplemental influenza vaccine ACIP recommendations because of problems with vaccine delivery delays, and in those we recommended changes in timing so that highest risk people and health care workers were vaccinated first, and other people were asked to delay vaccination until later in the season. So we heard from Dennis O'Mara earlier that the vaccine projections for this coming year are somewhere around the high eighties or low 90 million doses of vaccine, so we know that those -- there are no guarantees.

So one option would be, considering the uncertainties, that we don't change the vaccine recommendations. We stick with how they have been in the regular ACIP recs, which is that the optimal time to vaccinate is October through the end of November, and that you should continue vaccination

in December and later.

Another option that has been suggested is that we go to the tiered form that was used which was passed at the -- in July, which basically recommended that 65 and older plus other high risk people less than 65 and health care workers get vaccinated in October, and then in November we would vaccinate essentially all other groups of interest. There was some discussion within the influenza ACIP working group whether health care workers and household contact should be altered with the months that they're in, and again we would encourage -- again -- vaccination in December and later. That was one option.

The other option that was most recently suggested is that we stick with the current recommendation, which is optimal time is October through November, and the only group that we would ask to defer to November would be campaigns that are directly mostly towards health adults. So workplace vaccination programs, recommend that those occur in November and everyone else can begin

vaccination in October. We would still, again, encourage vaccination in December and later.

DR. MODLIN: So again we have, in essence, three options here. Let's open this up for discussion. This is an important topic that in some respects could signal at least a -- if not a permanent change, one that is built in where we haven't built in recommendations around vaccine supply in the past.

Bonnie, do you want to lead off?

DR. WORD: I was going to say, one of the reasons that this whole -- this concept came up was for the last two years we've had to -- after making recommendations, you had to come back and revisit it, and so the rationale was that why don't we put something in place. We spent a couple of years educating people already on how to prioritize. And go on and initiate something that's similar to that. If you don't run into any problems, you can always ease the guidelines. It's a lot easier to change them as opposed to say everyone can get them if they want right now. The reason -- so I'm

supporting -- really supporting number two, primarily because it's been somewhat the same way it was prioritized previously for the last two years. And so you've tried to teach people out in the field to do it that way. I think it lends to less confusion if you suddenly want to introduce something new.

DR. MODLIN: Bill Schaffner?

DR. SCHAFFNER: I'd just like to reinforce what Bonnie has said. We've done some training out there now. People are kind of more or less -- perhaps a little bit more -- used to option number two. Let's not change the rules of the road yet again. People out there are looking for some semblance of consistency.

DR. MODLIN: Jane and then Stan?

DR. SIEGEL: I agree. I like option two, but I feel strongly that health care workers need to be maintained in the first year with the highest risk.

DR. MODLIN: Stan Gall?

DR. GALL: John, I'd just like to remind the Committee that the season runs from October through

March, and there seems to be a big spurt in about November, and then it -- there's no more enthusiasm. And if you look at which years flu peaks, it's sort of divided over the years. So I -- somehow it has to be reminded or people have to be reminded that this does go until March and that continued immunization is needed.

DR. MODLIN: I think that's exactly getting at what Bonnie and her work group are trying to do. I do know, speaking at our small institution, that there was considerable more immunization activity going on through December this year than we've seen in the past, even though there were some fits and problems with it and didn't always understand the nature of the guidance, it seemed to be going in the right direction. And I -- so I think I would support the work group's recommendation here that if we continue with the same message that we may be achieving something.

Other comments? Yes, Gary, and then --

DR. OVERTURF: It's not on the slide, but I assume it's meant to be included, and that is

children -- healthy children six to 23 months would be included in the early immunization, because that's going to be critical to, quote, encourage feasibility.

UNIDENTIFIED SPEAKER: Especially since they need a second dose.

DR. MODLIN: Rick?

DR. ZIMMERMAN: The experience in my office when we were doing a site in the inner city to try to raise influenza vaccination rates, we found that our mailed reminder to high risk people less than 65 and persons 65 and older in November was -- actually in October, late October, was successful and a number of people came in. We then attempted to follow the recommendations and realized we had enough vaccine to vaccinate more and sent another reminder out, to people 50 to 64 who were healthy, in December. There was almost no response to that second. And I think people were into the holiday season. There's a lot of other mail, a lot of other activities, and we had almost no response to that second.

Now you could -- it's the same basic letter, so there wasn't a difference in the letter. I think it was a difference primarily in timing, and so that's our experience.

DR. MODLIN: Ben Schwartz?

DR. SCHWARTZ: I'd like to present an alternative perspective to what some of the members of the Committee and others have just offered in the past few comments. And I think there are several pieces of data that are important for us to consider in making a recommendation. One of those pieces of data is that in each of the past two years where we've had these significant delays and have made recommendations for phased vaccination, the outcome has been that there have been millions of doses of vaccine that have gone unused. And some of the preliminary data that have been analyzed have suggested that the numbers of elderly people who had been vaccinated also had decreased.

The second piece of data that I think is important is data that have been analyzed from the National Health interview survey by Maria Rangel in

our adult branch. She looked at data on individuals with cardiovascular and cerebrovascular disease and focused specifically on looking at Hispanic and African-American populations and found that within those groups there were significant health system barriers to vaccination, including difficulty getting appointments with health care providers and not having regular health care providers. So that for minority populations, there may be increased emphasis needed on being vaccinated in community settings rather than in health care settings. Therefore, recommendations that propose delaying vaccination in community settings I think might disproportionately affect the minority community.

Given those data, I think it would be reasonable to support option three, which would suggest that in community settings where substantial numbers of high risk people indeed are vaccinated, that if there was no shortage of vaccine that those campaigns could occur in October and that we would encourage those campaigns to

focus on high risk people and we would encourage those campaigns to be implemented in areas where a substantial number of minorities may be vaccinated.

I think it certainly is reasonable to delay workplace campaigns where perhaps about maybe 15 percent of vaccine doses are used -- to delay those campaigns until November, in part because the people who are vaccinated in work places tend not to be the highest risk individuals, and secondly because those campaigns are planned way in advance and can easily be scheduled in November as other times. But I would be concerned that by implementing the phased system for every year that we're going to have problems using all the vaccine available, and we'll have problems vaccinating high risk minority populations who depend on community settings, perhaps more than the white population.

DR. MODLIN: Bonnie?

DR. WORD: I guess I just have two comments. One, when you were looking at the racial disparities, racial and ethnic disparities of vaccine, when you look at that -- I guess -- I

think you referred to it as BRETHAS (phonetically) data, it's the behavioral risk assessment, and when you look at the number one reason that they actually cited was that they didn't know that they needed it. So a lot of it is more -- goes back to public education on what they need. When they broke it down by socioeconomic status that -- it was -- there was no difference between the racial groups based on that. It went back again to the lack of education. And I know the National Medical Association, one of the things they've been targeting has been to try to push educating families. They have this campaign called "Immunization, a Family Affair" to try to get more people involved. I don't know if that's going to really harm people.

DR. SCHWARTZ: The analysis -- I don't know if Maria is here right now, but the analysis incorporated a multi-variant model that looked at a number of risk factors and then included health system factors like having a primary care physician, like difficulty making appointments, and

the data were stratified by African-American and Hispanic groups, and those health system factors were independently significant risk factors in the analysis. Certainly education is an important thing, as well. But I think that the availability of health care and the availability of regular health care providers does differ between communities. And if we say high risk people can go get vaccinated at their physician's in October but we have to delay community campaigns until later, I think there will be a disproportionate impact on different populations.

DR. WORD: I guess, not to debate forever, I don't think it's going to -- because when you look back at that data when they actual -- well, I don't know exact -- I know the most recent one that I had seen. When you looked at individuals by -- you looked at them by race. If you said when's the last time you've had a contact with a physician, even -- you can have more physician encounters, and it still made no difference. So I think it's not so much the encounters, knowing that you need it.

And I guess the other thing, too -- I'll go off that, so I guess I'm still pushing for number two. I don't -- I'm not sure how number two's going to really affect the disparity 'cause that's persisted all these years. It's only reached the healthy people goal 2000 in one segment of the population. But when you talk about -- However, when you talk about health care workers, I think I would agree with Jane and a couple of the others that they still should be in the first wave because these are people who are in contact with all your high risk individuals. So if nothing else, they're going to -- they'll be infected, they'll be exposed and then subsequently transmit to other people.

DR. MODLIN: Phil Hosbach.

MR. HOSBACK: Phil Hosbach, Aventis Pasteur. Just a couple of comments and one kind of clarification for Dr. Schwartz. Over the past -- as far as -- as long as I've been involved in influenza immunization programs with Aventis Pasteur, we've seen return of vaccine at a similar rate, so whether there's been a delay or whether we

had a return policy in place, so I don't know what the impact really was on those delays with the return. Certainly on the special CDC contract that we engaged in a couple of season ago, that was an issue. But we have had vaccine returned at similar rates for a large number of years.

In terms of our position on these options, I just want to point out that we have a saying at Aventis, when you've seen one influenza season, you've seen one influenza season. And essentially, there are certain variables that you can't control, certainly how you produce the vaccine and how viable the virus is going to be in eggs. Also it's difficult to determine when and how often the virus is going to circulate during the course of a season. But you can get your arms around things like distribution, which we're trying to do and we started essentially a little bit of a new paradigm in distribution. The other thing is you can also get your arms around recommendations, and I would vote for consistency and option two kind of gets you there. There could be

modifications. You may not need to have hard and fast tiers, but I think you've sent a clear message for the past two years, and to change and have to shift based upon things that will occur naturally in every influenza season or we might have a bad year in production, it's better to be consistent not to change course during the course of a year.

DR. SMITH: John?

DR. MODLIN: Carolyn, could I ask a question, and that is that a couple of meetings ago Keiji presented some data to us regarding -- historical data going back over time, looking at a number of influenza seasons and when the flu season peaks, and whether or not that's going to affect --

DR. BRIDGES: It's Table 2 in the back.

DR. MODLIN: If we had a very early influenza season, what would the effect of option two be as opposed to --

DR. BRIDGES: In the last 25 years -- why don't I look at the -- it's Table 2 in your draft, but 16 percent of the years the peak season occurred in December, and in those years the peak

is generally towards the very end of December. And correct me if I'm wrong, but this is the updated table for 25 years. The month most likely to be peak influenza month is February.

DR. SMITH: John --

DR. MODLIN: Yes?

DR. SMITH: -- I polled a number of states at our recent immunization managers meeting and the sense was that this whole phase paradigm, the sense was they don't necessarily like it and wish it could go back to the way it was several years ago, but that given production realities that were -- you need some sort of sense of prioritization and we need to continue that. Whether it's the rigid categories like this, I'm unsure about, but certainly it leaves some sense of the phase process.

DR. MODLIN: We need to draw this to a close fairly soon, but let's have a couple more comments. Walt?

DR. ORENSTEIN: The real issue to me in option two is not so much I think the physicians' offices

where I think it probably is more readily implementable, but in the community campaigns. I was just looking at some data from the -- I forget what year, a recent year -- 1999 behavioral risk factors, said something about a third of even the high risk do not get their vaccinations in a physician's office. And the issue to me, and I guess -- is the practicality of either focusing all clinics in November or are we going to lose ground with people not holding -- essentially we're talking about having two kinds of -- two community clinics, one with high risk and one not, and is there going to be confusion or are we going to lose ground if we adopt that as the standard now. Whereas if we -- option three at least says our ideal is to have and make it available October through November and clearly work sites, there's absolutely no reason why work sites have to take place earlier than that, at least would get a percentage of the vaccines. I'm looking at here, it's -- I don't have the totals there. It's by age group and the younger age groups, workplace

accounts for 20 percent or more of the -- 20 to 33 percent of the vaccinations in the younger age groups.

DR. MODLIN: Okay. I'm sensing a consensus, at least among the voting members of the Committee, for option two. Is there anyone who feels strongly that we shouldn't go for option two?

UNIDENTIFIED SPEAKER: Option two or three?

DR. MODLIN: Well --

DR. BROOKS: Could we see option three up on the screen again?

DR. BRIDGES: Option two is the tiered and option three is the only group that would be moved to November or recommended for November would be work site vaccination programs.

DR. MODLIN: Myron?

DR. LEVIN: One question. I'm hearing or I heard that there are some disadvantages to option two that Aventis spoke to. There of course advantages when there is a problem with the vaccine supply. How likely are we to know about vaccine problems before the end of the summer, and could

you have a situation where you said -- where you had two possibilities? If the vaccine supply is adequate, you do one thing; if it's inadequate, then you go to the tiered system.

DR. MODLIN: I think we've heard from Mr. O'Mara and others over the last couple of years. We really don't know until we get well into vaccination season. That's certainly been our experience the last couple of years.

DR. LEVIN: Well, even not knowing, if you had it written in as either/or, by the time you get around to vaccinating, you would know which you have to choose.

DR. BIRKHEAD: I think we need to take into account the advance planning that's needed for this, though, and if you have to wait until September to decide whether you're going in October or November, it's too late. You really need to be making those plans even before the summer, so I think it's better to have a clear recommendation.

DR. MODLIN: Kristin?

DR. NICHOL: Just a couple of quick comments.

I would agree with getting the word out sooner rather than later if there is going to be some kind of tiered or stepped approach, either option two or three. I would wonder whether or not the tiered approach which we adhered to very stringently in Minnesota last year actually makes more vaccine available for high risk people in October. It was our experience that vaccine did not travel between providers, and so what ended up happening is the agents just sat on vaccine for work sites until November, but they actually had it in October. Finally we just looked at 90,000 people who came into Cub Food Stores in Minnesota. In October 68 percent of them were in a high risk group.

DR. MODLIN: Dr. Neumann?

DR. NEUMANN: Thank you. For 15 years now the National Coalition for Adult Immunization has sponsored National Adult Immunization Awareness Week in October. We would argue that we would like to see a consistent recommendation from this Committee. The suggestion that we have either/or capability -- if this happens in September, then we

do this -- becomes much too complex. Many of our constituents organize their community immunization programs around flu and pneumococcal immunization in October around the Week. We certainly have no trouble pushing that back into November or sometime, but as Dr. Schaffner said earlier, a consistent plan that our constituents are comfortable with is the thing that probably works best for everyone.

DR. MODLIN: Deb, last comment.

DR. WEXLER: Deborah Wexler, Immunization Action Coalition. I really like option number two because I think it helps us through these shortage periods and delay periods, but I'd only like to say that I think -- over the years it seems like flu vaccines administration season ends at the end of December, and I think it's from -- you know, a lot of messages that have come out over the past 20 years that you stop vaccinating at the end of December, so I'd just like to suggest that as you -- in this section on option 2 under vaccination in December and later, that two little changes be

made. And one is, instead of saying after November in the first sentence, say while October and November are optimal -- are the optimal time to vaccinate. And then later on you can just say many people should still be receiving vaccine.

But what I'd like to add is in the next sentence, to improve vaccine coverage and utilization, particularly among high risk persons and health care workers, influenza vaccine should be continued to be offered in December through March. You know, get -- people want to know when they -- they call us and they want to know when do I stop giving flu vaccine? And I don't think there's really good guidance in here. I think it could be clearer, in December through March, as long as vaccine supplies are available, while influenza activity is still documented in the community. I just think we need a little stronger message about how long you can keep vaccinating if you haven't gotten vaccinated yet.

DR. MODLIN: I think that's very reasonable. I'm sort of debating whether or not to make -- how

formal to make this. I think the best thing to do is just ask the voting members of the Committee, which of you prefer option two? Let's see a show of hands.

(Indicating)

DR. MODLIN: Which prefer option three?

(Indicating)

DR. MODLIN: It looks like option two is the clear strong consensus.

DR. BIRKHEAD: Were we clear on adding health care workers to that?

DR. MODLIN: Yes. Yes, I think --

DR. SNIDER: John --

DR. MODLIN: Would you like -- I'm sorry, Dixie, did you have --

DR. SNIDER: It wasn't necessarily a formal vote, but if you would just call out the names so that --

DR. MODLIN: Okay. Those who preferred option two would be Dr. Smith, Dr. Tompkins, Ms. Salamone, Dr. Deseda, Dr. Brooks, Dr. Offit, Dr. Levin, Dr. Birkhead and Dr. Word and Dr. Modlin.

Those who preferred option three was Dr. Zimmerman and I'm going to suggest that Dr. Rennels abstained.

All right. Carolyn, what's --

DR. BRIDGES: Those are it for the major changes. I don't know if we need a vote to approve the entire document as what the amendment suggested or if there are other --

DR. MODLIN: I think we should. I'll entertain a motion that we adopt the influenza statement with the suggested options and changes.

DR. ZIMMERMAN: (Indicating)

DR. MODLIN: So moved by Dr. Zimmerman.

DR. WORD: Second.

DR. MODLIN: Seconded by Dr. Word. Those in favor of the motion? Okay, those in favor, Dr. Smith, Dr. Zimmerman, Dr. Tompkins, Mr. Salamone, Dr. Deseda, Dr. Brooks, Dr. Offit, Dr. Levin, Dr. Birkhead, Dr. Word and Dr. Modlin.

Those opposed? Those abstaining? Dr. Rennels. Thank you.

Do we have anything else, Carolyn, on

influenza? Dr. Myers?

DR. MYERS: I couldn't raise my hand fast enough --

DR. MODLIN: Okay.

DR. MYERS: -- so this may be irrelevant because you already voted, but like on the yellow fever, this doesn't have a recommended surveillance research section and I thought I heard a lot of discussion about it needing to have such a section.

DR. MODLIN: And it would be an issue of what goes into that section. Maybe that's something for the working group I think maybe to focus on. And again, maybe if we can't get it into this year's recommendation, to bring it back in June and say these are the specific issues that we should be adding.

Yes -- Foster?

DR. FOSTER: I wonder if I can get one more comment, too. On the table that talks about the vaccine doses, for the last two years we've recommended for the United States to use whole vaccine, and yet we put an asterisk that says it's

not available. Why is that continued in that particular table?

DR. BRIDGES: This document is used by -- or used as a reference by many countries, and so that was kept in there for countries that my also have available whole cell vaccine so that they know not to use -- with the recommendation, at least in the US, is not to use whole cell in young children.

DR. FOSTER: But yet the table top says recommendations for the United States.

DR. MODLIN: Melinda?

DR. WHARTON: Carolyn, maybe that's a nuance that could be dealt with in a footnote.

DR. BRIDGES: Okay.

DR. MODLIN: Good suggestion. Mr. Reilly?

MR. REILLY: Could I ask clarification on the moving forward on the influenza discussion? My understanding is we will have a discussion in June that will include specific recommendations for the 2003 season?

DR. MODLIN: We'll be moving in that direction, yes. What we're voting on in 2002

recommendations right now, we have a -- and what we carry on in June will be forward-looking beyond, yes.

MR. REILLY: I think that will be a -- just a point from -- that will be a big help in planning any increase in volumes, and the longer notice is really important to --

DR. MODLIN: Carolyn, Bonnie, Keiji, everyone else, thank you very much -- Lynn Brammer. A marathon session, but let's move on.

The next item on the agenda will be a discussion and hopefully a vote on the adult harmonized immunization schedule. Dr. Sneller is going to lead us through this discussion.

I think for this discussion it would be very helpful if everyone does have a copy of the proposed adult immunization schedule. They have been mailed out to members of the Committee and to liaisons and ex officio -- Pardon? It's also in the binder, but I'm addressing my remarks mostly to everyone else in the audience.

DR. SNELLER: A little note on all the updates

that we've had with the adult immunization schedule, we've been revising this even as of yesterday, and so some of you probably have the older versions. If you would just sort of pencil in the changes as we go along and I'll highlight the changes that were made yesterday.

DR. NEUZIL: Vishnu, it may be good to tell everybody which date at the top is the most recent version.

DR. SNELLER: The most recent version is yesterday, February 19th, 2002. I think all the members have the most recent version, but there may be handouts that were older.

This work on the adult immunization schedule, which is the tabular form that you see now, it was actually put together during the past -- since June -- since before June by a subgroup of the adult immunization work group of the ACIP and the members are Dr. Schaffner, Dr. Neuzil, Dr. Clover, Dr. Gall and at CDC it's Ben Schwartz and I have been working on this.

On behalf of the adult immunization schedule

work group, I thank this Committee for the opportunity to present an age-based vaccination schedule for persons 18 years and older. In addition to this age-based schedule, we in the group also included a schedule for persons with special conditions or chronic diseases. The ACIP members who worked on the adult immunization schedule and their liaisons are, for the American College of Physicians, Dr. Kathy Neuzil; for the Infectious Disease Society of America -- I'm sorry, it was American Hospital Association before -- Dr. Bill Schaffner; for the American Association of Family Physicians, Dr. Rick Clover; for the American College of Obstetricians and Gynecologists, Dr. Stanley Gall; and at CDC, Dr. Ben Schwartz and I.

We started the process of summarizing the schedule in June and brought the ACIP's permission to proceed. At that time we presented the areas of agreement and disagreements in the immunization recommendations distributed by the ACOG, the AAFP and the ACP to their members, and we highlighted

our approaches towards developing a concise tabular summary that would be easy to use by the medical specialties caring for the adults.

The ACIP approved continuation of this project, and then we presented a progress report in October, 2001. At that time we presented a draft -- a prototype of the printed schedule and we received comments and suggestions on the format, the color scheme and the revisions to the content of the table and the footnotes. The printed adult immunization schedule that is a letter-sized, bi-fold brochure with an age-based schedule and the disease/condition-based schedule on facing pages, if you'll see that, and the format is very, very similar to that that was used for the childhood immunization schedule.

The additional notes for the age-based schedule are printed on the back cover of this brochure, and they're referenced by numbers which are associated with each vaccine schedule. The footnotes for the disease or the condition-based schedule highlight additional information that was

specific for the condition and the vaccine.

The Committee accepted this format and provided revisions and suggestions. The version that is submitted to you for acceptance today is very, very similar to that that was presented in October. Some of the content has been changed to go with the comments and suggestions that were received since October and as early as this morning.

There are some suggestions that were incorporated and these are the changes. One, the cover indicates that the schedule is a summary of the recommendations of the ACIP. Could you just have the transparency on, please? This was changed since this morning, so even the members didn't have this cover. It was suggested that nowhere on this is it indicated this was a summary of the ACIP recommendations that had already been printed, and so this would look this way instead of just the recommendations before, and they would be that the affiliation of the Health and Human -- the Department. And inside the titles of the schedules

-- the titles of the schedules are changed to be consistent -- sorry, can I go back? Just shift back? Okay, thank you.

The titles of the schedules are changed to be consistent and include the word adult, without indicating the age range. The schedule, as it is, was accepted by ACOG. AAFP is reviewing the document, and we will hear from the members who have been in communication with the specialty groups later on. You will notice then that the sentence below which says that it is accepted by the ACIP also says it's accepted by ACOG and nobody else.

In the schedule for the immunization for the adults with chronic disease and conditions, there's one change made. There's an adult -- there's an additional footnote, J, which goes with the recommendations for the MMR for HIV-infected persons. The ACIP has recommended that MMR be administered to all asymptomatic HIV-infected persons and that MMR be considered for administration to all symptomatic HIV-infected

persons who would otherwise be eligible for measles vaccine, even though the immune response may be attenuated in such persons. Because there may be a diminished antibody response to measles vaccination among severely immunocompromised persons, ACIP considers it prudent to withhold MMR or other measles-containing vaccines from HIV-infected persons with evidence of severe immunosuppression.

This definition of severely immunocompromised is from the CDC 1993 revised classification system for HIV infection, which indicates that persons who have less than 200 CD4 T-lymphocytes or a CD4 plus T-lymphocytes percent of total lymphocytes less than 14, or who have been diagnosed with tuberculosis or invasive cervical cancer or recurrent pneumonia. Therefore the additional note says withhold for persons with extreme immunosuppression, and I've given the references of the MMWR where this note has appeared. I did not include -- it is prudent to withhold, although our group is equally divided on whether to use the word prudent to withhold or just withhold, and I leave

it for the Committee to decide.

We also proposed that the schedule in the adult immunization recommendations be reviewed annually and revised if necessary. We don't expect that the schedule will change each year, but we will consider other issues that might affect adult immunizations.

We called ourselves the harmonized adult immunization schedule group, and we hope to have a harmonization of the schedule soon. We will continue to work with the medical societies towards harmonizing the ACIP recommendations for immunizing adults with recommendations of their own. We propose to present the outcome of our discussions regarding revision and/or updating of the adult immunization schedule or recommendations during the October meetings of the ACIP and published in the MMWR by December of each year or by January.

In our next steps, assuming that the ACIP votes to accept the adult immunization schedule with or without further modifications, our group will prepare a report for publication in the MMWR

and we will then present a draft of the document to the ACIP during the October, 2002 meetings for comment and revision.

We'll now hear from the members of the group who served as liaisons for their member societies. And Dr. Clover, would you like to go first?

DR. CLOVER: Sure. I presented this document to our commission in January, and they are taking this under review. I haven't heard specifically back from them yet, but there was general positive responses from this document, and we're just reviewing line item by line item to make sure it doesn't go against any of our other policies.

The one that I know was raised was the meningococcal recommendations since the AFP has not supported that in the past, but that's the only one that I'm aware of at this moment.

DR. SNELLER: Dr. Gall?

DR. GALL: This has been presented to the -- to ACOG and we endorse this enthusiastically. We look at this as a stepping stone to a continuation toward a age-based schedule rather than risk-based.

If you look at the back page with all the footnotes, you have tons and tons of risks that nobody knows about, doesn't remember and that the sooner we get to an age-based for adults, the better we are.

DR. MODLIN: I think this process has brought CDC and ACOG closer and that we'll be working towards improving vaccinations among obstetricians and gynecologists in the near future. Dr. Neuzil?

DR. NEUZIL: Yes, the American College of Physicians also reviewed this document, their scientific policy committee, and I think, similar to AAFP, they just didn't feel comfortable with the time that they had and the extent of their review. Where they express concerns is they express concerns with the evidence supporting the lyme and meningococcal recommendations, and they would like to see more supporting data on those recommendations, which has been sent to their office.

They were also concerned about some of what they called reality issues in terms of making

recommendations with significant supply or delay issues with vaccines such as influenza and tetanus vaccines. And so I will be involved in their next committee meeting in March and will continue to review this document.

DR. SNELLER: Dr. Schaffner, do you have any last comments before we place this schedule for the Committee to vote?

DR. SCHAFFNER: Vote yes.

DR. SNELLER: Well, then I'll put the schedule to you for a decision to vote and I'll be eager to take any comments or suggestions for modifications.

DR. MODLIN: Yes, Natalie?

DR. SMITH: I very much applaud all the work that's gone into this. I think this is very good way to go forward with adult immunization.

One question just in formatting, having worked a lot on the childhood schedule. You've got on the right, as we've done in childhood, the green hatch bars.

UNIDENTIFIED SPEAKER: We can't hear you.

DR. SMITH: You have on the -- is it working?

You have on the right the green hatch bars, catch-up vaccine, whereas on the left the green color is used a little bit differently. Like under -- flu obviously isn't a catch-up vaccine, and I think people -- especially those who see kids and adults -- may start associating that green hatch color with catch-up.

And then just like we're going to recommend for childhood, once -- as this starts getting used, that it be evaluated for how well folks out in the field are using it and working with it.

DR. MODLIN: So we need a second look at the format for -- we've got green hatched -- legends meaning two different things on the schedule.

DR. SNELLER: I think we addressed this last time and I don't really remember what it was and I -- the green hatches were used separately and I think in this particular version -- on the one that was submitted in October, the green is supposed to represent the vaccinations that should have been received at this time, even for people with these chronic conditions. That is to say, pregnant women

should have had their Td and the people with diabetes, heart disease should have had their Tds and so on, should be current with them, and the people with diabetes should have also had their MMR, but for pregnancy if they have not had their MMR that it should be withheld.

DR. SMITH: I think the issue was the schedule on the left is not necessarily catch-up for everything, like there's influenza yearly vaccine, which isn't a catch-up vaccine.

DR. MODLIN: I hate to get bogged down in wordsmithing here, but it does look like we need -- do need to pay attention to a little bit of an inconsistency there. I would agree with Natalie.

Other comments? Yes, Eric France?

DR. FRANCE: Just the comment that on the footnote on the first page, I notice ACIP, ACOG and AAFP, but not ACP, and is that on purpose?

DR. SNELLER: We should probably take out the American Academy of Family Physicians also until we have formal acceptance from them.

DR. MODLIN: We just heard the background from

that, Eric, so I think we're on the same page. Gus?

DR. BIRKHEAD: I also agree that this is a great, much-needed and a nice job. A couple of just practical suggestions. It would be good to have a version of it where the shading is such that you can Xerox it on black and white because that's commonly how things are --

DR. SNELLER: I think there is a black and white that's floating around, and it shows the patterns.

DR. BIRKHEAD: A second suggestion would be to add on the footnotes the actual citations for the statement from which it's -- that it's coming so people can look it up, and perhaps even include the ACIP web site address on this because people do now refer to that for copies of the documents.

And just a final comment, under footnote J on the right-hand side where you're talking about HIV, you mentioned a number of other conditions other than CD4 less than 200 for which you would withhold MMR, like pulmonary tuberculosis, and is it

possible to either include those there or somehow make it clear that CD4 less than 200 is not the only condition with HIV --

DR. SNELLER: Sorry, sir, the definition I was reading was for an AIDS-defining condition and the defined extreme immunosuppression in response to the AIDS, and I -- perhaps -- do you think --

DR. BIRKHEAD: Well, I'm just saying what you have here, CD4 less than a reading of 200, is not a complete listing of those conditions with HIV that you defer, so I --

DR. MODLIN: Gus, you're new to this process.

DR. BIRKHEAD: Sorry.

DR. MODLIN: And we struggle with the childhood harmonized immunization schedule each year, and some of the major issue we struggle over are, in addition to what it looks like, the footnotes. And the overall intent has been to try to keep these as concise as possible, to have them not all-inclusive, with the idea that there are -- it's appropriate to refer to individual recommendations and references where --

DR. BIRKHEAD: Perhaps then we could just say AIDS-defining condition rather than CD4 less than 200.

DR. MODLIN: All right. Rick?

DR. ZIMMERMAN: One of the things that concerns me as I think about harmonization, one of the things that I'm concerned about as I think about harmonization is the potential that there are different recommendations from these different organizations. And with the childhood schedule, in various years we have had differences where AAFP. ACIP and AAP had different policies. And the way we finessed that was by dealing with footnotes that would explain the differences in policy. And I'm afraid -- my guess is that we would have a hard time getting all four organizations to agree on exactly the same policies 'cause I think meningococcal and tetanus are both going to be problematic for different reasons in different organizations. And so I would suggest that some latitude be given to negotiate footnotes that would differ by organization so that we can have harmony

and not only have potentially -- you know, just two organizations endorse it, but have all four, and allow there to be differences. I don't think the differences are going to be reconcilable in a couple of points.

DR. MODLIN: Jane Seward?

DR. SEWARD: I was just going to suggest for an addition to footnote 8 to use the same last two sentences in the MMR, do not vaccinate pregnant women or those planning to become pregnant in the next four weeks, and if pregnant and susceptible, vaccinate as early in the postpartum period as possible. I was going to suggest adding that for varicella vaccine, as well.

DR. SNELLER: Thank you, Jane.

DR. MODLIN: Other comments or questions? There -- you, as I recall, raised an issue regarding a single word, "prudent", for the footnote J, and the basis for that again was that the ACIP recommendation suggests that it may be prudent to withhold MMR from patients with HIV infection with fewer than 200 cells. Is that

correct?

DR. SNELLER: That is correct.

DR. MODLIN: And that the consensus of the group was to drop the word "prudent" -- I guess we'd better address this issue. Kathy?

DR. NEUZIL: If I might make a comment, I'm hoping perhaps I have a compromise here because I'm one of the ones that didn't like the way it's worded now, and this will take into consideration what Dr. Birkhead brought up. I would just take out the CD4 count less than or equal to 200. And then it says withhold MMR, and people are making their decision. It's a physician decision what severe immunosuppression is, and then I'd feel better about that. Because in the age of heart, we do have people with CD4 counts less than 200 who we do believe are not severely immunosuppressed. That may solve the problem.

DR. MODLIN: I'm not sure that's the case. Myron, do you want to address --

DR. LEVIN: Well, I'm not sure that we know that if we immunize them it'll make any difference,

and so I'd agree with leaving it as people with severe immunosuppression. I thought one way of handling it is to change the i.e. to e.g., actually, so it's just an example, a low CD4 count, but --

DR. MODLIN: That's a good --

DR. LEVIN: -- I thought severe immunosuppression pretty much covers it. It leaves it to the physician and our opinions actually don't matter.

DR. MODLIN: Thank you.

DR. LEVIN: I have one other question --

DR. MODLIN: Myron?

DR. LEVIN: -- that had to do with number four. The way I read that, if somebody were age 65 or 66 when they first got their pneumococcal vaccine, they would not get a second booster any time else in their life. Is that what you're trying to say?

DR. SNELLER: For the pneumococcal vaccine?

DR. LEVIN: Yes. You never get a booster if you got your primary immunization after age 65.

DR. SNELLER: That's what the recommendation says, and the -- because it's a revaccination.

DR. MODLIN: I think that is the case, Myron.

DR. LEVIN: Well, why is that? Does it not help to revaccinate an older person?

DR. MODLIN: I'm not certain we have the data. Bill, do you want to address that? You may be the most appropriate person to raise that. We have discussed this before.

DR. SCHAFFNER: First of all, this is not a time nor place to make new recommendations. And number four is consistent with the current recommendations. And the reason the current recommendations do not recommend revaccination routinely is there's no proven benefit, either immunologically or in terms of efficacy.

DR. MODLIN: Okay. We -- the ACIP is being asked to put our stamp of approval on this document now. Are people comfortable doing that with the changes that have been suggested? Do I see a -- some general nodding. Fortunately, no one is conflicted here. Can I entertain a motion that the

ACIP adopt the --

DR. BIRKHEAD: So moved.

DR. MODLIN: So moved by Dr. Birkhead.

DR. SMITH: Seconded.

DR. MODLIN: Seconded by Dr. Smith. Any further discussion? If not, those in favor of the motion? Those in favor of the motion are Drs. Smith, Zimmerman, Tompkins, Mr. Salamone, Dr. Rennels, Dr. Deseda, Dr. Brooks, Dr. Offit, Dr. Levin, Dr. Birkhead, Dr. Word and Dr. Modlin.

DR. SNELLER: Thank you.

DR. MODLIN: Thank you. The next steps will be that we will get an update on this I assume after we hear back from the other partners in the process, is that not the case? Yeah, Bonnie?

DR. WORD: I'm sorry, will this just be published every January then?

DR. MODLIN: I think the intent, as we heard earlier, was to have this published on very much a similar cycle to that of the childhood immunization schedule.

Let's move on, speaking of the childhood

immunization schedule. The next item on the agenda will be an update on -- in essence, what the process is, and Melinda's going to take us through that very quickly.

DR. WHARTON: Well, actually I'm going to introduce Dr. Cortese and Dr. Smith, who are going to take us through it quickly. Margaret is going to provide us a brief overview of what ended up happening with the 2002 schedule, and then Natalie will provide an overview of how we hope to do things better this year.

DR. CORTESE: Thank you. I'm just going to spend a minute or so on the published schedule for 2002, simply to show you how the schedule appears in a few different sources, and most of you are aware of these. This is the look of the schedule on the NIP web site, and it is now also available in a two-page landscape format. This is very similar and how the schedule appeared in the publication American Family Physician in January of this year. And in the publication Pediatrics in January of this year. And finally in the MMWR on

January 18th of this year. And you can see in comparing the NIP web site version with the MMWR version that the format of the footnotes, the style of the footnotes, is somewhat different in that in the MMWR the footnotes extend across the page, whereas in the other -- NIP web site, they're in two columns. And symbols were used in the MMWR instead of numbers, as are on the web site version. So this will be one issue that will be discussed for the upcoming schedule on the use of a single format, at least through NIP and the MMWR.

Last year part of these schedules, format and footnote, was revised by -- was revised outside of the working group after the original schedule had been approved by the ACIP at the fall meeting. This resulted in the AAFP having a very limited time in which to approve the schedule before certain publication deadlines. So in part to avoid this from recurring, the working group has revised a time line for the preparation of the schedule for 2003 and Natalie Smith will review that briefly with you, as I put up the overhead.

DR. SMITH: We had a conference call just last week of the childhood schedule working group, including the Academy of Pediatrics and Academy of Family Physicians, and we all agreed to this time line, which was that at this meeting we established in February the working group. We continued to have conference calls, and then by the June meeting we really have pretty much our schedule for the following year, and we will provisionally approve the schedule. Of course we all understand that there are always issues that may come up such as surround vaccine safety or some other issues, and we certainly, if it's very urgent, can make changes. But we would like to get most of the work done by June. And then, as it says, in July and September, schedule modified only if necessary. And the Academies both felt that this time line was workable with their systems, and then of course the idea is, as we have been doing, to publish in early January every year. So we'd like to avoid some last-minute difficulties like we had this past year.

DR. MODLIN: Terrific. Any comments from Gary or Jon or the AAFP?

DR. SMITH: I just had a couple other -- Some of you had heard that we'd been working on a catch-up schedule for the flip side, which would cover kids that start late or get behind, and we would still like to continue to work on that so that it's actually eventually a two-sided schedule. We also -- and Academy of Family Physicians recommends that we formally evaluate this tool, essentially, and see how well with the new format it's being understood out in the field.

DR. MODLIN: Thanks, Natalie. This obviously is an effort to avoid -- so the crunch that we typically have in October over the harmonized childhood schedule and we think this is a time line that will hopefully prevent that from happening and undertake the process in a little bit more of an orderly manner.

Are there any comments or questions? Any further issues regarding the harmonized schedule? Yes, Geoff?

DR. EVANS: Just a reminder. I think that if it's possible -- I know the font's small enough that it's going to be a negative number pretty soon, but we have an immunization program that does have a safety side to it, and certain requirements under law, and if there's some way that we can at least put in the availability of the compensation program, and just as importantly, the fact that VAERS is a system that's functioning and needs to be remembered in case any kinds of adverse events do occur. I think it's important that be attached to the schedule as soon as it can be.

DR. MODLIN: Other comments? If not, we'll take our break that's scheduled and we'll start up again at 3:45.

(Whereupon, a recess was taken from 3:15 to 3:45 p.m.)

DR. MODLIN: Can I ask everyone to please return to their seats so we can finish up for today.

The next item on the agenda will be an update on CDC preparedness activities around smallpox and

vaccinia vaccine, and the purpose today is to largely present some information and have a brief discussion, and that'll be led by Hal Margolis. Hal?

DR. MARGOLIS: Thank you. Obviously a lot of things changed after September 11th, including some of us are doing other things now within CDC. What I'd like to do is give -- kind of take you through CDC's interim smallpox response plan and guidelines which were released the end of November. In fact, this is a plan that has been around since the kind of early seventies at the time it was becoming evident that smallpox was going to be eradicated. And the view there was, should a naturally-occurring case reappear, what would we do? The plan has clearly gotten much larger with age and also now in terms of trying to put it into today's context.

Our view is that at this point this is a working document. That's why it's called interim. At some point we will have to come to at least closure at some point in time. It really

identifies Federal, state and local public health activities necessary to respond effectively, and I highlight this to a confirmed case of smallpox, as you see as I go through some of this and at least I think some of the current thinking, it's extremely important that we're dealing with a confirmed case because at this point in time a confirmed case of smallpox would be considered a bioterroristic event. I think we also, at least from public health and international public health perspective, have not seen any change in known risk of smallpox being out and about, in terms of its use for terrorism. But again, with anthrax and all the things that have happened, there's clearly been a dramatic change in preparedness levels.

The plan basically gives the CDC Director, in consultation with the Department, the opportunity to implement all or any portion of the plan. What it goes through is provides guidance in a number of different subparts -- provides for surveillance in laboratory activities to identify or rule out smallpox, works through notification procedures for

suspected cases, talks about control strategies including how one would get vaccine out, case and case contact identification, patient care and isolation and quarantine.

Now a number of these are clearly in -- at a framework. Some of these have not been fully developed and I'll go into some of those issues and where we see -- what we see happening with this over the next year. There are, again, very specific guides and ultimately the goal is to have something in hand so that should an event occur, one doesn't have to begin to create the things needed and the framework needed to do any number of these activities which are shown here. And some of the new things that are there include information about communication. I mean I think we all recognize in this Committee -- we all recognize is the issues of health communication and risk communication in terms of -- both for providers and the public. And again, as we're all aware, should there be smallpox, essentially almost the mass panic that might occur is something that has to be

dealt with on the front end. For those of you who are -- you should have copy of my slides sitting out in front of you.

Again, some of the annexes specifically addressed -- clinical presentation of smallpox with pictures, development of care plans for patients, what to do in a vaccination clinic, how to set up a clinic, adverse event reporting and some of the pre-event planning activities that state and local health departments are going through right now in terms of general public emergency preparedness and bioterrorism preparedness.

So how do we view some of the revision issues? We clearly want written comments from professional organizations, NGOs and the public, and at this point we actually don't have that framework together. That's something that's yet to come. Our goal is to get this out. We said we wanted comments. We haven't quite put the framework together, but it's coming.

One of the things that we are going to do to help build that framework at CDC is actually take

these various guides and annexes and deal with them either through advisory committees such as yourselves, you know, dealing with the immunization issues, or one with isolation with HICPAC and others, or actually have, as we do at CDC, consultants meetings where we bring in a number of, again, professional organizations and others to give us best advice. And then ultimately it becomes -- CDC puts this together with all the various input. There'll be a revision, and then somewhere down the line obviously there'll be review and periodic revisions and, quite honestly, how that will be and how that'll be dealt with I think we really haven't figured out yet.

Now let me talk about I think a couple pieces that are near and dear to this group, and one has to do with the diagnosis of smallpox. And again, what's happened since September 11th is suddenly everybody -- you know, I think we -- all of us in infectious disease, you saw even the most severe cases chickenpox are a little unusual, and smallpox hasn't been around for almost 30 years, or more

than 30 years in this country. And so that moved out of the back of your mind, but in fact, that's changed a bit. And so what this really focuses on is differential diagnosis of vesicular-pustular rash illness in order to provide a high level of specificity -- and I'll talk about that a little bit more. It clearly requires the wide availability of laboratory diagnostics for varicella, which is the most common look-alike for vesicular-pustular disease. The proposed algorithm does not identify early smallpox, that couple days where in fact someone might be infectious and can be transmitting in that macular-papular phase. And the problem right now is the diagnostics for those look-alike diseases are essentially non-existent and would be extremely difficult to get out. And also this whole diagnostic algorithm would need to be modified for an intentional release. And again, we're really dealing with what went on in the past with naturally-occurring smallpox. But should there be something as is called a weaponized approach where there's a release, you're going to

have exposed people and that's, again, part of some of the things that are really being thought about in terms of being put into the plan.

Now you have in your handouts in your book the full diagnostic algorithm. I just put this up here and I'm not going to go through it, but you should have the color poster -- at least it was told to me it was -- yes, I see people with it. It's got pictures and it's got all the differential diagnosis, and in fact, this is what -- this has been -- was developed with a number of the partner groups here, the AAP, IDSA and others, saying this is the most logical approach and if in fact you have a patient that winds up over in this both yellow or red area, this is where health departments want to hear about this. And clearly if you're moving to the red side where in fact you cannot rule in varicella for this vesicular-pustular disease, then currently diagnostics for variola really only reside at CDC. And that kind of comes to a bit of the diagnostic thing. I just put this cartoon up here to -- in fact, it's really

varicella diagnostics that we see needing to be available, not just at state health labs and at the large hospitals, but everywhere. And that's with direct FA. Clearly PCR's going to be in there as part of this, but having it there and having the right proficiency testing and having it widely available is going to be extremely important.

Question of where vaccinia diagnostics might occur again in places outside of CDC or those specialized hospitals or labs that are doing vaccinia-vectored vaccine work is honestly open for discussion right now. And depending on how many people comes around to the vaccination issue an dhow much vaccinia might in fact be circulating at various times in communities, this issue's going to have to be resolved and that's part of, again, one of those consultation and working groups. And I can tell you at this point, the Association of Public Health Lab Directors is engaged and involved in this. There's going to be a lot of discussion.

And then I put in this very small arrow variola diagnostics, which again, the bottom line

is you can't have a false positive in this diagnostic algorithm. And right now there are not well-qualified, real-time PCR tests that can speciate the orthopox viruses. That needs to be done, and then the question is where besides CDC should these reside and how do you then maintain quality control and proficiency testing for that. So there's still a lot of unknowns that go with the support of this.

All right, let me talk a little bit now about vaccination and control. Again, the plan really discusses it and is focused on the issue of what worked to eradicate smallpox worldwide, and that is -- as ring vaccination or, as some of us call it, is search and containment. It's finding cases -- it's providing a ring of immunity around each case with vaccination not only of contacts of the cases, but contacts of the contacts. And how wide in fact that outer ring gets becomes public health and operational judgment as one is in fact trying to control an outbreak. And again, for the smallpox veterans in the room who worked through this and

lived through it -- and I'm not a smallpox veteran; I came to CDC just as it was being eradicated -- there are judgment issues there and that in fact is part of the expansion.

But in fact, this was a strategy used to eradicate smallpox. It's the only thing that worked in the face of routine immunization, and you can go through a number of countries where smallpox was aggressively occurring and they were having routine vaccination and with vaccination rates in the 50 to 70 percent range. And until this strategy was employed -- and it's Stan Foster who has to really stand up here and show you the pictures of Bangladesh for four years with what became hundreds of thousands of cases -- but persisting with this in fact eradicated disease in that country. And that's -- you know, I think we know something about this disease. It also minimizes adverse events, and I'll talk about that a little bit more because this vaccine, as we know, has an adverse event profile that's acceptable in the face of disease, but not really probably

acceptable in the face of no disease. And then lastly, it deals with the most efficient use of vaccine supplies.

The ACIP, as you know, in June of 2001 put out a new recommendation that talked about smallpox vaccination in the face or in the context, actually, of possible bioterrorism event. These are the groups that were seen as priority, again, if there was a disease circulating, and that's the face to face contact with a smallpox patient. That's that six-foot -- you know, comes from best experience, not well-defined studies at that point. Persons exposed to intentional release, and that's one where, again, I think we -- be a lot of discussion about that. Household members of contacts of cases, and then the issue of persons who are involved in face to face evaluation, care or transportation. That's pretty clear in terms of a release event that may occur.

Again, you can pick up the newspaper and magazines at any time and everybody has an opinion about this disease. But this strategy will work

with multiple introductions. You just multiply the strategy. It will work with cases in multiple places. Again, that occurred during the eradication program. So that part shouldn't be anything that is foreign to this approach. Success obviously depends on amount of vaccine, personnel resources and readiness, and effective use of other outbreak control measures, which include isolation and quarantine, and also for the individuals caring for patients, personal protective equipment -- masks -- remember, this is large droplet spread virus in terms of transmission.

But this is the one that I'm bringing you to and that's the issue of should there be pre-event vaccination. And before I get to what was said in the previous ACIP statement, I put a cartoon together just trying to tell you -- because this comes up all the time -- what's our smallpox vaccine supply look like and what's the future of it in terms of resources that have been put in.

The current vaccine is Dryvax, which is licensed until -- until, and I use that word -- I

know it's not exactly correct, my colleagues in FDA will cringe a little bit, but in the middle of 2001 when in fact there were some irregularities with the diluent that was with it, and so actually the vaccine then moved into -- and that's that shaded area -- into an IND situation for the use of it. And there are 15 million doses of the currently undiluted Dryvax. As you all know and as has been described here, there've been evaluation of dilution studies and for that the data are not available. I put up just that if in fact the one to five dilution worked, there would then be 75 million doses. However, it's my understanding that this vaccine would always remain in an IND usage situation. It would not come back to being used again. The manufacturer's not looking for an indication coming back with the currently -- the new diluent that's with it.

Now there's new vaccine being produced by Acambis being called ACAM1000. Those contracts were let at the end of the fiscal year at the end of 2001. I may not have my arrows lining up quite

right, looks like they shifted a little bit. And that would start obviously with an IND and a comparative trial for non-inferiority. There's 54 million doses being produced in the first contract. This is cell-culture-derived vaccine whereas Dryvax was the calf lymph-produced vaccine, but same virus, no expected differences in terms of adverse event profiles.

And then there's a second production level being called ACAM2000. It's going to start somewhere later in this year in terms of production. This is Acambis and Baxter, and for that there's about 155 million doses. So that kind of gives you the picture. And somewhere out here there would presume to be licensure. These would be licensed vaccines once the large phase one, two, three trials occur. But in fact there would not be true efficacy because there is no disease.

Now I want to take you to the statement in June of 2001, which the ACIP said that (reading) because the risk of smallpox occurring as a result of deliberate release is considered low, and the

population at risk for such an exposure cannot be determined, the risks of vaccine complications outweigh the benefits for pre-attack vaccination.

And that's where we are today in terms of routine vaccination of the general population. And I put this table up here and this has been a compilation of data -- published data and some projections made by Mike Lane and it's my understanding this is going to be out soon -- Mike may be able to tell us. I can't remember where it is right now, but what it -- if we just focus on the issue of deaths, and what you get out here is -- realizing that most of the data in the younger population is extrapolatible to what we would see today, it's the older population where there are higher prevalences of immunodeficient, HIV positive individuals, and then the one that's always the bugaboo with this is the person who had eczema as a child, doesn't remember it, but still has whatever it is about their skin physiology that allows vaccinia to progress and essentially begin to disseminate. So these are some of the adverse

event profiles that get in this range as high as one percent and potentially -- I mean back in the late seventies with the surveillance data that Mike and others at CDC did, death rates were one per million vaccinated individuals and these -- the question marks are might these not be higher, given what we know about immunodeficiency in the population today.

So when you get to this issue which is now the issue of the group for which pre-attack vaccination was recommended by the ACIP, and that in fact were laboratory or medical personnel working with non-highly attenuated orthopox viruses. So it's really a very small group. It amounts to several hundred people a year.

And what we come to now is the question I'm going to pose is -- in the document from last June the ACIP indicated that if the potential for smallpox release increased, pre-attack vaccination might be indicated for selected groups who would have an identified higher risk for exposure because of contact with smallpox patients or infectious

materials.

And the questions are: Does our current increased preparedness preparation equate with increased potential for an attack? Should selected groups with an identified higher risk of exposure to smallpox patients or infectious materials be vaccinated? And if so, how should these groups be defined and identified in terms of guidelines, which are not in the June 2001 statement?

Thank you.

DR. MODLIN: Hal, do you want to add some information or data regarding the CDC employees who received -- approximately 106, as I recall, employees who have been -- and have received vaccinia, the circumstances under which they did and what was observed?

DR. MARGOLIS: In October/November of this last year, CDC, in developing preparedness, put together a series of smallpox response teams, the total number being -- to be 20, and on these teams were senior medical leader and senior public health

advisor, two epidemiologists, a laboratory technician expert, a health communications expert, an information technology expert and a community liaison expert. So that was the constituted teams and in fact smallpox training, smallpox 101, which I went to the first course. There were a lot of us there.

These teams, the first group of teams, which amount to about 120 people, were vaccinated. That has now stopped, and the reason that has stopped is that in fact -- this is my last question up there -- we really don't have a framework of guidelines for vaccinating.

Now what was the rationale? Well, the rationale was -- as I go back to that front end of the diagnostic part -- is that a case of smallpox, if it should occur, is going to be confirmed by a CDC team. That is the starting point for all of this. Now I realize that other people are going to see that person first, but that was the rationale and that's the reason that those people were vaccinated and that's where we are today.

DR. MODLIN: Is Chuck Helms still here or did Chuck have to leave? I guess Chuck has left, unfortunately. He would -- has been chairing the bioterrorism working group.

I think at this point Hal has posed a couple of questions to us and I think we have some time here for discussion, so let's open this up for questions and comments. Lucy?

DR. TOMPKINS: Hal, Lucy Tompkins. I had a question about containment in the ring analogy. When we were developing our own smallpox plan, how to deal with a smallpox outbreak at Stanford Medical Center, we essentially thought we would follow the WHO program and so we presumed that patients -- or people who were contacts but were not ill would be essentially confined to home. We would use home confinement and we used the word quarantine. And when we were describing this to our county executive, I used the word quarantine and he said impossible, it will be impossible to quarantine people. And so my question is, at what level is CDC working with the public health

departments and county health departments to define what containment really is going to look like? I mean obviously it's not something any of us as individual providers or medical centers can do for the community, and whether this is going to be legislated or there's going to be a big stadium or what are we going to do about containment?

DR. MARGOLIS: A major issue, and one that has -- I don't think there -- your experience I think is what's going on in many states. We actually had all of our state and territorial epidemiologists, immunization and bioterrorism leaders in in December to, again, kind of go through this smallpox 101 issue, and this comes up immediately. They're -- some states -- you know, clearly if this occurred, this would be one of those national disaster emergency things, and that kicks in a lot of issues -- who finally has control -- you know, those still aren't all worked out yet. But the point is that if there were smallpox, if there were cases, some type of quarantine -- and most every state has laws that allow some type of quarantine

and Natalie could probably talk about California specifically. There's also a -- some model legislation that was -- been published recently in terms of trying to deal with this. And again, where this is going -- I mean this is really fairly recently, so I think everybody's beginning to look at it. I guess that's where I am with it. And probably with cases, it'd probably be the easiest.

The more difficult one, in fact, might be the hoax, where somebody purports to either have released this virus and until you can figure that out -- and you may not be able to figure out -- what are you going to do? And those are the discussions that we're saying states need to have, we need to have together and come up with at least thinking about it. We don't know that we have answers for those, but most states would be able to truly quarantine. Natalie, you may want to --

DR. SMITH: Yes, just to add to that, we certainly have been having these discussions at the state level and county levels, and hopefully -- mostly we'd like to -- we focus on isolation, but

certainly people feel they already do have the power to quarantine, but also that the legislation -- the model language -- I'm sure that word, model, is not appropriate, but anyway, that also is going through our legislature right now and I think it is in other states, as well.

DR. MODLIN: Rick -- Did you want to follow up, Lucy, on that?

DR. TOMPKINS: No, I had an entirely different -- just for clarification.

DR. MODLIN: Go ahead.

DR. TOMPKINS: What is weaponized smallpox? Is that supposed to be aerosolized?

DR. MARGOLIS: Well, I used that word as being -- this is not naturally-occurring disease, so how somebody --

DR. TOMPKINS: Yeah, but how is it supposed to be delivered?

DR. MARGOLIS: Well, none of us know because, at least in the medical and public health community, there's no -- nobody knows that anything was ever done with it other than people grew this

in cell culture and worked with scabs, and so there's lots of speculation and at any one time you can pick up any --

DR. TOMPKINS: Don't the Russians know what they did?

DR. MARGOLIS: The Russians that most of us at CDC work with never did this, so I'll just put it that way and --

DR. TOMPKINS: So but we made all these millions -- they made all these millions of doses, but they don't -- they didn't know how they were going to deliver it?

DR. MARGOLIS: You know, if somebody else can stand up and talk about it, fine. I don't know anything about that and I work with the Russians a lot, just to be very honest about it.

DR. MODLIN: Rick?

DR. ZIMMERMAN: Back in the -- obviously the 1970's, jet travel and mobility was much less common, when the disease was still epidemic or -- not epidemic, but endemic in certain areas, and in those areas that it was at that point clearly were

third world countries with even perhaps less. What do we know about -- do we have any experience with more mobile populations or societies in terms of the effectiveness of ring containment?

DR. MARGOLIS: Well, again, I can tell you -- and actually I may pick on Walt, if Walt wants to -- can't hide totally from this. But again -- and Mike Lane's in the back of the room, too, but people traveled in India and traveled on very -- in very crowded settings and situations. And again, at the point you are -- you know, have pox, you're probably not going to get on an airplane anywhere. Yes, you might with a macular-papular rash, but you're probably going to have a temp of 104 and, again, all the experts -- most of these people are prostate (sic), so how much true dissemination would occur that way -- for those who dealt with it in other parts of the world, I actually don't think it's a major issue. Walt, is --

DR. ORENSTEIN: Probably Mike is the one to answer this, but certainly there was mobility. Maybe not jet travel, but there was a lot of train

travel, bus travel and a whole variety of things with very, very large populations in India, and many of them were fairly poorly immunized. I mean the last case of smallpox I saw was in a town called Aligar, India, which as I say, is the last place that Type II polio has ever been isolated, but it was a large city. This was in the main marketplace. We never found the source -- loads of people coming by all the time, and to this -- major market and we never saw any spread. So the spread has been variable. And I think there are other factors that suggest spread is more limited. If you look at most studies of secondary attack rates in families, the attack rates were substantially lower for smallpox than a disease like measles, let's say, or chickenpox. Now clearly anybody who's incubating can travel and go many places.

I think the other issue about contagiousness is that the patients -- as opposed to measles -- are -- who are very contagious during the prodromal phase -- is smallpox, they're not contagious during the prodromal -- the beginning at least of the

prodromal phase. It's only with onset of rash. Now they do get a little bit better, but they're usually not feeling chipper and walking around quite as much. So that there are a whole variety of factors that suggest this would be less contagious than some of the other diseases we deal with, even with a fully susceptible population. But Mike may be -- want to comment on --

DR. MODLIN: Mike, anything else? Neal and then Jon.

DR. HALSEY: Yeah, Hal, a small group at Johns Hopkins Hospital working under the auspices of the infection control has been struggling with what we would do if a case or cases were brought to us. And I suspect that the same process has been going through -- many, many other institutions have been doing the same thing. But the one thing that I think would help everybody is reaffirmation of the point that should there be a case or cases or whatever, CDC would very quickly provide the vaccine for post-exposure prophylaxis, which should be the primary strategy because of the high

reactogenicity. I mean there are many problems which are covered in the large document that you've referred to, but there's fear that people won't transport patients. There's fear that people won't collect or transport specimens or process them in laboratories, which are absolutely essential. And I -- you know, I have stated with certainty that CDC would mobilize within a day and get the vaccine to us. But it's not -- that's not evident that -- the statement isn't out there. If there was some way to get a simple statement that that would happen. I mean you have enough vaccine to do that for a limited amount of exposure, but that's my one suggestion is to make it very clear in something fairly simple that -- so that there will be some people who are willing to take the risk of transporting patients or caring for them. I think there are many, many other aspects to that, but that's the one thing that I think would help the most.

DR. MARGOLIS: Thank you. We agree and that's part of this whole communication of what in fact

would happen.

DR. MODLIN: Jon Abramson?

DR. ABRAMSON: Yeah, Hal, I think -- Jon Abramson. As part of this, one of the things I thought was missing but perhaps will be in a later version is who is going to take care of kids if the adults are sick or the whole family's sick? I mean there's nothing in there about -- even in a ring strategy, it's potentially possible that a whole group or a whole neighborhood will get infected, and then who's going to take care of them? That needs to be incorporated into the strategy.

DR. MARGOLIS: Yes. I mean these are some of the things actually -- when we did our training and actually did an exercise, these are the kinds of questions that came up. And again, I would say that we at CDC, working with the Academy and others to figure out -- at least have thought this out. We may not have the precise answers, but to realize that these are issues that are going to have to be dealt with.

DR. MODLIN: Steve Foster?

DR. FOSTER: Did you -- there was approximately you said 120 of you in this training program that got the vaccine. Was there anybody looking at take rates and adverse effects in that particular group?

DR. MARGOLIS: The take rates were 100 percent, and including even one person who had a -- was considered to have a -- you know, an inferior take, but revaccinated the same -- presumed to have immunity. Adverse events, there was some very aggressive primary takes that some people might have considered cellulitis, but in fact if you go back and look at the clinical literature, they were just aggressive primary takes. And that's one of the other things is that aren't many people around who have seen smallpox vaccination. It's again all part of the mix of what goes into delivering a vaccine that hasn't been around for 30 years.

DR. MODLIN: Sam and then Gus.

DR. KATZ: I wanted to comment on two things. One was Neal's statement, and only to remind us that in the post-epidemic era in the sixties in

Europe, when there were still introductions of smallpox, more than 50 percent of the cases occurred among health personnel or people working in clinics, emergency rooms or hospitals. So that when you think about primary groups for immunization, I think that's a high priority group, in my estimation.

The other was, Hal, I didn't understand what you said in answer to somebody's question about you didn't know about delivery or something. There's a gentleman named Kenneth Alabeck who talks all the time about this who was second in command of the Russian Biopreparat and has been in this country since 1992. Any meeting I've gone to in the last six months, he's been there to talk. I'm sure you guys must have talked with him.

DR. MARGOLIS: Well --

DR. KATZ: Yes or no?

DR. MARGOLIS: Yes, he makes a lot of statements. And I guess I would just put out things like -- and so how many tons -- as he says, they made tons of variola. How many tons of

varicella vaccine have ever been even made in this world, if you really do your back-of-the-envelope calculations? I guess the facts I could put out, as best I know them, is that all the virus work was done at Vector which is in Novosibirsk. You can talk to some of the Russians within CDC who knew him, worked around -- he was never at Novosibirsk. And so I think there's some questions about whether anthrax and smallpox kind of got paired together in some of these descriptions.

Now again, that's from those of us who were not there and who worked with others who are currently now working in those weapons labs, but yes, he makes some very strong statements.

DR. MODLIN: Yes, Gus?

DR. BIRKHEAD: Gus Birkhead. I'd just like to try and address the pre-vaccination issue a little bit if I could. In New York and in many places we're engaged heavily in planning -- disaster planning as a result of 9/11 and subsequent anthrax, and people have probably seen in the paper that there's significant dollars now flowing to

state and local health departments to do planning, preparation. There's also a pot of money to fund hospital preparedness that is coming out literally as we speak to states. In New York our discussions have focused partly on the issue of isolation of smallpox cases. We will need some place to care for these individuals, be they in an isolation setting in a hospital or some other location. And the idea of having a -- particularly in a place like New York City, having several locations identified with staff pre-identified, I think the concern I would have with the scenario of providing vaccine within a few days is if you actually have health care workers caring for patients who then may have been exposed will then have to rely on a -- not a 100 percent take vaccine. The concern that we've heard expressed over and over again from the large medical centers in New York City is staff will not come to work and care for patients. And so I think we keep coming back to this idea of even a small number of medical staff who are pre-positioned in predesignated facilities, funded to

be prepared to deal with smallpox, that in a situation like that you could justify on a volunteer basis pre-vaccinating a small group who could be the initial care givers. And then you can -- if you wait until a smallpox case is happening, it's going to be chaos. People are not going to be coming to work. Potentially that may be a worst-case scenario. Maybe -- you know, people rallied in the anthrax situation and they'll probably rally again, particularly health care workers. But I think -- everything we're doing is to plan, be pre-positioned, ready to go and to not have that last piece sort of on the table as a discussion point. I think it sort of grinds a lot of discussions to a halt.

DR. MODLIN: Yes, Natalie?

DR. SMITH: We've certainly been having similar discussions in California, as well as with Astona and CSTE about this issue. And I think the states feel that -- you know, confident in CDC's ability, but that in some sense all public health is local and that, at least in California, our idea

is to form a small response team at the state level and probably at the big county levels, at the least, and that -- there is a sense among the states that there should be very limited vaccination, but that there should be some pre-event vaccination. I agree that for any given medical practitioner who's -- that the -- obviously the chance of them ever contacting smallpox is vanishingly small and certainly we're not advocating for a widespread use, but that there be very limited use.

DR. SNIDER: John?

DR. MODLIN: Yeah, Dixie?

DR. SNIDER: Just my -- contribute to the discussion in terms of some lessons learned around the anthrax vaccine. Part of the issue here that the Committee is going to have to grapple with over the next few months -- and Hal had mentioned a time frame -- but we are anticipating that we would certainly continue these discussions through June and at the October meeting, perhaps even longer. But that's kind of the time frame we're talking

about. Meanwhile there would be some other activities going on to engage communities and the public around not only vaccine issue, but other issues in the plan.

But I think around this particular issue there are several problems. One of course has been having vaccine immunoglobulin available, because just having smallpox vaccine doesn't do you any good unless you have VIG available to you to be able to handle the complications. So that's been one of the points that's had to be dealt with, and it's not completely dealt with yet. And so that's something that has to be handled.

The other issue is when we talk about having groups of people vaccinated, whether we're talking about at CDC or at the state level or at these hospitals that are being funded or whatever, is how we're going to be able to draw the line, define who gets it and who doesn't, and explain that in a way that is acceptable to those people who do and do not receive it, and that it is rational and is acceptable to politicians and so forth. Because as

D. A. Henderson always says -- I mean all of this is a slippery slope. And given where we are in the production cycle of all of this, trying to make these determinations in a very clear, consistent way throughout the country and then articulate it so that it is accepted by the public as a rational way to use a limited supply of product, is a major challenge.

DR. MODLIN: What you're saying -- we have to be very good at what we are about to do, I agree. Yes?

DR. BIRKHEAD: I take Dixie's comments -- I think are very right-on and that we may not be ready right now for a change in the recommendation, but I just am saying that I think as we move forward, as vaccine supplies become more readily available, as VIG becomes more readily available and the plans at the state and local level become much more developed and facilities are actually designated and equipped and staff are trained, that this discussion needs to go on. And I -- at some point it may make sense to go ahead, and I agree,

the slippery slope is a big problem that we all need to be aware of.

DR. MODLIN: Carole, are you in any position to say anything more about the NIH dilution study?

DR. HEILMAN: Yeah, I guess what I can tell you is that -- I'm sure some of you have read in the paper that the data at this point in time are very good in terms of dilution studies. We did a one to five and one to ten and an undiluted and the data looked very promising in terms of take rates. We've had over 10,000 safety data points to enter in and we're doing a double-check on them. We've had our first set just released today and, again, everything looks pretty consistent. The goal is February 26th to have our second set of data entry, just validated the first set, and so we have -- everything is already mocked-up for an article to get out as soon as the data can be plugged in there.

We have shared with CDC, because they were involved in the dilution and the protocol -- to do a dilution study protocol, all the data that we

have.

DR. MODLIN: So we're looking for a public release within a couple of months?

DR. HEILMAN: No, couple of weeks.

DR. MODLIN: Excuse me, couple of weeks, terrific.

DR. HEILMAN: Yeah, we're really trying to move a very fast track on this.

DR. MODLIN: Terrific. Other comments or questions? Georges?

DR. PETER: A couple of questions. First, Hal, did I understand correctly that originally the plan was to have 20 response teams and that this has been stopped with the first 100 or so members of these teams?

DR. MARGOLIS: No, actually all the response teams are trained.

DR. PETER: I see.

DR. MARGOLIS: Not everybody's vaccinated and, again, we would use -- what's being discussed now, that if somebody had to go out the door, they'd be vaccinated at that point if there was a -- you

know, if there --

DR. PETER: So right now the plan is to stop the current 112 or how many it is that have been vaccinated, and then to vaccinate others as you gather more data about which dilution --

DR. MARGOLIS: No, actually the plan is to -- those questions that I posed is that we would like to see a structure and approach to figuring out who to vaccinate. And that was what kind of as we came around with this of, you know, having definitions of risk or the kind of person that ought to be vaccinated in a response team.

DR. PETER: But I'm still not clear. Now there's -- you have 20 teams of eight each, which is 160, and you say you stopped and didn't vaccinate all of them. Did I understand that correctly or did I misunderstand?

DR. MARGOLIS: Correct.

DR. PETER: And that's --

DR. MARGOLIS: There are 20 teams of -- yes, of eight people. There are about 100 people -- they were in two waves of training, actually,

that's --

DR. PETER: I see. All right, I won't pursue it then. The second question I wanted to ask Carole was I'm not sure I understood when you said that there are many data points and how many persons have been vaccinated in the NIH studies and --

DR. HEILMAN: Just over 680, but we asked a tremendous amount of safety questions, so that --

DR. PETER: I see.

DR. HEILMAN: -- we have a complete safety look at this at each one of the doses.

DR. PETER: And you may even find that the one to ten dilution is -- gives you a high take rate.

DR. HEILMAN: We do know at this point in time that all the take rates look very good.

DR. PETER: And do you have any evidence that the local reactions are less severe with the dilutions?

DR. HEILMAN: We only have -- the only thing I've seen is aggregate data, so I don't know how it has partitioned out. It was on my blackberry but I

couldn't get it just now.

DR. PETER: Third question, John, for the group is -- for the state representatives is how much of the state plan's differing? How much communication is taking place between the different states in terms of developing of the plans, how much coordination? I'm sure quite a bit is taking place, but I'd be interested in knowing what efforts are made to develop that coordination.

DR. MODLIN: That's a question I'd direct to Hal, I would guess.

DR. MARGOLIS: Well, actually when we had all the state participants in in December, we asked the question and really very few states that have a fully developed plan. I think states -- again, this has been all part of the bioterrorism and emergency response preparedness, and suddenly this just got dramatically accelerated in post-September 11th. I think people have been working on these things. I think smallpox has probably the most components and there's actually something out there now to use as a target and a framework. But there

are really very few states that have a fully developed plan. And again, part of our view is to, yes, get people talking to each other, sharing, and us finding out what they have. But at this point it is not very mature, I guess that's the way to put it.

DR. SMITH: Most of us have had BT plans, and obviously smallpox has always been a category agent, so we've always included it. But with the recent training and 9/11 and anthrax, and then with the new BT money, all of us are feeling quite pushed to develop -- flesh out these smallpox plans. And we are having a number of discussions among ourselves, but --

DR. MODLIN: It sounds like it's very much a state in flux and that -- I would suspect that there are many, many states that are waiting for the CDC to develop a cohesive plan that they can hand to them and to follow, and then there are other states -- particularly larger states -- that are taking the initiative on their own, as with many other things. Jaime?

DR. DESEDA: I just wanted to know if the new vaccine, ACAM, is it any different from Dryvax or is it basically the same?

DR. MODLIN: It's cell culture-based vaccine from the same seed. Is that correct? Right now. Walt?

DR. ORENSTEIN: I think, as Natalie said, the situation has changed dramatically since the ACIP last made its recommendations. I think some of the questions that perhaps were not considered as seriously as they might be today are now serious issues, and I think those decisions need to be made as to who would be the best people to vaccinate, which groups, et cetera, et cetera, especially as the supplies increase. And so the question I think we have for the Committee is I think it would be appropriate, in my opinion, to reconsider that prior statement in view of the new information and see if there are changes called for in your recommendations to us.

DR. MODLIN: Yeah, that leads us to the next phase. Thanks, Walt. And that is where do we go

from here as a Committee? Sam?

DR. KATZ: I want to follow up on Jaime's question, which was to ask Karen Midthun -- the vaccine that we're talking about that's the 1981 Dryvax is calf skin, as Hal pointed out. The vaccines that are contracted for are tissue culture and I wondered if you had any comments to make about FDA's approach to phase one, two, three studies, licensure of a new vaccine, even cell culture, in contrast to the old calf lymph vaccine.

DR. MIDTHUN: Yeah, as has been pointed out, the ACAM1000 is being grown in MRC5 cells, which is a human diploid cell line. It's the same cell line, for example, that varicella vaccine and Hepatitis A vaccines are grown on. It would go through the same -- I mean process in terms of characterization of the cell banks, characterization of the viral seeds that would be done for any viral vaccine under development. It would go through the same process of having phase one, phase two, phase three studies be done to start out by evaluating the safety primarily in

phase one, going into phase two where you have expanded numbers, additional safety, immunogenicity and typically dose ranging studies; and then phase three studies where you would gather a much larger body of safety data. As Hal pointed out, clearly we don't have any smallpox at this point so you would not have a clinical end point study, but we would intend to use an immunogenicity and a take rate and look to see how that compares with this new vaccine to the Dryvax vaccine and form a bridge to efficacy using those parameters.

DR. KATZ: On the basis of the old data, do you have any concept of what numbers you would require in phase three for testing for unusual events?

DR. MIDTHUN: Obviously that's -- will by some extent be influenced -- you know, what we see as we move along through phase one and phase two. Obviously there may be issues that arise there that make us have a particular focus as we go to phase three. Typically for a lot of live viral vaccines, we usually had numbers well into the thousands to

evaluate and get a basic safety database. Clearly though, even with numbers in the several thousands, you're not going to have a sufficient number to address certain rare adverse events such as post-vaccinal encephalitis or those very serious but very rare adverse events.

DR. MODLIN: Georges?

DR. PETER: One other point that I think is important, obviously, that the staff at CDC is well aware of is this issue of public communication and acceptance. And I think Neal mentioned the concerns of the health care providers in wanting to know, then be assured, that CDC would be available. But I think the public at large has a lot of anxiety and I'm sure you've probably had many phone calls from congressmen wanting to know when smallpox vaccine would be available, much of which is based upon lack of knowledge of the reactions. But this must be a major issue that you face and that the public reassurance is an important component of the program because their anxiety is considerable, particularly if we have another

attack of any bioterrorist agent.

DR. MODLIN: Okay. Even though there doesn't, as far as we can tell, appear to be any change in risks that we're aware of, very certainly things regarding preparedness have moved along very swiftly and you are dealing with a very different atmosphere -- situation than we were when the statement was updated, so we have had some discussions amongst ourselves and I think the way in which we'd like to proceed would be to continue to work with the smallpox bioterrorism working group, but recognizing that -- and this is a group that has been led by Chuck Helms -- recognizing that there has been changes -- considerable changes in membership, both on the ACIP and on NVAC, as well, that we're going to have a small group of us re-examine the membership of the working group and reconstitute the working group. Get it up and continuing to work and we'll be working, I guess, with you, Hal -- wherever Hal went -- and others to move on this agenda that you've laid out for us. And I think that's the best way to conclude this

portion of it.

Hal, thanks very much.

Let's go on to a very important topic, which is update on the vaccine supply. This is an issue that seems to change daily and there are a number of issues that may not even be on the agenda that we need to discuss, and Dean Mason, are you going to be leading the discussion here? Terrific.

MR. MASON: Hello. My name is Dean Mason with the National Immunization Program. I appreciate this opportunity to update the ACIP on vaccine supply, although I know we all look forward, including everyone in the audience, to the day when that is relegated to the background of historical perspective.

I thought my opening chart should reflect the condition both of the stock market in vaccines and also the fact that I'm a messenger, but I've still brought some equipment for the tomatoes that are going to be thrown my way.

In December, to give you a very brief background -- and I know many of the ACIP members

no longer need this type of background, but just to review for the audience, Wyeth-Lederle announced its intent to cease production of tetanus-diphtheria. For 1999 Wyeth had 32 percent of the whole diphtheria and tetanus products market share. Though that had been reduced to 19 percent in 2000, it still is a significant part of the market. To the best of my knowledge, none of us had planned for this withdrawal.

Aventis Pasteur is the only national producer of the tetanus-diphtheria. There is a minor supplier of this product, FFF Enterprises, which obtains vaccine from the University of Massachusetts Medical School.

One thing I should note is that the next bullet really should belong under the DTaP slide and I apologize. Thimerosal preservative, when it was removed from the DTaP production with Aventis Pasteur, it did result in less of a yield and overfill issues with respect to manufacturing, but that really should reflect a DTaP situation as opposed to Td.

At this time, and for the past 12 months, all decisions about the sale and supply of Td are being made by Aventis Pasteur.

Just for a very quick reference for you, I've included some information on the evolving recommendations that the ACIP and the AAP and AAFP have acted upon. The bottom line is that since June 11th of 2001, Td has not been available in health department or doctor offices, with some rare exceptions, but rather is being centrally -- to maximize efficiency, centrally shipped or sold to hospitals, burn centers, trauma units, et cetera, to maximize the targeting of this product.

In terms of tetanus-diphtheria supply, the -- if you can see it on the graph, the yellow line is what we estimate -- somewhere between the yellow and the blue -- 18 to 20 million doses is what we estimate the national need to be if people were fully compliant with getting Td boosters and so forth. And you can see the red line represents the actual distribution based upon biologic surveillance information, and it shows the steady

decline in availability of the tetanus-diphtheria product, such that for 2001 only 9.7 million doses were actually distributed for the US market.

So the outlook for Td is basically the same. The demand continues to substantially exceed the supply that's available. Tetanus is the limiting factor in the production of those products listed. It takes about 11 months to produce this toxoid and while this is the case, Aventis has been able to respond to national emergencies, the most recent one of course being the tragedy of September the 11th, when they were able to meet a substantial Td need of New York City, Virginia, Washington, D.C. area and Pennsylvania. A return to the recommended schedule for Td boosters may occur in late 2002. Our previous estimate before the ACIP was that it would be a little bit earlier than that, perhaps as early as early fall, and we will stay tuned.

With respect to DTaP vaccine, our recent national supply experience, we estimate the national need to be 18 to 20 million doses. The calendar year 2001 supply was 18.5 million doses.

That would appear to meet the national need. However, the absolute need of CDC contract, our minimum absolute need, is a million doses a month, and part of the problem with the Dt experience is that it's not equitable distribution between the public and private sectors, so that now distribution and contract issues are resulting in public providers and private sector providers who depend on public purchased vaccine may be suffering disproportionate shortages compared to the private sector.

To substantiate this observation for the period of time of January 2001 through January 2002, very current, the blue dotted line represents the national monthly need of about 1.7 million doses. The red dotted line represents the absolute CDC contract need minimum of a million doses. The total supply for the 13-month period through the CDC contract was 10.4 million doses, which if we needed 13 million as a net minimum, you can see our problem. The private supply for the same period was 2.8 million doses, so the private supply almost

equaled the public supply, but our need is about 60 percent of the total product. Only in February, October -- only in February, October and April -- February, April and October was the CDC contract need met for DTaP supply. However, for the private sector, the supply was met nine of the 13 months.

When we evaluate the impact that DTaP supplies relate to the CDC contract, the 866,000 doses on back order, this represents the amount of vaccine that was over 15 working days in not being filled by the companies. This reflects back orders both from Aventis and Glaxo Smith Kline. However, after the date in February, all subsequent back orders are reflected of Glaxo Smith Kline, primarily because we closed out or canceled most of the back orders with Aventis when we were informed that they would prioritize product to the private sector. So you can see that Glaxo, we've had fairly consistent significant back-order situation, around three-quarters of a million plus doses, going into January. Please don't think that we were able to catch that up. We administratively canceled our

back orders and that's why we have a zero back order as of February 1st. We reached our contract maximum because we had to exercise our purchases primarily with one company. We had to negotiate a bridge contract with that one company, which gave us a million doses for the month of February. We've exhausted that million doses this month. We hope to have a new contract in place with both Aventis Pasteur and with Glaxo Smith Kline effective March the 1st, though that's not established yet. We're in the negotiation phase.

Another way of evaluating the impact of the DTaP shortage in the public sector is we asked all of our projects -- N equals 56, we're not asking of the Pacific trusts, but we asked all of our projects to report to us the status, how much vaccine doses they have in their central depot inventories at the end of each month or at the beginning of each month. You can see that we have 65 percent of our projects -- the majority of our projects, 33 -- or 65 percent are at zero inventory or have less than two weeks of DTaP vaccine in

inventory in their central depots. This has been a fairly consistent problem for the past few months.

Only about 78 percent of the public sector need is being met. Most of that's being met by Glaxo. Aventis Pasteur is prioritizing their supply to the private sector. Aventis Pasteur is limiting DTaP supply to private providers because of their own supply circumstances to equal to or less than 80 doses per order per practice per week, though those orders can be adjusted up or down based on practice size and other considerations. NIP will continue to monitor the orders, work closely with the companies to prioritize supply to those grantees that we judge most in need. A return to the full dosing schedule for all providers, based upon our current knowledge, we have had to revise and to have to acknowledge that it may not occur in 2002. Previously we felt that by mid-year the public sector would have sufficient product to return to the full five-dose schedule similar to what the private sector enjoys. This may change. There are market factors or influences

that could positively accelerate to our getting more product. One of the chief considerations would be the licensure of the product that is widely used in Canada. And of course another consideration is if we're more successful in the establishment of our true needs through our contracts for this year.

To move on to pneumococcal conjugate vaccine, the green represents the number of doses per month purchased through the CDC contract. The blue represents the total supply of pneumococcal conjugate. Obviously our problems began in September. We had a rather significant upsurge for November and December in product supply, indeed, the highest for the entire calendar year. Unfortunately, our January experience has been more similar to September and October. So it's difficult to predict, at least for the recent history, exactly what we're going to have for the near future.

Reasons given for the pneumococcal shortages and delays, the rapid implementation of this

product in the public sector, demand exceeded manufacturing projections. There were good manufacturing practice issues with the company and the FDA. The more recent situation has been attributed to a, quote, production bottleneck that has been corrected.

What's the recent national supply experience? For calendar year 2001, 15.5 million doses were shipped, 52 percent of that through the CDC contract. The average doses shipped per month, January to August, was a little over 700,000. Beginning in September, as you saw, we had a significant month to month variance in both the public and private sectors, so in this case the pain of the shortage, as best we can determine, is being equitably felt. The September/October average was only 379,000 doses, which is a 54 percent decline from the previous eight months. November/December we had the upsurge, and then a disappointing number, January, 689,000 doses.

So we evaluate this independent of the manufacturers -- well, actually I shouldn't say

that because the source for this information is the manufacturer, but comparison of pneumococcal conjugate back orders for selected months, you can see that we were making steady progress from our peak back order situation. We enjoyed the supply of late November and December, which brought down our back orders. Again, these are orders that we have supplied to the manufacturer that they have not filled within 15 working days, per the terms of our contract. And we actually had got that down to the lowest level since we've been tracking it, but because of the January supply situation, you can see that our back orders are quickly climbing again in February.

Here's an independent evaluation and that's the inventory in the central depots of our immunization projects. With 55 projects reporting, our actual shortages are more depressed than what we reflected with the DTaP vaccine. We have 53 percent of our project have less than a two-week supply, which 13 of those -- which is what, about 24 or 25 percent -- are reporting to us now they

have zero inventory. Which means of course all of the VFC providers in those states if they're a universal state, all providers are unable to obtain pneumococcal conjugate vaccine at this time.

What's the outlook for pneumococcal? Both the public and private sectors are experiencing equitable shortages in an equitable fashion. There is significant supply fluctuation. We can anticipate that for February and for next month. Wyeth-Lederle states that their production for 2002, however, will soon meet the demand, though inventory build-up may not be sufficient for the ACIP to consider a return to the routine schedule before mid-year.

Varicella vaccine, the saga continues. This may be the product of which we have the most acute shortages. The annual need is estimated to be six to seven million doses or 500 to 583 a month. CDC need is about 60 percent of the total US market. You can see for calendar year 2000 and 2001 there was roughly equivalent doses supplied, 300,000 doses down in 2001; 600,000 dose monthly average

for the first ten months of the year. However, the November/January supply was a 65 percent decline from that ten-month average. The February supply is expected to exceed the monthly supply need of the nation, but of course will not be sufficient to entirely catch up the recent experience of November, December and January.

With regard to the varicella vaccine distribution in the US market, the green characterizes the CDC contract purchases and the blue characterizes the supply to the private sector. And again, it's easy to determine why we're in the shortages that we are based upon the experiences of the last three months, all of which were the three lowest months for the entire calendar year.

The outlook for varicella vaccine, supply is at a record low. Shortages are occurring in all states among providers in both the public and private health care sectors. All orders received through December 21st have been shipped, and it's first in/first out. Because these shipments go

directly from the manufacturer to the end user, it is -- there's no distinctions made between public and private providers. 325,000 doses are on back order through the CDC contract over 15 working days. One should expect on average about 60 days to fill orders for the next four to six weeks. Supply amounts, we are informed, should substantially exceed national monthly need beginning in March. March, April and perhaps thereafter we should have a significant production and supply. For 2002 school, day care or Head Start attendance, CDC is advising the states that they should consider options with respect to the enforcement of immunization requirements for school attendance. Those options might include in-progress declarations or other types of waivers such that children who cannot obtain vaccine are not suspended from school because of the shortages.

Merck will contact all of the states March the 1st or soon thereafter to provide a supply update for informed decision-making by the states. Merck predicts the supply may be sufficient to return to

the recommended schedule by late spring or early summer, based upon their projections of supply upsurge in the next several months.

The recent experience with MMR vaccine, this may be the one that's been perhaps the most difficult for us to evaluate or predict. The national need is about a million doses a month. Again, CDC fairly consistently -- approximately 60 percent of that. The calendar year 2000 of 12.9 million doses. There was a decline of 2.3 million doses for calendar year 2001. As of 1/21 all 700,000 doses that Merck requested from the CDC stockpile of 3.3 million doses had been shipped. We notice that the pattern of vaccine supply had considerable variance with MMR: 942,000 shipped on average from January to September, keeping in mind that our national need is about a million doses a month; October/November average fell precipitously; December had a nice comeback, in part attributed to the stockpile; January, a little over a half-million doses. Stockpile was also a part of that product, so this doesn't represent new production

necessarily.

The outlook for MMR, some states are receiving partial shipments. However, over 30 of our states reported over a 30-day inventory. We did have several states, however, that reported zero dose inventory for MMR and we will need to work with Merck to prioritize to those states. February supply should exceed January and be sufficient to meet the national need for the month. One should expect ordering delays between 15 and 40 days into March of this year. Merck predicts a significant supply beginning in March. Based upon these predictions we stated that perhaps there's no adjustments to the schedule anticipated. However, that's a consideration for the ACIP, based upon other information that you may possess.

The outlook for other vaccines, Aventis Pasteur's meningococcal vaccine, we get regular -- frequent phone calls at CDC asking why the nation is out of meningococcal. The company states that the supply of this product is sufficient to meet all of the requests. However, sometimes when one

is depending on a vendor or a source other than the manufacturer, because Aventis at this point I understand is selling only directly to providers, one may be informed that they have no product to distribute, when in point of fact, by calling the manufacturer one could obtain the product.

For Merck's other vaccines, we're informed and according to our evaluation the Hepatitis A vaccine is sufficient to meet the need. HIB vaccine, current orders are being filled on time, but soon this will deteriorate. It may take up to 60 days to fill, and that may not be resolved until June of this year. Hepatitis B/HIB combination, CDC orders with Merck date back to January the 8th, currently taking about 30 days to fill. We anticipate this lasting through April of this year. Some delays are being experienced with the Hepatitis B vaccine. One should allow up to six weeks for supply, at least into April.

It's important to remember that in some instances there may be a shortage from one manufacturer but not another. For example,

Hepatitis B is available within the 15-day time frame from Glaxo Smith Kline. So when we discuss national shortages, we are mainly characterizing those shortages on the basis of lack of product from all companies that produce it, not just from one.

What is NIP doing in response to the shortages? Of course our close contact with the ACIP and the ACIP deliberates schedule modifications for prioritization of available product. We're working with the manufacturers. We enjoy a very close working relationship with the manufacturers in terms of their future supply. We're receiving more information now than we have ever had, at least in my experience, so the cooperation is outstanding. It doesn't ameliorate the supply shortages, the frustration related to that, but it does help us to better direct available product. And we're also working with the states to prioritize orders to those who have low inventories and to those who have special needs. We're collecting project inventories on a monthly

basis. This is time-intensive effort on the part of the states. We're very appreciative of that, but it's -- and it fundamentally serves our intelligence needs. We're giving highest priority to those projects that are nearly depleted inventories or depleted inventories. We are allocating supplies on what we judge to be the 30-day -- 30 to 45-day basis, and we are providing routine updates on vaccine supply.

And of course what are we asking of the projects? To accurately report their central depot inventories so that we can honestly evaluate who has most need; order only in 30 to 45-day increments. Some of our states are used to ordering 60, 90, 120-day inventories. That's a luxury we can't afford at this time. We're asking states even if they don't feel that they're having a shortage situation to nonetheless adhere with the ACIP recommendations. We're asking states to be conscious of their budgets when placing orders for different vaccines so that they don't obligate large orders and funding tie-ups which makes it

difficult for them to place orders for other vaccines. We're asking for cooperation from the states in not making sweetheart or side deals with the manufacturers, and we're advising that they should plan on supply disruptions of some vaccines certainly for the next three to six months.

That concludes my part, Dr. Modlin, if you will take over questions. I think Shannon Stokley is to follow me and Dr. Myers, also on the same subject.

DR. MODLIN: Why don't we go ahead and ask if there are some specific questions regarding the information that Mr. Mason has presented. There are several other things we need to be talking about on this topic, but specific questions for Dean? Comments?

Why don't we go ahead and, Georges, even though we don't have it on the agenda specifically, we definitely should have an update on the NVAC meeting last week.

DR. MYERS: That's what I'm going to give.

DR. MODLIN: Are you planning on that, Marty?

Thanks.

MS. STOKLEY: Hi, thank you, I'm Shannon Stokley. I'm also with the National Immunization Program and today I will be presenting some preliminary findings about the impact of the recent vaccine shortages.

Recently we just conducted two studies, with the main objective to evaluate the impact vaccine shortages have had on state and urban immunization programs, as well as immunization providers.

First I would like to discuss the findings from the first study, and that is a survey of the immunization program managers. On January 22nd during the program managers meeting we distributed a brief one-page survey to all the program managers and we mainly focused on PCV7, DTaP and the Td vaccine shortages. Of the 56 programs that we surveyed, 54, or 96 percent, did respond to our survey.

Our first question was whether or not the programs have changed the way they distribute vaccine to health care providers, and at least for

the Td vaccine, almost all the programs did indicate that they had changed the way they distribute vaccine. And over 85 percent of the programs indicated they changed the way they distribute PCV7 and DTaP. Of the programs that did indicate they made changes, almost all the programs indicated that they either distribute partial orders or they limit the amount of vaccine that a provider can order. Only for Td do we really see programs prioritizing which providers actually receive the vaccine. And in this case they were prioritizing to emergency rooms, acute care facilities, things that were recommended. We really didn't see this practice in place for PCV7 or DTaP.

We also asked the programs about what kind of information they'd been giving health care providers, especially about vaccine administration and in the time of a vaccine shortage. For PCV7, 76 percent of the programs distributed the ACIP recommendations for vaccine administration, and a few programs also had some state-specific

recommendations that were different from ACIP, although we didn't collect the information to know how they differed.

For DTaP, 61 percent of the programs distributed the ACIP recommendations for vaccine administration. What I think is interesting is that 30 percent of the programs did not distribute any sort of information to providers for DTaP. And then again for Td, almost all the programs distributed some sort of information or they distributed the ACIP recommendations to providers. What's also interesting is that about three-quarters of the programs did give some sort of general statement or general guidance to providers about recalling children who were unable to receive vaccines because of the vaccine shortages, and in a few programs they actually sent information to the schools asking the schools to conduct the recall when vaccine supply is sufficient.

We also asked about day care, Head Start and school entry requirements, and what we found was that 48 percent of the programs have either changed

or suspended school entry requirements for tetanus-diphtheria vaccine. Very few programs have suspended or changed any recommendations or requirements for PCV7 and DTaP.

Finally we asked programs what other problems they were experiencing with any of the other recommended vaccines. Eleven percent of the programs said that they're not having any problems to date with any of the other recommended vaccines, but of course varicella is definitely a big problem. Seventy-six percent are experiencing -- or they're not receiving full orders or not receiving any vaccine at all. And also with the programs that indicated problems with varicella vaccine, about 17 percent of the programs are already starting to consider their school entry requirements for the next school year and actually suspending the requirement for varicella vaccine.

MMR is also a problem for the programs and HIB and Hepatitis B was mentioned, but it doesn't appear to be as big a problem at this time compared to varicella.

So in summary, the majority of the programs have implemented some sort of change in their distribution of vaccines to health care providers, especially for Td, DTaP and PCV7. Almost all the states have sent out some recommendation about vaccine administration in the time of vaccine shortages to providers, and almost half the programs are changing or suspending their school entry requirements for Td. And again, varicella and MMR are starting to appear to be a bigger problem than some of the other vaccines.

Next I want to present the preliminary findings for our second study, and that was a study with immunization providers. Between January 21st and February 1st of this year, immunization program staff conducted interviews of providers during the regularly scheduled VFC and/or AFIX site visits. We had 30 immunization programs participating in the study, and we had good representation from both the state and the urban programs, and overall, 447 provider site visits were conducted during this two-week period.

I just want to stress, though, that this study was just recently completed and so all these results I'm going to present are preliminary.

The interview had three main areas of focus, and that was difficulties with purchasing vaccines, whether or not they've had to implement any changes in vaccine administration because of those shortages, and if they experienced any length of time where they actually had no vaccine in stock.

This slide presents the characteristics of the providers that were visited. You can see we had adequate representation from both the public and the private sector, and the majority of the private physicians were pediatricians, although we did have some family physicians included in this study. And almost half of the providers or half of the practices visited had two to five immunization providers in the practice.

For the remainder of the results I'll be presenting aggregate data. At this time we haven't had a chance yet to look at results by provider type, but that is something that we plan to do in

the future.

We first asked if providers were having difficulty purchasing or receiving vaccines, and you can see for PCV7, varicella, Td and DTaP, they did indicate having problems purchasing or receiving vaccines, and it does appear that public purchase vaccines are having more problems with these vaccines.

Just something to note, Gary Freed and other researchers at the University of Michigan, in the fall they conducted a study focusing on PCV7 and they also asked about difficulties with purchasing vaccine. And in that study there did not appear to be a difference between public versus private purchase vaccines. We're not quite sure with our study why public purchase vaccines seem to be a bigger problem. That's something we'll be looking into in the future analysis. But for the other vaccines it doesn't appear to be as big a problem, nor does there appear to be any differences between public and private purchase vaccines.

We also asked providers if they had

implemented any of the recommendations for vaccine administration during the time of vaccine shortages, and 68 percent of the providers, at least for DTaP, indicated that they really didn't make any change in the recommendations for how they administer vaccine, mainly because they had vaccine in stock to give to their patients. However, about six percent of providers suspended administration of all their doses because they ran out of vaccine before they knew that there was a shortage going on and that they should maybe consider who they give -- or how they distribute their vaccine. Sixteen percent suspended the administration of the fifth dose of the series, and 11 percent suspended administration of the fourth dose.

We asked the same question, but this time focusing on PCV7 and this time only 45 percent of the providers said that they did not change the way they administered the vaccine because they had adequate supply. And this is definitely lower than what was observed with DTaP. And here 17 percent of the providers had to stop giving vaccine because

they ran out of vaccine before they knew there was a shortage going on, and this is definitely higher than what we saw for DTaP. And it did appear that a large percentage of providers were suspending at least one or more doses of the vaccines within the series.

And finally we asked if they had gone -- if there was any length of time that they had gone without vaccine, and for three-quarters of the -- about three-quarters of the providers for DTaP, they always had some DTaP in stock, and almost half the providers always had some PCV7 in stock. But what is important is that for PCV7, 20 percent of the providers indicated they had zero doses in their inventory for more than a month, and we suspect that this probably will have some impact on vaccination coverage.

And in summary, providers did experience greater problems receiving vaccines, especial public purchase vaccines for PCV7, varicella, Td and DTaP, and approximately 25 percent of providers had to suspend administration of one or more doses

of DTaP and PCV7 because of the vaccine shortages. And providers experienced a greater length of time with no PCV7 in stock compared to DTaP.

And that concludes my presentation, but I'd like to thank and acknowledge the people who helped me work on this study, and I can take any questions.

DR. MODLIN: Thanks, Ms. Stokley. Let's see if there are questions or comments for Ms. Stokley. Georges?

DR. PETER: You mentioned that about a third of the immunization program managers had experienced problems with MMR, and yet very few of the private providers had experienced problems. And I had been under the impression from last week's meeting that because of the stockpile that the MMR supply in physicians' offices that comes through states or directly to the offices was sufficient. So I'm wondering what the problem was the immunization managers were experiencing if there indeed was not a shortage in the physicians' offices.

MS. STOKLEY: Right, that's a great question. Actually Dean and I were discussing that earlier today and we were trying to figure out why there might be some differences, and it might be the way we asked the question, because when we asked the question we just said what -- how -- are you experiencing any problems and with other vaccines, and we didn't really specify exactly what problems. We didn't ask them to quantify problems. So I think Dean did mention that some programs were receiving partial orders of vaccine, and so that might have constituted a problem to the program manager because they didn't get their full order. So it is sort of -- we're not quite sure why.

DR. PETER: Presumably the immunization managers experienced the problem but were able to manage it appropriately. And by the way, I meant to thank you for a very nice, complete presentation. If you can provide the data to us -- we understand that it's preliminary, but it's very useful in assessing the problems at the practical -- at the level of delivery.

MS. STOKLEY: I can work with the coordinator to get handouts.

DR. MODLIN: That'd be terrific. Dean?

MR. MASON: Just to try to respond to Dr. Peter's question, it is true that the public sector workers are probably in a little bit better shape than private sector. The orders through CDC contracts were filled through January the 23rd, which means that orders that we have placed since then have not been filled. However, the orders for the private sector date back to January 8th. It's my understanding that Merck's intention with their next lot release is to target most if not all of that vaccine to the private sector to more equalize the period of time it takes to get vaccine -- MMR.

DR. MODLIN: Walt?

DR. ORENSTEIN: I think the lesson on MMR is that the stockpile may have been ameliorating some of the problem, but it has not solved the problem. It's clear that there are physicians who are having problems, physicians with back orders, physicians who've been unable to vaccinate. And I think the

Committee I think does need to consider, in my opinion, recommendations about what to do if supplies are tight with MMR. Certainly with MMR we have a first dose and a second dose and they're quite different in terms of what their meanings would be, and I would hope that the Committee would consider that perhaps in that varicella set, with varicella afterwards.

DR. MODLIN: Eric France?

DR. FRANCE: My understanding is that the new pneumococcal recommendation is that we withhold the fourth dose at this time. And yet 28 percent in your survey were actually following that recommendation. So -- and 45 percent of them had not changed in January and February, even though ACIP recommends that we withhold that fourth dose to be able to better distribute things. Did you get a sense whether people had heard that message as you talked to providers, that the new policy was not to provide that booster dose at this time?

MS. STOKLEY: That's a great question. We didn't really -- what we received from the state

administration programs was the aggregate data and some individual provider forms. I haven't had a chance to really talk to people who actually conducted the site visits to get a feeling -- you know, to get what their feeling was about why some providers suspended the fourth dose and why others didn't. It could have been that some of the docs -- either they don't vaccinate that many children each week and so they had adequate supply in their stock where they could administer all the vaccines that they need to, but that's something that we'd want to look at in our future analysis is do some comparisons by provider size and provider type and just see what is really going on.

DR. PETER: John?

DR. MODLIN: Questions or comments? Georges?

DR. PETER: I think, Eric, one of the problems is that if a state, for example, has adequate supply, they have to wrestle with the issue do they change recommendations in order to conserve supply for other states at the expense of great confusion that happens in the practicing community when you

have change in recommendations. I mean we have a very complex immunization schedule that at times is very confusing to physicians and therefore whenever you make a change, you create a further problem in the sense of the -- of just increasing the complexity of it. I'm not arguing against the changes, I'm just saying that's simply a practical problem that exists with any change you make. It illustrates a further problem of these shortages.

DR. FRANCE: And I think -- the reason I brought it up is to ask the question whether making this kind of a short-term change in the policy of suspending a fourth dose changes practice patterns within the -- and leads to better distribution of the vaccine. And I'm asking that -- we're thinking about the fourth dose of DTaP or fifth dose of DTaP where there's an obvious imbalance, and the recommendation to date is if you are running out, suspend it. Whereas with the PCV7 there's a specific policy that says let's not do the fourth dose for now.

DR. PETER: John?

DR. MODLIN: Georges?

DR. PETER: One other point is that Donna Williamson from the State of Alabama made the point at the NVAC meeting that many of these children will not -- who don't receive the fourth dose, will never be successfully recalled. And I think perhaps that is a very good argument for the need for registries because if indeed we had effective registries in effect, when we had shortages and indeed had to delay dosages, the recall system would be much, much easier than most practices would have now.

DR. MODLIN: Thanks. Ms. Stokley, thank you very much.

MS. STOKLEY: Thank you.

DR. MODLIN: And Jean -- are you next, Marty? Or is -- I actually have -- okay, got it. Dr. Myers.

While Marty's getting ready, I wonder if we ought to begin to think about -- or sketch out what a recommendation or an interim recommendation for MMR might look like.

DR. MYERS: Well, obviously assuring vaccine availability is a fundamental priority for our national immunization -- our programs. And last week NVPO, NVAC and the interagency vaccine working group convened a meeting in Washington to consider strengthening the supply of routine recommended vaccines in the US. We also considered some of the issues surrounding availability of vaccines, the broader issue of developing vaccines for where there's a limited market, but we really -- we tried to concentrate on the routine recommended vaccines.

Just to recount what Dean said and the other discussions we've had, we've had delays of influenza vaccine, shortages of Td and all the tetanus toxoid-containing vaccines -- DTaP, pneumococcal conjugate, MMR, varicella and anthrax. We have limited smallpox vaccine. There's no oral polio virus vaccine for outbreak control. We've had the issue of transition to thimerosal-containing vaccines and reduced-thimerosal-containing vaccines, and then there's this last point that Eric and Georges were talking about, and

that is that change -- when we make changes in recommendations, we change coverage levels and we increase the disease risk.

This slide was shown or variations of this slide was shown multiple times at the meeting. You made a change in recommendation concerning the infant dose of Hepatitis B vaccine and it had a profound long-lasting impact on infant immunization. Donna Williamson made the point, as Georges pointed out, at the NVAC meeting that this looks at immunizations in the first five days. It doesn't address the issue of what happened to those children who didn't get immunized in the first five days and missed their vaccine. So when we start thinking about having to respond to the shortages, there's this profound impact on disease risk.

The NVAC formed a vaccine supply working group last February to examine the issue of shortages of the routinely recommended vaccines and to identify possible solutions. And our first task was to look at potential causes -- and as you've heard from each of the vaccines, they are multi-factorial --

then to develop a comprehensive list of potential strategies for strengthening the supply of vaccines, and then finally this meeting which was to enlist the key stakeholders to consider how those potential strategies might have averted or might ultimately impact subsequent similar problems.

So the meeting objective was to bring together the stakeholders, and we had industry representatives, multiple agencies, states, providers, purchasers, consumers. We had Congressional staffers and academics and others. To address the issue of the scope of the problem, which Dean has covered well today, to look at the contributing causes and response strategies, and then to develop a limited number of pragmatic options. And Dr. Slater, our new Assistant Secretary for Health, opened the meeting and emphasized the fact that she had charged the inter-agency vaccine group to bring forward to the Department a series of issues that would intervene in the shortage and to try and avert the types of

problems that we've been dealing with in a response mode over the last year.

So the strategies that we considered were the issues of the financial incentives, the whole issue of vaccines as commodities and problems of the financial incentives were there were competing financial issues relating to price of vaccine to the end user as opposed to profits for manufacturers and manufacturers being willing to stay in a narrow-margin market. The whole issues of the regulatory process, streamlining it and looking at various aspects of that. We considered the various types of government-directed programs, government-owned/government-operated, government-owned/contractor-operated. We considered the Institute of Medicine's consideration of a national vaccine authority. We looked at contracting mechanisms.

Then we explored vaccine stockpiles, and as you've seen, the MMR shortage is -- has been blunted somewhat by having a stockpile, although not completely ameliorated. We examined liability

issues, the impact of the Vaccine Injury Compensation program, and then we touched on a number of other issues around the vaccine supply.

There were a number of common themes, and the first one is -- I think the strongest message that came out is vaccines are under-valued. Just recall what we talked about earlier today, how much money do we save per dose of vaccine is the way in which we generally think about recommendations. Whereas in other health prevention strategies we think about how many thousands of dollars the health strategy costs to prevent one quality-adjusted life year or whatever measure.

But clearly restructuring or re-evaluating financial incentives was very important. Setting national vaccine priorities, and creating stockpiles to smooth out supply disruptions seemed like very obvious opportunities for us.

And then one of the points -- as I was listening to Dean talk, you should know how difficult the data is that CDC collects, and the fact that much of the data is proprietary in nature

and it's voluntarily provided by the manufacturers. And we spent a fair amount of time talking about the particular barriers that exist to providing communications across the various stakeholder groups, but how important this was. And in fact, Wayne Pisano from Aventis gave a particularly pragmatic, elegant discussion of some very concrete proposals that industry wanted to put on the table, and this was one of the major ones, that we need to find a mechanism by which we can communicate when there are going to be supply problems for any one of a number of reasons, for example.

So there was -- just to look at each of the strategies from the perspective of the regulatory process, there was a general consensus that there was support for the current regulatory process. That's not to say everybody's happy with the FDA suddenly, but rather that the process is good. It could be -- there were some things that could be specifically addressed, but this wasn't the core problem.

And reassessing manufacturers' incentives from

a variety of aspects seems like a very, very important thing to do, to maintain manufacturers in the market and attract new manufacturers. But I think one of the things that was a common theme was that we need to carefully consider what those are before we implement them so that we don't have unintended consequences.

The whole issue of Federal prioritization, of the government speaking with a single voice, particularly for development of new vaccines, is a priority. But government-owned and directed solutions seem to be less likely to accomplish long-term goals. They might be ways of solving a short-term -- objectives.

And then vaccine stockpiles were felt to be a very high priority issue across all the stakeholders. Not that it would help us now if we started building stockpiles. Obviously if the vaccine is in short supply, it's hard to build a stockpile. But rather to prevent the disruptions that occur with temporary supply problems -- and we can anticipate that supply problems will occur

again, and this is something we should anticipate.

And finally there was a lot of support for the Vaccine Injury Compensation program. There was some discussion of things that might make it even better, but I think there was general consensus that it was critical in stabilizing the market when it was implemented.

So the next steps are, as I said, the Assistant Secretary has asked the inter-agency vaccine group, on a very tight time frame, to develop short-term and long-term strategies to strengthen the vaccine supply, and especially to examine the issues surrounding expanding current vaccine stockpiles and developing new ones.

NVAC will publish the workshop proceedings and the working group is providing actively input -- and will in the future -- to the development of options for the Department to consider. And then just to mention in passing, both the GAO and the Institute of Medicine are considering related vaccine supply issues.

DR. MODLIN: Thanks, Marty. Questions or

comments for Dr. Myers?

DR. PETER: You know, John --

DR. MODLIN: Georges?

DR. PETER: -- the meeting was very informative and I think Marty did a wonderful job in a short period of time of summarizing two days of meetings. And I think that the theme that emerges about the importance of stockpiles in terms of preventing public health crises -- and the stockpile concept is not new; it's one of the 15 major points that's made in the measles white paper which served basically as the blueprint for our vaccine programs for the 1990's, and I think that's an issue on which we might spend some time in the future, hearing more about how it's worked and how it hasn't worked.

DR. MODLIN: Thanks, Georges. Questions --

DR. PETER: I think maybe Walt wishes to add a few points on that.

DR. ORENSTEIN: I would agree. I think our strategy on stockpiles had been to focus on single manufacturer and mature, predictable market because

these are really not stockpiles in the way many people think of them, which is sort of a static collection, but there's really storage and rotation kinds of -- and since bubble inventories is vaccine -- new vaccine is produced, goes into the stockpile and new vaccine is rotated out so that there's a shelf life of at least six months for vaccine that's rotated out. I think we've clearly learned that when there -- even when there are multiple manufacturers, that when one goes out, one does not have security and I think we feel strongly the need to develop stockpiles for all of the vaccines that we can. I think the most complicating factors are vaccines like influenza, for which you really can't stockpile. The other conundrum is dealing with new vaccines, such as pneumococcal conjugate vaccine, in which it's more difficult to predict what the market will be initially. And also when often a lot of the capacity may be going to just meeting initial need as opposed to the excess capacity, and that will need to -- be addressing and thinking about, as well.

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

DR. LEVIN: I wanted to ask Marty, was there any analysis of what went wrong in each case, if there was a technical problem and whether there's a technological fix like do we need better methods, more equipment, support for investing in these changes that might have -- avert some of these problems?

DR. MYERS: The format of the meeting was to look at strategies first from the perspective of the different groups, the stakeholders, and then to look at specific vaccines and to look at the issues related to each one. When you look at each of the different vaccine shortages up close, there are a lot of different types of factors. They're not -- there's no sort of common theme, although the issue of the older vaccines being commodities with low margins is a common denominator across a lot of the -- it's not all of the issues. It's really a multi-factorial -- it's not a simple answer, I guess -- not a simple question.

DR. MODLIN: Natalie?

DR. SMITH: Just I also thought the meeting was useful, and you already mentioned the communications piece, but the sense -- we did a number of these provider site visits ourself, and certainly the sense from the providers were confusion that -- first we had one antigen that was short, then another one, then another one, then another one, and trying to keep it all straight. And the plea to put that kind of information -- it is on NIP's web site, for instance, but not all sort of together at the moment. It's in different pieces, but the plea that we really work on that aspect. And also in communicating with the public that it's not a safety issue, per se; it's more of a production issue -- when that's the case.

DR. MODLIN: That's a good point. Mr. Reilly?

MR. REILLY: I'd just make a few general comments on behalf of the manufacturers. And I think first of all, I think you can see from your reports back from CDC and Marty and the agencies, we treat this very seriously and we are working very concentratedly to try to solve the problems

leading to the supply shortages.

I think this should also in a way be a reminder, though, that vaccines are complex products to manufacture. We are running into a lot of different types of problems. There is no single simple solution and it's across different manufacturers. It's also a highly regulated business or a highly regulated manufacturing process, and I think the complexity of the regulations and the complexity of the interpretation of the regulatory environment has been increasing quite significantly over the last few years.

I would pick up on the stockpile -- I don't like the use of the word stockpile. I think it's much better to think of strategic inventories, but it's the same thing. And I think what you're seeing is some of the problems we, the manufacturers, have always lived with. But they're more aggravated now and normally we are holding inventories that are sufficient to compensate for the variability in manufacturing processes.

You've seen on some of Dean's charts the variations in month to month shipments. And frankly, what's happening now is we are sitting with no inventories and each manufacturer is shipping as soon as he has product release. Normally you will get variations from month to month in your manufacturing output, but that will be compensated for by holding sufficient inventories so that you can have a steady supply or steady flow to the marketplace. And I think we're face -- you know, the variability issue that you're seeing is really something that's happened because the inventories have been stripped out. So we very strongly support a much more serious approach to holding strategic inventories in place by the CDC that would be a buffer between the variability of manufacturing and a steady, smooth supply.

DR. MODLIN: Thank you. Lucy?

DR. TOMPKINS: Marty, I had a question about manufacturers dropping out of the market. I know that you mentioned that prior notification in a timely way would be helpful, but were there any

other suggestions for how to keep manufacturers in the market, or what the incentives might be?

DR. MYERS: The answer is yes, there was a lot of discussion. There were a lot of issues that are really buried in that, varying from the price of vaccines is kept low, the older vaccines, and yet the manufacturing expenses may increase over time for the need to maintain a current good manufacturing practices. That's one example, which may lead to a business decision that isn't necessarily in the best interests of the public health. And so there was a lot of discussion around the issues of both sides of that equation and various incentives.

I think at this point we've tried to do is identify what sort of the basic problems were and come up with a sort of a strategic approach. And we're sort of early in that process. This is an opportunity for the NVAC working group and for the inter-agency vaccine group to begin -- with all of the stakeholders present, to begin to grapple with the problems and the magnitude of what some of the

solutions.

So it sounds like a simple thing to create stockpiles. Our inter-agency vaccine group met yesterday or the day before for three or four hours and there are extraordinary, complex issues. That's not an inexpensive proposition to create a rotating stock inventory of the type that Walt was talking about. So I think at this point what the inter-agency group is trying to do is come up with things that can be pragmatically implemented pretty quickly, and then some longer term strategies of the types that you and Myron were alluding to.

I think one of the big things that -- one of the really valuable at the meeting and a lot of other people that were there was -- everyone was saying and that is that we had all the stakeholders there and it's -- although everybody has sort of a different -- they're coming in with a different set of issues, they have this common urgency to try and find ways to ameliorate the problem, for the reason that when you make changes in recommendation or we make changes, we've missed opportunities at

immunization that we have a long-term outcome -- negative impact from that. I think that was a general consensus across the group.

DR. MODLIN: Sam?

DR. KATZ: Marty or Karen, I wonder, what consideration is ever given in the event of a shortage where there are manufacturers outside the United States who make high quality vaccines that might meet the same criteria? Is there any attempt to induce or offer incentives to other companies to come into the United States market?

DR. MYERS: Maybe I ought to take a crack at it first and then we'll let Karen answer because she sort of gets in a spot there.

DR. KATZ: And especially with a single source.

DR. MYERS: Not surprisingly, Sam, the whole issue about vaccines in other countries and should we shortcut the process, should we consider other ways of bringing vaccines in by bypassing certain steps, and it was generally consensus I think at the meeting that, from the credibility of the

vaccine program, there's a real value to having a standard, high-quality, licensed product in the United States. Using an IND product is very difficult, as we heard before, and that -- and including the manufacturers, so that this is really -- the issue is we need to have the quality product that parents will trust and that -- although some things that -- there were some suggestions that were made about the size of the truckload of paper that was needed and so on, but I think there was a general feeling that the -- it's true that the regulatory bar is raised because good manufacturing practices is an evolving process, but that that was a standard that we should expect of vaccines, particularly those that we administer routinely to normal healthy children.

DR. KATZ: But that is not to deny that there are excellent, high-quality products made in Italy and Belgium and a number of other countries, so it's really FDA's problem.

DR. MIDTHUN: No, we wouldn't deny that at all -- is this on?

DR. MODLIN: Yeah, it is.

DR. MIDTHUN: We wouldn't deny that at all, and certainly I would say we encourage anyone to come in with a license application. We need to have an application in-hand so that we can go through the process of evaluating the data and hopefully bringing something to licensure. And so certainly I guess a bigger question, Sam, might be -- and I think you just mentioned it -- what might be the incentive? I mean the incentive we can provide is that ultimately the goal is to be able to license new products. But I think that is there some other way through some other mechanisms to encourage or incentivize that process and that's -- we're ready. We're ready to work with anyone who wants to come in and try to work towards licensure of a product.

DR. KATZ: Thank you.

DR. MODLIN: We've got to bring it to some conclusion here, but Peggy, why don't you -- Peggy and then Stan and then I think we need to wrap this up.

DR. RENNELS: Just a statement, and that's that I think all of our credibility is very impaired when people like those of us sitting around the table find out that there's a vaccine shortage by our colleagues in practice calling us and saying I can't get vaccine, I don't know what's going on. And we are clueless. And it seems like we're always caught off-guard and reacting, and there needs to be a more proactive monitoring in some way.

DR. MYERS: That's a really important point and one of the messages that came out of the meeting is that though we need to have a mechanism to monitor supply -- and this is -- when I was talking about the communication, that's the piece that -- there are obviously some barriers to communicating, and one of the suggestions at the meeting was to find a mechanism by which information about vaccine supply could be available to us in a more timely and proactive fashion so we could anticipate. So for example, if a producer is going to leave the market, there needs to be a

mechanism for the producer to let the rest of the market -- and the governmental agencies -- make them aware of this so that they can anticipate and so on. This is one of the key recommendations that I think came out of the meeting.

DR. MODLIN: Stan Plotkin?

DR. PLOTKIN: Yeah. Two points about the NVAC meeting. One is, as Marty was just alluding to, one of Wayne Pisano's ten points was an industry pledge to let CDC know well in advance if there are going to be changes in vaccine supply, either because of production problems or because of marketing decisions.

The second point I wanted to make relating to the meeting was the most interesting paper at the meeting, from my point of view -- if I may say so -- was Boyd Clark from Aviron who gave a paper on the development of the intranasal flu vaccine. Now Boyd has a lot of experience in the industry, and the point he made was that when you talk about the cost of developing a vaccine for a big manufacturer, the costs tend to get lost in overall

employee costs and what-not. But he was able to calculate what it actually costs to bring a vaccine to the point of licensure -- and it's not -- of course not yet licensed. His figure, if I recall correctly, was $700 million. Now that may be, because of the history of this vaccine, that may be a little bit higher than most vaccines, but the point here relates to the question of how to incentivize manufacturers. And the problem is that a return on that kind of investment requires a high vaccine price. That is the nexus of the problem.

DR. MODLIN: Thanks, Stan. We do need to move on, and actually the next item on the agenda continues with the same theme.

DR. ORENSTEIN: I wondered this morning, John, if it would be worthwhile since we're potentially talking about varicella and MMR is to just hear from Merck in terms of what their projections are.

DR. MODLIN: Okay, do you want to -- shall we do that after Jane presents?

DR. ORENSTEIN: Whatever you --

DR. MODLIN: Okay.

DR. SEWARD: Good afternoon. Thank you for staying awake, and I hope we can go through this sad story fairly quickly.

I'm going to -- in order to be able to think about recommendations for use in limited supply of varicella vaccine -- myself, anyway -- I have to be able to understand the pre-vaccine epidemiology and were we are now with implementation of the varicella program, because we're in the mid stages of the vaccination program and there's still some disease around and we need to understand the post-vaccine epidemiology well, I think, to be able to make recommendations.

You've seen this slide before. Just quickly, the pre-vaccine disease burden, about four million cases of varicella a year, resulting in about ten and a half thousand hospital admissions and 100 deaths a year, most of these deaths and hospitalizations occurring in healthy children and adults.

Here we see the proportion of varicella cases in the orange bars, hospitalizations in aqua and

deaths in red, by age, showing that most of the cases occur in children, as you all know; about two-thirds of the hospitalizations and about half the deaths. And it's apparent here that there's a disproportionate risk of severe disease and death in adults, with less than ten percent of the cases, a third of the hospitalizations and a half of the deaths occurring among adults.

These risks by age are shown better here. The bars show incidence and the red line shows risk of hospitalization for every 1,000 cases, and showing that the lowest risk for hospitalization occurs in children five to nine and the highest risk by far is in adults. They have about a 14 times greater risk of being hospitalized if they are a case than children. A similar pattern for deaths, but more dramatic for deaths with adolescents and adults, adults having the highest case fatality rate, about 20 deaths for every 100,000 cases. And adolescents following adults and then children under one. Again, the much lowest risks in children one to four and five to nine, where most of the cases are

occurring.

Looking at age-specific incidence in a little bit more detail, often we describe these incidences in pre-defined age groups, like one to four and five to nine, which masks the real pattern of disease. So here you see from National Health interview survey data before vaccine was licensed, in fact the high incidence years were one or two through six. So as soon as children got into elementary school, they got chickenpox, if they hadn't had it already, and then you had a dramatic decline in disease after that.

And similar patterns from two state surveys in Kentucky and in Minnesota, showing the highest incidence years in the preschool years, but extending into early elementary, with peak incidence at six in two of these three studies, and at two years in Minnesota.

There's been a well-defined risk shown from attendance in child care, also. This was published ten years ago showing about a two times greater risk of getting chickenpox if you -- if a child

attended child care, and this was independent of presence of older siblings in the household.

So a summary of pre-vaccine epidemiology is highest incidence in the preschool and early elementary age groups, increased risk of exposure and incidence among children attending child care, and highest risk of severe disease in adolescents and adults, as well as immunocompromised persons.

Just very quickly, you should all know this, but there may be some new members on the Committee, the ACIP does recommend the vaccine routinely for all children susceptible to older children, as well as adults, two doses four to eight weeks apart, and there's also been updated recommendations for use of the vaccine post-exposure for outbreak control and for school and child care requirements.

So where are we with program implementation? Here we are with vaccine doses distributed, as Dean indicated, about 6 million doses distributed in the last two years, well above the birth cohort. We don't have very much data on doses administered by age. The data I do have to show you is from the

active surveillance areas where they do document administration by age, and here you see for 2001 in Antelope Valley and in West Philadelphia -- no, and in Travis County, Texas, which is just VFC data -- about half of the doses are going to routine childhood vaccination at one year, about ten percent of the doses is going to adolescents and adults, and about 40 percent to child catch-up.

I think Philadelphia is really cutting edge with use of the vaccine. They're vaccinating a lot more adolescents and adults. I think that is the exception rather than the rule.

With coverage, coverage rates 75 percent in the first and second quarters of this year, and with school requirements, as of this week 27 states have implemented child care or school requirements. Before the next school year four states will add school to their existing child care requirements and four additional states will implement child or school requirements or both. And some of those -- North Carolina, for example, was planning to implement in April.

We've talked to state health departments about responses to the shortages that exist right now of varicella vaccine. We certainly hear from them that they would prefer to maintain child care and school requirements if at all possible. However, we are aware that three states at least have temporarily suspended child care and/or school requirements, and these are listed here. Oklahoma just last week sent a memo out suspending child -- temporarily suspending child care and school. Connecticut has suspended school and Oregon had to suspend school because they do their roundup for their vaccination in January and February rather than waiting for the summer.

State health department responses vary for dealing with shortages. Several states, though they haven't suspended their requirements, have already implemented preferential vaccination to these groups, trying to maintain coverage of young children and those in child care and early elementary school.

So quickly now, post-vaccine epidemiology,

this is data from Antelope Valley in California, one of the three active surveillance sites, updated through January 2002, showing a continued decline in disease or stabilization of disease, with vaccine coverage reaching almost 90 percent one year ago.

And this shows reduction of disease in the two sites that are continuing active surveillance for this five years of the project, showing again to 2001, the data just completed, 75 to -- 76 to 86 percent decline in disease and evidence of herd immunity here with declines in children under one and adults. And also declines in severe outcomes of disease, hospitalizations, in the last three years.

Also in states that do passive surveillance, we can see a decline, a very similar pattern to the active sites, and a very similar decline in percentage also. Which is interesting because the coverage is lower in these states. So this is 2001 reduction in cases compared with average cases reported in '93 through '95, Michigan and West

Virginia, that have been typically good reporting states for varicella through passive systems.

Now I'm just going to quickly take you through changes in epidemiology in Antelope Valley. And here I'm showing cases by single year cohorts, and I'm calling that incidence because the births are approximately equal in each age group. So when the project started, the peak incidence was two to six. As you see, as the vaccination program proceeds, the disease is going down. But at the same time, age groups are shifting to the right. And so by this last year, in 2001, greatly decline incidence in all age groups, but peak years of incidence is now five to ten, where it started being two to six.

There's also evidence from Dennis Clement's studies -- perspective cohort studies in 11 child care centers in North Carolina, a decline in disease in both unvaccinated and vaccinated children, evidence of herd immunity and he reported to me yesterday there's hardly any disease transmission in those day care centers now.

So in summary, there's a substantial disease

decline in active and passive surveillance systems. There's evidence of herd immunity. In areas of high coverage, we see the highest incidence of disease in children five to ten years. I suspect that in areas with moderate coverage that the highest incidence may be a little lower than that. We know that children one year have low incidence and low risk of severe disease, and that adolescents and adults and high risk children are at highest risk for severe disease. By high risk children, I mean children with HIV, leukemia, asthmatics on steroids, et cetera.

So groups to consider for prioritization of varicella vaccine use are listed here, and this is what we propose the Committee consider for vote. Shall we have discussion first or will I present?

DR. MODLIN: Maybe the next thing we ought to do is ask if there is someone from Merck who would like to address the issue of both varicella and MMR at this stage and sort of serve as background. Thank you.

MR. BEEMAN: Sure, thank you, Dr. Modlin. My

name's Don Beeman, I work at Merck in the vaccine area. A couple of points I'd like to make. I mean we've had a good opportunity to interact with Dean Mason and I think he did an excellent job of covering the projections that we anticipate being able to deliver over the next few months.

We have been working very hard to ramp up our production and accelerate availability of vaccine because the biggest concern I think that we all share in, as many people in this room have already commented, is getting enough vaccine to the marketplace to meet demand and have a cushion there or a buffer, as was discussed earlier, to ensure that during other disruptions, we've got adequate supply so no one gets missed. In the short term, there could be situations where individual clinicians do have back orders, as Dean very clearly presented. We anticipate those back orders for MMR and for VARIVAX being cleared up probably by late spring. So over the next month or two, as Dean highlighted, we do anticipate vaccine supply to exceed normal demand in the marketplace. But

given that we've got back orders, it'll take a little bit of time to catch up there. So our goal is to work continuously with this group, with the CDC, to ensure vaccine is available and do our best to not have problems occur because children or others are missed.

DR. SMITH: Can I ask a question?

DR. MODLIN: Of course.

DR. SMITH: So catch up would be sometime in the summer, you would think, or --

MR. BEEMAN: I would think late spring, late April, May, depends a --

DR. SMITH: To take care of those back orders?

MR. BEEMAN: Yes.

DR. SMITH: And then secondly, since you're the distributor obviously, is there some mechanism so you're ensuring all providers have at least partial doses, or what's --

MR. BEEMAN: What we're trying to do is ship out vaccine as fairly as we can, so as orders come in, we fill those oldest orders first. We're also working with CDC on the public sector doing

everything we can to make sure if there's a dramatic need or a state has a certain level of supply already in place, that we don't short somewhere else on the public side in favor of someone that might already have vaccine. So we're working closely along those lines.

DR. MODLIN: Okay. Walt -- Jane, do you want to put up the proposed line that you're giving for use of varicella?

DR. SEWARD: Yeah and I'd like -- I guess I'd comment that I've worked closely with the AAP on this -- on these recommendations and with states, so the language is that there's currently a shortage throughout the United States. Vaccine providers should therefore prioritize their use of available supplies. If administration of varicella vaccine is delayed, vaccine providers should implement a call-back system when vaccine is available.

In the United States while a vaccine shortage persists, recommendations for use of the limited supply of varicella vaccine are: maintain

vaccination of health care workers, family contacts of immunocompromised persons, adolescents 13 and above, adults and high risk children. I estimate that this group will use about ten percent of the annual doses.

Secondly, to maintain routine childhood vaccination but to delay the 12 to 18-months dose until 18 or 24 months, unless the child attends a child care center.

Three, to maintain vaccination of susceptible children five to 12 years, with focus on children entering school and adolescents 11 and 12 years. States should provide guidance on priority cohorts for vaccination.

And then four, maintain vaccination of children two to four years who attend child care centers.

DR. MODLIN: Let me just quickly ask Jon or Gary how they feel about this aspect of the recommendation.

DR. ABRAMSON: Yeah, I think -- Jon Abramson. I think we're in agreement, but my problem is that

it's too complicated. And I honestly prefer just number two. And basically all we're saying is do everything you're doing except delay the immunization of children reaching -- who wold get the booster dose at 12 months, take 18 to 24 months. If it gets more complicated than that, we -- I'm afraid that we won't get anything done. And since the shortage well may be only for the next four to six months, that recommendation two alone would deal with the shortage if it only lasts the length of time predicted.

DR. MODLIN: Well, that raises a critical issue, and I guess I'd ask you, Walt, if we aren't zigging when everyone else is zagging here. In other words, how long would it take for an ACIP update or recommendation to get through the editorial process and in MMWR and be published and be disseminated and --

DR. ORENSTEIN: It would be about two weeks, I would think, if we -- if all went well.

DR. MODLIN: So it could be done fairly quickly.

UNIDENTIFIED SPEAKER: This would be in a weekly, it wouldn't be in a recommendation report.

DR. ORENSTEIN: Right, right, and it would be very, very short and clearly once we're -- we know where we're going, there are other ways of at least trying to notify through e-mail or other organizations that may also use e-mails to get the information out.

DR. MODLIN: Peggy?

DR. RENNELS: I think the -- I fear the reality is, practitioners have no way to predict what their supply is going to be until they run out, and then they find that they don't -- you know, the order doesn't come in and they don't know when it's going to come in, and so I think the reality is, some practices are going to run out of vaccine and then what do they do? They're going to postpone until they get vaccine. And so I think the reality is if you run out of vaccine, you're going to just recall the kids when you get it at their -- or wait till they come into their 18 or 24-month routinely-scheduled visit and give it

then.

DR. MODLIN: And that's going to hold for both MMR and varicella, I would assume.

DR. RENNELS: I fear. I fear.

DR. MODLIN: I think you're right. Walt?

DR. ORENSTEIN: I would just say -- it certainly will happen, although I think from the data from Shannon Stokley, at least some are implementing some of the changes so that while we realize that this is really a stopgap limited measure, it may save some providers some vaccine. I think that -- clearly we're all concerned about what happens in three or four months, how short-term will it be, will this really be long-term, will the projections actually come to pass -- because we're also basically saying that if we postpone this, there'd better be a hell of a lot of vaccine available in a number of months because I think we all would like to come back down with a dose at 12 to 18 months rather than leaving it at the higher age.

DR. MODLIN: That was going to be my question.

Is your best estimate that this is a measure that needs to be done now or published now, or is this something that we could do like we've done in the past, which is the Committee basically agree that if -- based on your estimate at some time between now and the next meeting that if it's necessary to institute such a recommendation, that we would basically delegate the program to go ahead and do so. We did that in the past with DTP, as I recall, DTaP, successfully, and I wonder how you would -- and Melinda would feel about that as an option?

DR. ORENSTEIN: I think -- I guess our feeling was we need to do this now. We're hearing enough problems. The obvious thing is what we don't know is whether -- when the -- whether the projections will come out as they are, and by the time this happens, whether it's unnecessary. But we're certainly seeing -- hearing enough problems right now. We saw some of the data from Shannon Stokley on varicella that I think something needs to be done.

DR. SEWARD: I might add that we did -- sorry.

We did -- Kelly, the APHA fellow who works in varicella, called all the states that have requirements, and a number -- I mean three had suspended, many were about to and they're waiting for ACIP recommendations, so you really -- and a lot are worried, like Natalie has shared with me. You know, can she wait till the summer for her school requirement in California? Some can wait, but some can't.

DR. MODLIN: Rick and then Jon.

DR. ZIMMERMAN: I like Jon Abramson's idea of highlighting number two. I wonder if we could, instead of being perhaps so direct, qualify it -- if the provider has a vaccine shortage, rather than basically -- this is giving direction, whether you have 100 doses or none, do this. What if we qualify by if you're experiencing a vaccine shortage?

DR. SEWARD: Yeah, that's in the language before, but actually it was intended to be a national recommendation because it's fairly hard to monitor the supply of this vaccine. But I'd ask --

I don't know what --

DR. SNIDER: Yeah, I guess Rick -- I wonder -- I'd like to hear some thoughts about it because I would wonder if that doesn't feed into what Peggy was talking about earlier. If you don't have a shortage, you just keep using it and then you're out and then you're not giving it to anybody. I think what we're trying to say is don't give it in the 12 to 18 month; defer it to this age group and we hope that deferral is going to be enough to get us over the hump. And say it to everybody instead of just some subset.

DR. BIRKHEAD: But that vaccine then just sits in the provider's office for that period of time?

DR. SNIDER: No, they use it for these populations.

DR. MODLIN: They use it for their older kids and they delay the likelihood that they'll be short as a result of that.

DR. ORENSTEIN: But it would sit, because if essence they've been vaccinating at 12 months, then those kids are going to age through and won't need

it at 18 months so that it would be sitting in the offices, potentially.

DR. SMITH: And I think that there's a perception out there that somehow redistribution is going to take care -- place it at the provider level, and that's extraordinarily difficult and I think rarely happens, so.

DR. MODLIN: Peggy?

DR. RENNELS: I didn't mean to imply recommend to the whole country, delay. I think the -- what I'm saying is, the reality is, 12-month-old kids are going to come in. They're not going to have vaccine and so we tell them, you know, vaccinate them at 18 to 24 months when they come back for their next well child visit. Simple, I think it fits reality.

DR. SEWARD: And what if that's not enough?

DR. RENNELS: And by then I'll be off the ACIP.

DR. MODLIN: Honest answer. Jon, did you have another comment?

DR. ABRAMSON: I hate to tell you this, but I

actually -- I'm thinking about varicella and MMR differently. I'm looking at varicella as a true recommendation. I think the shortage is severe enough that we have to recommend delay. And I'm not saying that will result in everybody stopping and a true redistribution the way you would want. But it is severe. It's very clear to us at the Academy, with the number of calls we're getting, that it's severe, and I think we have to make a true recommendation.

For MMR, I'm not convinced that it's severe enough that we have to do that, and rather -- in that case, I'd like to provide guidance, as we do for DTaP. So in one sense I'm making -- it's a confusing recommendation because we're making one a recommendation for varicella and another a guidance thing. But as Walt and I talked about it at lunch, skipping that dose of MMR has substantially more implications as far as the disease burden than not skipping it, but delaying it from 12 months to 18 months, than it does to say with MMR don't give the second dose if you don't have the vaccine.

DR. ORENSTEIN: And in fact the draft that we will show you is very much along those lines of an individual physician-based kind of decision-making on MMR.

DR. MODLIN: Okay. Deb, did you have a comment? And then we need to kind of close up this --

DR. WEXLER: I was just trying to figure out what -- Deborah Wexler, Immunization Action Coalition -- what is being undone by all these maintains. What I see is who you're not vaccinating would be the 12-month to 18-month-olds and also the two to four-year-olds who are not in day care. And maybe you want to say that clear -- I mean if that's what you're undoing, maybe you should just say that, so --

DR. SEWARD: Yeah, that's an --

DR. WEXLER: -- stop vaccination of two to four-year-olds who are not in day care.

DR. SEWARD: Yeah, that's another way we could do it. We've gone back and forth. We could put the -- children at the bottom and say do not

vaccinate children at 12 to 18 months, wait until 18 months to two years, and then have it as a priority listing; if that's not enough, then stop vaccinating children two to four not in child care. If that's not enough, then make decisions in the five to 12-year-old catch-up group.

DR. MODLIN: Okay. Yes, Georges?

DR. PETER: I would urge that we strengthen number three in the sense that we do not recommend suspension of school laws and day care center requirements, if at all possible, because at least if children don't receive it at 12 months or even at 24 months, you have a chance to enforce it at school entry. If you lose them at school entry, you've lost them.

DR. MODLIN: Good point. Larry?

DR. PICKERING: I just have a comment about child care. If you want to add confusion to it, you should include that. Day care centers account for about 20 percent of the children that are in some day care facilities. They average about 55 children per center. They're regulated and so on.

Day care homes are smaller units that care for an average of 6.2 children per home. They're not regulated, and we have, I think, Jane, very little data about varicella in day care homes. Most of the studies have been done in day care centers. So if you're going to include child care centers, then you really need to be very specific and define what a child care center is because there's a lot of confusion in differentiating those two.

DR. MODLIN: Eric?

DR. FRANCE: I think -- this is Eric France. I think it's important to remember that if these are the priorities that we try and get a sense of how many doses are actually going to be coming out in the next few months because it may be that it's such a small supply that we focus on health care workers, family contacts and adults, and consider whether or not we can -- we even have enough of a supply in the next two, three months to provide any vaccination for young children. I know at K-P Colorado, Kaiser-Permanente Colorado, I don't think we have any doses right now. And when we do have

them, they're prioritized for families of immunocompromised members, and we're going to hold off on giving them to children so that that number one priority can be hit. And you might then take that to a national level and say is there enough of a supply to go beyond number one, but down to number two and number three expected over the next few months. And if really it's -- it's really quite diminished nationally, then we might be really focusing more on health care workers and adults.

DR. MODLIN: Dean, do you want to address --

MR. MASON: I'll try, yeah. Understanding that some of this is proprietary and can't be discussed in terms of absolute numbers, variables, you know, respect to all goes well in production and FDA process. But basically, national need for varicella vaccine is -- may be 550,000 to 600,00 doses a month. That's not including catch-ups or inventory build-ups, just the national need, dose per child. And what I can say is that for March, April and May, the next three months, the

projections would exceed the national need in every one of those months, if all goes well. And indeed in one of the months, the projections of the rollout would come reasonably close to doubling what the actual monthly need is, if that helps.

DR. MODLIN: Thanks, Dean, it does, a lot. It sounds like we need to act on each of these issues separately. They are sufficiently different, varicella and MMR. Let me entertain a motion that we -- the ACIP recommends the prioritization for varicella vaccine and the -- so long as there is a real shortage and that we do have a set of priorities before us. At this hour of the day, I think I've been sufficiently vague.

Is the Committee ready to act on Dr. Seward's recommendation here?

DR. ZIMMERMAN: The question I have is do we need to do the whole prioritization or can we follow Dr. Abramson's suggestion about just delaying that one cohort?

DR. MODLIN: Okay. It sounds to me, from what Dean just said, that we might -- may be able to get

by. Walt, what's your feeling about this?

DR. ORENSTEIN: I would think that certainly by delaying that one cohort, you ought to be freeing up a hell of a lot of doses that would make --

DR. SMITH: With the idea that we will have explicitly voted on the other prioritization if the shortage doesn't get better. Is that the idea?

DR. MODLIN: Yes.

DR. SMITH: At this meeting. Right.

DR. MODLIN: Gary?

DR. OVERTURF: Yeah, I really have to emphasize again that we really need a strong, single recommendation for that delays, the only simple thing to do. If you want to put down that, in a second sentence, that you maintain all the other things, that's fine. But it really need to be up front with that simple recommendation to delay to 12 to 18 -- 18 to 24 months.

DR. MODLIN: Okay. Let me ask the members of the Committee if you would like to see new language on this or whether you are comfortable with what we

have before us now to go ahead and take a vote this evening, or whether you'd like to take a second look at this early in the morning. Lucy's saying no. Let's go ahead and deal with it?

DR. TOMPKINS: I'm ready to vote.

DR. MODLIN: Pardon?

DR. TOMPKINS: I'm ready to vote.

DR. MODLIN: Okay.

DR. BROOKS: We'll vote with the proviso that the important language on delaying the dose to 18 months would be the key point. Is that what I'm hearing? And the rest would be just --

DR. MODLIN: You're comfortable leaving the language and wordsmithing up to --

DR. BROOKS: Yes.

DR. MODLIN: -- Dr. Seward and to the program. Good. Everyone is nodding their heads yes. Okay. I still will entertain a motion.

UNIDENTIFIED SPEAKER: So moved for item four.

DR. MODLIN: Okay. It's been moved and --

DR. TOMPKINS: Second.

DR. MODLIN: -- seconded by Dr. Tompkins that

we adopt this recommendation.

DR. SEWARD: We're delaying the infant dose -- the childhood dose for children not in child care only, 12 to 18 months, to give it at 18 months or 24 months.

DR. MODLIN: Do we want to add something at the end of this as to when we would be comfortable going back to 12 months of age and that there would be yet another update that would notify --

DR. ORENSTEIN: Well, I think we have to have another update that -- I think we need to have in there that it is hoped that we can return to that schedule by late spring to early summer; however, we will be notifying you when we recommend a return. I think that, to me -- we certainly don't want to put a date for return, but we want to get the message across that our goal is not to keep that as a permanent schedule.

DR. SMITH: And I think if you could put in the web site of where this information's going to be so that providers can keep checking, if they want to, on the NIP web site.

DR. MODLIN: Well, it sounds like it's going to be -- it's certainly going to be published in the MMWR and that will be the -- as all of our recommendations, that will be the place at which it does become official.

DR. BIRKHEAD: I did like the suggestion, though, before to have all this information on all the delays in one spot on the web site where they can all be found together.

DR. MODLIN: I think that's certainly possible. Melinda and then Bonnie.

DR. WHARTON: Just a point of clarification so that I understand what it is the Committee's about to vote on, is this a recommendation for all providers, whether or not they personally are experiencing shortages, or a recommendation for providers who are currently experiencing shortages?

DR. MODLIN: My interpretation is that this is all providers. I think our --

DR. WHARTON: That is how it was proposed.

DR. MODLIN: It is. Our expectation is that we hope that many providers will follow suit, but

as Peggy was pointing out to us, the likelihood is that there will be some partial following of this recommendation. Jon?

DR. ABRAMSON: I must admit I have concerns about throwing in non and child care, because it's muddy waters. You remember when we got into Prevenar we got into 80 percent by the Academy's -- 80 percent of children in day care versus 20 percent by the CDC. I think we need to leave it out. We need to deal with it. At 12 to 18 months, the risk is what the risk is. It's fairly low.

DR. SEWARD: And the risk is probably lower now, too.

DR. ABRAMSON: And then down in a paragraph below, write anything you want about prioritization thereafter. But the message needs to be crisp and clean. Delay the immunization in children 12 to 18 months.

DR. MODLIN: How do others feel about that?

DR. SMITH: I totally agree. I think we need a simple message. And we've got 50,000 family day care homes in California that -- it just gets very

complicated.

DR. MODLIN: For an interim recommendation, the simplest message is the best.

Is everybody clear about what we're voting on?

Those who are conflicted with Merck? Dr. Rennels, Dr. Offit, Dr. Levin.

Okay, those in favor of the motion? Those in favor are Dr. Smith, Dr. Zimmerman, Dr. Tompkins, Mr. Salamone, Dr. Deseda, Dr. Brooks, Dr. Birkhead, Dr. Word and Dr. Modlin.

Those opposed? And those abstaining? Those abstaining are Dr. Offit, Dr. Levin and Dr. Rennels.

Let's take up measles. Melinda.

DR. WHARTON: It is our hope that the MMR shortage will be short-lived, and you've already heard an update on this from both Dean and manufacturer. And the question we have for you is does ACIP wish to make recommendations to providers in order to provide them assistance in how to respond to this shortage.

What we are proposing is guidance to those

providers who are currently experiencing shortages, not a recommendation for all providers. And perhaps this language could be improved, but what we came up with this afternoon was: If providers are experiencing difficulties in obtaining all the MMR they need to fully implement the current recommendations for MMR vaccination, ACIP recommends that they defer the second dose of the MMR vaccine series and institute a tracking system so that unvaccinated persons can be identified and recalled for vaccination when supplies improve.

DR. MODLIN: Since there inevitably will be implications for school entry, do we need to add something to that effect that -- similar to what we just did with varicella?

DR. SEWARD: We didn't add anything.

DR. BIRKHEAD: What did we do with varicella?

DR. SMITH: It's sort of being triggered later.

DR. WHARTON: Again, this is an issue which really came to the forefront today, and it's my understanding that the feeling is that there at

least are spot shortages of MMR. Walt, would you --

DR. ORENSTEIN: I think our impression is that if all goes well, then by sometime in the spring supplies will return to normal. I think what we're trying to say here is if -- we hope that the numbers of providers soon will be very limited, but if they -- there are providers having problems, and we know there are providers having problems, that some guidance might be helpful. And certainly we would not want them to just run out of all their MMR and not give first or second doses, that we would prioritize to the first dose.

DR. MODLIN: So this is very different. We're not making a recommendation to all providers. We're making a recommendation to those providers who are running short.

DR. ORENSTEIN: Right, right. Our hope, in fact, is that the numbers of people who this might apply to will be limited. But I think a lot of it depends on projections and whether everything goes well through production and lot release and all the

other aspects of production.

DR. SMITH: Because we certainly won't -- I don't think we want to get into the position of suspending our measles requirements.

DR. ORENSTEIN: I don't think we're saying that here. This is similar to what I think we initially did with DTaP about -- where we said to, on an individual provider basis, if you can't get enough, suspend dose four, and then if necessary, suspend dose five. Here we're just saying that if you can't get what you need, suspend dose two.

DR. WHARTON: And Natalie, if -- assuming this is just a matter of the next few months and there would be an opportunity for catch-up before school starts in the fall, what degree would a recommendation like this impact these children as far as school entry's concerned?

DR. SMITH: Some states -- it does hit sort of late summer, but a lot of states do their kindergarten roundups and other roundups in the spring, so it would affect states. In our state we would probably just let those few kids in

conditionally and not do a blanket withdrawal of the requirement. How about New York?

DR. BIRKHEAD: It would be similar. I think they'd have to have some physician note that they were in progress. There's no mechanism for us to suspend our school, but a physician note of in-progress would probably be sufficient.

DR. MODLIN: Yes?

MR. HAUPT: Hi, Rick Haupt from Merck. The other -- in consideration of this, the other thing you might consider is delaying the second dose till five instead of giving it at four, because there are a lot of providers who give their second dose of MMR at four years of age. And if you just recommend to them wait till five, then you still have the school age catch-up, you still can get those children to have their vaccine before school and you may buy some time if you're worried about extra doses.

DR. MODLIN: That may complicate things a bit. Some states are first grade, some are kindergarten -- most are kindergarten, are they now not, Walt,

for school entry?

DR. ORENSTEIN: It's kindergarten, and I think it would complicate things. I think -- my hope is this is going to apply to very, very few people in the near future. But I mean if not, I think we need to at least help people in prioritizing.

DR. MODLIN: Marty?

DR. MYERS: I'm confused. Doing a little math, it should be two and a half million doses in a stockpile. Why can't more of those doses be utilized to smooth out the disruption of in fact we're anticipating a return of vaccine supply in three to four months?

DR. ORENSTEIN: I think perhaps we ought to ask Bob. Do you want to comment on why there are problems with this -- drawing down that number of doses?

DR. MYERS: It just seems to me if we have the stockpile -- we were just talking about this where solving these problems in the future for other disruptions, that maybe before we consider putting out guidelines like this, we ought to anticipate --

we ought to at least explore the possibility of increasing the supply short-term.

MR. MASON: I'll be the fall guy for Merck. It's our impression that these projections for the next three months include our stockpile.

DR. MYERS: I think maybe we ought to hear that confirmed.

MR. BEEMAN: I mean we've been working over the last few weeks and months to make sure there's as much vaccine in the stockpile and in normal production to get out there. Over the next few months we expect to have, as Dean outlined, enough vaccine that far exceeds what supply -- or I'm sorry, what normal demand would be. That includes doses from the stockpile and doses coming through normal production. So we would anticipate, you know, millions of doses becoming available, portions from the stockpile working with the CDC and portions through ramped-up production and trying to accelerate our ability to supply.

DR. MODLIN: Does that clarify things for you, Marty?

DR. MYERS: Not really. I guess I -- it seems to me -- what we're really talking about is a profound change in immunization recommendations, and we're talking about measles, mumps and rubella, three of the single most important vaccines. We're talking about making a change in recommendation, and what we've seen is every time we make a change in recommendation we have a coverage problem and so on, and it sounds like we don't have all of the dosage flow information expected from the manufacturer. We do have a substantial stockpile. And if we're going to spend a lot of time and not insignificant money developing other stockpiles, we'd better understand the use of the stockpile in this disruption, which is expected to be short-term. And I think it's very important that we understand that before we consider making guidelines for changing recommendations.

DR. MODLIN: It's an important point. Neal?

DR. HALSEY: Just to reemphasize Marty's point, and there's also an issue that no one here has brought up yet but I think will be mentioned

tomorrow and that is the continued controversy over MMR and potential adverse events, any statement you issue on MMR that is interpreted as delaying, deferring or somehow we shouldn't be continuing might very well be misinterpreted. So I would be very cautious in what you say, and I think the least disruptive might be the delay of the age four to age five, but you just really have to be very cautious in anything you say. It'll be over-interpreted and over-used.

DR. MODLIN: That's a good point. Rick?

DR. ZIMMERMAN: Could -- in my notes from the earlier -- in our discussion, the supply was supposed to be better in March, which would be about -- supposed to be improved in --

UNIDENTIFIED SPEAKER: Next week.

DR. ZIMMERMAN: Yeah, which is fairly soon, and maybe we need to clarify --

DR. MODLIN: I think the supply will be better, but I think there's still considerable question as to whether it will be adequate or not, is what I'm hearing from Walt and --

DR. ORENSTEIN: Yeah, I think the concern is we're not clear that the supplies will return to normal until springtime, even with the stockpile. And now spring is March 21st, but I think what we're hearing is a little later in the spring than March 21st, and so I think what we're doing is rather than making a blanket recommendation is trying to give some guidance to those providers who are having troubles, and we know there are providers that are having troubles getting the MMR they need.

DR. MODLIN: Well, for the voting members of the Committee, we can deal with this now, we can decide not to deal with it and have a conference call two weeks from now or a month from now. I think we do need to deal with it right now. What is the sense of the Committee on this recommendation? Let me just go around -- Natalie?

DR. SMITH: I certainly thing delaying the second dose is the simplest message. I think we're going to have to be careful how we communicate this already that -- you know, that it's very limited.

DR. MODLIN: How do others feel about this?

DR. ZIMMERMAN: One of the questions I had was could this be a -- something similar to the DTaP where the ACIP empowered language like this should the Immunization Program or CDC feel it was necessary to communicate it.

DR. MODLIN: Sounds like we're already there, Rick, is what I'm hearing from Walt.

MR. MASON: John, perhaps -- could I give you the numbers again, if that would help you --

DR. MODLIN: Sure.

MR. MASON: -- in your deliberation? Our national need is about a million doses a month for MMR. What we are estimating for the next three months -- and this, we believe, includes the stockpile, Marty, which we have remaining of 2.4 million doses. We believe that for the next three months there will be potentially up to twice the national average need, if you average those three months together. So that would be something less than six million doses available over a three-month period, not necessarily uniform availability each

month, but over the average national need each month and potentially up to about twice the national need for maybe one month.

DR. LEVIN: So what's left in the stockpile?

DR. MODLIN: Dean, I'm sorry. Myron asked what's left in the stockpile.

MR. MASON: We think 2.4 million doses, which will be part of this three-month projection.

DR. MODLIN: Over those six million doses over the next three months, that includes the 2.4 million doses in the stockpile.

MR. MASON: That's correct.

DR. ORENSTEIN: All most all of what would be coming out would be stockpile.

MR. MASON: I'm sorry?

DR. ORENSTEIN: If for three months -- if it's a million doses a month is the need and that's three months, and we've got 2.4, the vast majority of doses that would be coming out would be the stockpiled doses.

MR. MASON: Well, up to six million will be available, so it's not quite a majority, 40 --

maybe 40 percent.

DR. ORENSTEIN: I'm just wondering if maybe the empowerment issue would be the thing, and we will try and get some better assessments of -- this is only something we learned at lunchtime and --

DR. SMITH: Is there a way to get a better assessment by tomorrow morning?

DR. MODLIN: I think so. Rick, did you have something else?

DR. ZIMMERMAN: I was just pointing out to go over to four million, two doses, eight million, six million projected, eight million needed.

DR. MODLIN: Yeah. I tell you what, it is late in the day where we're probably at a higher risk of making a bad decision. Let's take this up at 8:00 tomorrow. Hopefully we will have -- with clearer heads and maybe clearer numbers, and maybe we can deal with it fairly quickly.

Wait a minute -- two announcements. First of all, for the voting members who have a yellow packet in front of them, please see Gloria now as you leave the room. Secondly, Myron, do you want

to make an announcement about the rotavirus group? Or you can just let me know -- 7:00 o'clock at the Magnolia Room for the rotavirus working group.

And again, we will start at 8:00 sharp in the morning.

(Meeting adjourned at 6:50 p.m.)

C E R T I F I C A T E

G E O R G I A)

DEKALB COUNTY)

I, Steven Ray Green, being a Certified Court Reporter in and for the State of Georgia, do hereby certify that the foregoing, consisting 383 pages, was reduced to typewriting by me personally or under my supervision and is a true, complete, and correct transcript of the aforesaid proceedings reported by me.

I further certify that I am not related to, employed by, or attorney or counsel for any parties, attorneys, or counsel involved herein; nor am I financially interested in this matter.

WITNESS MY HAND AND OFFICIAL SEAL, this ____ day of March, 2002.

_____
STEVEN RAY GREEN, CCR-CVR-CM
CCR NO. B-2102

[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

The verbatim transcript of the ACIP Meeting held at the Marriott Century Center in Atlanta, Georgia, commencing at 8:00 a.m. on Thursday, February 21, 2002.

C O N T E N T S

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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(Continued)

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(Continued)

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Mr. Dean Mason (NIP, ISD)
Dr. Tim Mastro (NCHP)
Dr. Alison Mawle (NCID, OD)
Dr. Walter Orenstein (NIP, OD)
Dr. Lance Rodewald (NIP, ISD)
Dr. Kathleen Stratton (IOM)

AUDIENCE COMMENTS:

Dr. Robert Chen
Dr. David Fedson
Dr. Roger Glass
Dr. Neal Halsey
Dr. Neal Halsey
Ms. Barbara Houk
Dr. Albert Kapikian
Dr. Dave Morens
Dr. Larry Pickering
Dr. Stan Plotkin
Mr. Tom Vernon
Dr. Dick Ward
Dr. Melinda Wharton
Dr. Tom Zink

P R O C E E D I N G S

8:00 a.m.

DR. MODLIN: We have a quorum. The voting members are here, even though not everyone else is, and we will continue with the February ACIP meeting. First up on the agenda will be to continue the discussion we left off with last night regarding the Committee's response to a potential MMR shortage and the guidance and recommendations that the program -- that the NIP is seeking in terms of being able to deal with this over the short run. Walt, do you want to lead off?

DR. ORENSTEIN: I think what has happened on the MMR supply issues is very late information, new developments, and perhaps it's premature to try and actually make a recommendation based on the numbers. But what we're asking for you, as we further investigate this issue and learn more, is to get the same kind of permission we've gotten with DTaP is should we, in looking at this feel that there is significant supply problems that we can issue a recommendation of priority use so that rather than trying to figure out how many exact doses we have -- we're not asking for a recommendation for a major change in the schedule, but some potential guidance, because quite frankly we

don't have the numbers together to try and completely understand the situation, although we are concerned. And so if Melinda can put back up her language, which would be a -- basically guidance for individual providers that we would issue if, on further look, we feel the situation is of great concern.

DR. MODLIN: So the question on the table, is the Committee comfortable with issuing sort of provisional guidance that if, in the opinion -- the judgment of the program, the NIP, that there was a significant shortage, they could go ahead and issue guidance under the ACIP imprimatur regarding delay of the second dose of MMR and this language would -- or language close to this would be appropriate for such -- which I presume would be an update in MMWR.

DR. ORENSTEIN: A notice to readers, yes.

DR. MODLIN: Any discussion regarding this?

DR. SMITH: Sounds reasonable.

DR. MODLIN: Dr. Smith says it sounds reasonable. Are you willing to make a motion to that effect?

DR. SMITH: I make the motion to accept this language in the event that --

DR. ZIMMERMAN: Second.

DR. SMITH: -- there's a shortage.

DR. MODLIN: Okay, the motion has been made and

seconded -- made by Dr. Smith and seconded by Dr. Zimmerman. Further discussion? Dr. Abramson?

DR. ABRAMSON: It's clear to us that we're going to have to -- we agree with this -- what you're doing, but it's clear to us we're going to have to provide guidance at this point. So it's going to have to go up on a website basically now because there are too many people calling in saying they have no vaccine, what should they do. And so I realize -- I think, if I understood what you were saying, you may or may not issue this, based on what you perceive as the true shortage or not over the next piece of time. But right now we're having people who do not have vaccine or are at very low supply and we're going to have to issue this guidance. I just wanted to make that clear.

DR. MODLIN: That's fine. Presumably if you're in direct communication with the NIP, I would assume that you could easily work that out.

Further discussion? Okay, those who are conflicted with Merck would be Drs. Offit -- Dr. Offit and Dr. Pennels. Okay.

Those in favor of the motion? Those in favor, Dr. Smith, Dr. Zimmerman, Dr. Tompkins, Mr. Salamone, Dr. Deseda, Dr. Brooks, Dr. Birkhead, Dr. Word and Dr. Modlin.

Those opposed?

(No response)

DR. MODLIN: Those abstaining? Dr. Rennels and Dr. Offit. Thank you.

At this time I'd like to ask Dennis Brooks to give us a brief update on the progress of the working group that he's been heading on a slight revision on -- or a slight update on the rabies immunization statement.

DR. BROOKS: Good morning. Yesterday John mentioned that there was a rabies vaccine supplemental statement that was in your packets. I just wanted to give you some historical perspective on why that statement is in there.

The work group members included the following individuals, which were very helpful. Excuse me if I've spelled anyone's name wrong. The goal of the rabies work group was to develop a supplemental statement of the current ACIP recommendation on human rabies prevention in response to the recent discontinuation of IMOVAX rabies ID vaccine. The issue regarding IMOVAX was brought to the Committee in June of 2001 by Dr. Charles Rupprecht. As he stated, IMOVAX is the only rabies vaccine licensed for ID pre-exposure use. It's important to note that the exposure vaccination is considered for those at high

risk for exposure -- veterinarians, animal control officers, laboratory staff. And IMOVAX at that time was considered the most economical pre-exposure use that was available priming those individuals if they did get exposed.

The supplemental statement that the working group came upon was basically just to state the facts related to the particular issue. This statement is a supplement to the Advisory Committee on Immunization Practices recommendations regarding human rabies prevention in the United States in MMWR in 1999. As of 2001, Aventis Pasteur discontinued sales of IMOVAX rabies ID vaccine manufactured for intradermal pre-exposure use.

Administration of rabies vaccine is intended for individuals at high risk, as I said before, and travelers to endemic dog rabies areas.

I think the most important part of the statement is stating what alternatives are available to those individuals who need pre-exposure. While this intradermal preparation is no longer available, three other products are licensed and available in the United States for either pre-exposure or post-exposure prophylaxis, administered in one milliliter intramuscular doses: human diploid cell vaccine, chick embryo cell vaccine and the rabies vaccine

absorbed.

We wanted to encourage further research and the development of safe additional effective and economical -- and we probably should highlight economical, but we'd want to just make it the way it was -- biologicals in human rabies vaccine. We did not want to encourage any off-label use of the current rabies vaccine, so we wanted to just state the facts as it was.

We'd like some comments on this prior to or up to March 1st, so if you have any comments on the statement that is in your text, please e-mail me or Chuck Rupprecht and that'll be very helpful to us.

Are there any questions?

DR. MODLIN: Dennis, thanks. This obviously represents largely information, but it does require a supplement to the rabies statement -- information rather than new policy, and I'm not certain that -- we certainly don't have to make a decision today, but if there -- if you would take a close look at the language in the statement here -- pardon?

DR. SNIDER: I think there would be no conflicts if you did want to take a vote.

DR. MODLIN: Okay.

DR. SNIDER: Because it is a factual -- it's a factual

statement.

DR. MODLIN: Right. Well, Dennis, I don't know why we shouldn't deal with it right here and now.

DR. BROOKS: Okay.

DR. MODLIN: Is there anyone who has any comments or questions or issues regarding this change? You're all shaking your head. Okay, those in favor of this change to the supplemental -- or to making a supplement to our current rabies statement? Those in favor are Drs. Smith, Zimmerman, Tompkins, Mr. Salamone, Dr. Rennels, Dr. Deseda, Drs. Brooks, Offit, Birkhead, Word and Modlin.

Those opposed? None. Those abstaining? None. Dennis, thank you very much.

We have one more item of leftover business before moving on to the reports. Drs. Word -- Bonnie, do you want to go ahead and introduce the topic or do you want Carolyn to?

DR. WORD: I don't know if Carolyn wants to start, but I know you thought we'd finished with influenza yesterday. However -- it's very small and brief. Towards the end we voted on just one of the comments or additions in terms of household contacts of individuals, and the vote went around. It was sort of split. If you looked at it, we broke it down by less

than six months of age. The reality of it is, the recommendation was to expand it to children six months to 23 months of age. Without that it could anticipate -- or should I say it would perpetuate a lot of telephone calls for the parent who has a child seven months old, who's eight months old who calls in the office. And just to avoid that and for more consistency, Carolyn and some others have come up with some modified language. And so we just want to run this by you to see, just for consistency purposes.

DR. BRIDGES: So yesterday what was voted on was to encourage vaccination of household contacts of children zero to less than six months. The suggestion late yesterday afternoon was to modify that, which is in the second part in blue, which is to change it to say (reading), Because children zero to 23 months are at increased risk of flu-related hospitalization, vaccination is encouraged for their household contacts and out-of-home caretakers, particularly for contacts of children age zero to less than six months since children less than six months cannot be vaccinated against influenza.

So it puts the emphasis on household contacts of children less than six months, but then also includes the whole age range for which a vaccine is now going

to be encouraged.

DR. MODLIN: Which for many of us is probably more consistent with the other things that we're trying to encourage, and this was the -- as Bonnie mentioned, the -- what led to a split vote on the part of the Committee yesterday.

Why don't we see if there are comments or questions regarding this proposed change to what the Committee did vote on yesterday.

(No response)

DR. MODLIN: Seeing none, those who are conflicted with Wyeth or with Aventis, who are Drs. Rennels and just Peggy, is that correct? Okay.

Those in favor of this change -- actually what we probably should be doing is voting on adoption of this language, which is the bottom paragraph here for the influenza statement.

Those in favor? Those in favor, Dr. Smith, Zimmerman, Tompkins, Mr. Salamone, Dr. Deseda, Dr. Brooks, Dr. Birkhead, Dr. Word and Dr. Modlin. Those opposed? Dr. Offit. Those abstaining is Dr. Rennels.

Carolyn, Bonnie, thank you.

DR. BIRKHEAD: Could we all get a copy of the new wording?

DR. MODLIN: The next item on the agenda will be moving

on to the updates from -- first of all, from the National Immunization Program -- I'm sorry, Dr. Zink, did you have a comment?

DR. ZINK: Thank you very much. I'm Tom Zink with GlaxoSmithKline, and it goes to unfinished business from yesterday. And I'm very respectful of the time of the Committee and would like to bring my compliments actually to Dean Mason and the CDC group that's worked so hard on the supply issues. And I wanted to point out, yesterday a lot of data was shown on backlog and problems with keeping up with the need.

And perhaps to complete the picture for the Committee, if I may, I would like to talk a little bit about the productivity of the manufacturers, especially in the DTaP realm, and just bring into focus the fact that in the year 2000 we brought in 7.1 million doses of DTaP to the US, and then as the supply issue started to gear up and ramp up as a problem for us all, in 2001 we brought in 12.2 million doses to the US, which represents a 70 percent increase of productivity.

And I think that goes to the Committee's -- I hope to the mindset of the Committee that there is the ability to ramp up in the need, that we're rapidly approaching the abilities of our capacity and capabilities as a company. And so we'd also like to bring up the idea

that there are other ways to improve vaccine supply, which goes to efficiency in manufacturing, as well as at the bedside.

And there are some techniques that we're developing and have introduced into the marketplace around pre-filled syringes that actually increase the amount of vaccine that's available at the bedside by ten percent. Using the pre-filled syringes, there's less waste. In a ten multi-dose vial, usually at the bedside there's a loss of one dose for every ten multi-dose vials because of the draw.

In a pre-filled world, which we've introduced in the pediatric hepatitis marketplace, you can gain ten percent there. There's not that loss. And so when we're looking at a 20 million-dose market of some vaccine, you can see that you can pick up considerable dosages in the context of a supply shortage.

So I thought that it'd be nice to start the day off with some positives about how manufacturers have been producing and contributing to help the shortage issue and I appreciate the time that you've given me to do that.

DR. MODLIN: Thanks, Dr. Zink. Walt?

DR. ORENSTEIN: In the spirit of continuing with some good news, I just -- with all the supply problems and

all the difficult issues we've been addressing, I do have some very good news. This is a slide I use essentially every update, and it represents many of the vaccine-preventable diseases or one complication, congenital rubella. Twentieth century annual morbidity, most of the times t his is representative and most of the times pre-vaccine licensure. 2001 provisional data and present decrease and what you can see here is that we've reduced the vast majority of these at 2001 -- the number by 100 percent or rounding to 100 percent, zero cases of polio, zero cases obviously of smallpox and a handful of cases of some of the others. And even pertussis has gone down some this past year. We're dealing with 96 percent or greater reductions.

I think perhaps one of the most dramatic reductions is rubella. We, in the late 1960s, had something like 45,000 cases of reported rubella. In 2001 we have a provisional total of 19 cases. We have never seen anything like that in terms of reported cases of rubella, and that probably correlates in part with substantial efforts on the part of Mexico and the Pan-American Health Organization to incorporate rubella immunization into their program, since much of the rubella in recent years has been focused in Hispanic

populations. But this is really a remarkable achievement.

Another piece of good news is immunization coverage, when you look at the individual vaccines, remains at or near record high levels for most of the vaccines. They are at 90 percent or higher. As Jane mentioned yesterday, for varicella, the last -- the first two quarters of 2001 were 75 percent and we continue to have our biggest problem with the fourth DTP at 83 percent. I need to remind you when you interpret these data that this is a survey of 19 to 35-month-old children, a median age of 27 months. And so all of the supply issues and changes of schedule that we've been talking about recently don't impact on these data. The children surveyed during the first two quarters of 2001 were born between February of 1998 and November of 1999, so these are -- because children have to age through the process in order to be measured, they have to age through to the full schedule, we are always slightly behind on what is actually happening today.

Now the individual vaccines can be the best measures, but they're an awful lot of numbers in terms of what the disease risk is to the population, and so we tend to use combined series, but as you're seeing here, the combined series is getting more and more complicated.

Here's four different combined series that could be used to look at the individual childhood protection, from three DTP, three polio, one MMR to four DTP, three polio, one MMR to addition of three HIBs to addition of three Hepatitis B and soon we'll be adding varicella and it will go up. In fact, in recognition of the combined series getting more and more complicated, the Healthy People 2010 goal is 90 percent for each individual vaccine, but for the combined series it's 80 percent, in recognition that it's going to be more and more difficult to get every single dose of every single recommended vaccine to children. So what you're seeing here, though, is that we do have some increase, at least from the first two quarters of 2000 to the first two quarters of 2001, particularly in these last two series, the 4-3-1-3-3.

On the good news side, in terms of appropriations, there were increases in the fiscal year 2002 budget. We had an increase of $23 and a half million in vaccine purchase. We had an increase of $18.7 million for operations or infrastructure funding for the grants. And we had an increase of almost $6 million internally, which will be going to vaccine safety, extramural research and mandatory salary and expense increases. We also had a substantial increase in our global

immunization funding, which covers both measles control and eradication efforts, as well as polio eradication.

In FY 2003, at a time of real concerns with the budget, we were able to get level funding, so we were kept at -- in the President's budget request, we are at level funding from FY 2002 to FY 2003. Obviously this will be discussed by the Congress over the next number of months.

To put it in perspective, the infrastructure side, we were down to -- in 1999 -- $139 million being appropriated for -- or going out to states for infrastructure. And what you can see here is that with the recent increases we are now up to about $200 million, and we estimate that if we had $220 million we would actually meet what the Institute of Medicine committee recommended in order to get $200 million actually going out to the states. So these are the appropriation levels. And the goal is to have $200 million actually to the states, which would require an appropriation, we estimate, of about $220 million. But we certainly have made major progress in working toward the IOM recommendations.

I think the other issue that I wanted to bring up is, I've already spoken with the Committee, but we've

talked over and over again about financing of our policies. VFC came up repeatedly yesterday and we are concerned about the whole issue of vaccine financing. We've contracted with the Institute of Medicine to answer the following questions: What is the role and responsibility of the public and private sectors and vaccine providers for purchase and administration with regard to vaccine financing? This will require some look at price determination for new vaccines in order to try and understand what is coming down the pike, and then to derive finance strategies from these roles and their implications.

The other issue is that we're asking the Institute of Medicine to look at the current levels of need in essentially children who are not covered by any system. These are generally children with insurance whose insurance doesn't cover immunization or very large deductibles, looking at financing issues with regard to reducing the time from recommendation to implementation of those recommendations, problems we had with pneumococcal conjugate vaccines, and to better understand reasons for the increases and whether there are lessons from other fields which finance medical devices or supplies.

This is an 18-month study. It started in November,

2001. It's director is Rosemary Chalk, who directed the prior report on immunization financing. The Chair of the committee is Dr. Frank Sloan, who is a professor at Duke University and is an economist. And I think we're hopeful that we'll get some out-of-the-box creative thinking on this that will be helpful to all of us in seeing our recommendations implemented. The first committee meeting is scheduled for March 11th and 12th in Washington. Thank you.

DR. MODLIN: Walt, thanks. Paul?

DR. OFFIT: Walt, just one quick question. What do you think accounts for the roughly ten-fold decrease in reported cases of rubella this year as compared to the previous years?

DR. ORENSTEIN: I don't have an exact as to why it happened this year and not last. I don't know. Melinda, do you --

DR. WHARTON: Well, of course anything I would say would be speculation, but what we'd had going on in the last couple of years were community-wide outbreaks involving foreign-born adults with rubella transmission in non-US-born communities. These outbreaks were often recognized in work places. My belief is that these outbreaks reflected a rubella epidemic cycle that was going on in countries outside

the United States, with an importation of rubella virus into the susceptible communities and subsequent spread in the United States. So it was indigenous transmission of imported virus, I think.

But what seems to be going on is -- or what I think is going on is that these epidemics -- that the rubella activity is decreased outside the United States, perhaps due to the waning of the epidemic cycle, and I'm sure that increased use of rubella vaccine in other countries of the western hemisphere has played a role in decreasing the activity. And so what we're seeing is a greatly diminished importation. It's not that we've done anything dramatically to reduce the size of these susceptible communities, but I think the risk of importation is markedly decreased.

DR. ORENSTEIN: That's what I tried to say in terms of particularly in Mexico and some of the efforts at rubella implementation. I think the other thing we should know, there's a tremendous amount of money flowing to states for bioterrorism. Some of that will be used for surveillance improvements, and we may start seeing some increases in some of these numbers, not so much as a result of real increases, but we may see some surveillance artifacts as overall infectious disease surveillance systems improve in the States.

DR. MODLIN: Sam?

DR. LEVIN: I think in his absence we should certainly give Ciro de Quadros in the Pan-American Health Organization some credit for what Melinda is talking about in that he has pushed very hard for using measles/rubella rather than monovalent measles. And I think they've exhausted a great deal of the susceptible population and the younger folks are getting measles/rubella so there's a lot less circulation of rubella I'm sure in the area of middle and South America, thanks to Cyro and the Pan-American Health Organization.

DR. MODLIN: Yes. Kathy?

DR. NEUZIL: Kathy Neuzil. There are clearly significant racial and socioeconomic disparities in adult immunization, and I'm curious if the IOM study on vaccine financing will be addressing those adult immunizations.

DR. ORENSTEIN: They're supposed to address adult immunization, as well.

DR. MODLIN: Other questions or comments? Walt, thanks very much.

The next update scheduled is from the Department of Defense, Dr. Diniega.

DR. DINIEGA: Good morning. I'd like to just briefly

update the Committee on the anthrax vaccine immunization program for the Department of Defense. As most of us know, BioPort received FDA approval on January 31st. As a result, the Department of Defense is considering various options for the resumption of the anthrax vaccine immunization program in protecting our forces. These options range from the current status, due to limited supply, of vaccinating special mission personnel only to the use of post-exposure vaccine and antibiotics and all the way up to total force. It probably will be several months before the senior leadership makes a decision.

Two and a half years ago, Lt. Col. John Grivenstein presented to the Committee safety studies that were completed, in process or planned. Since then, much has been done in this arena and we've provided a handout today, a 32-page synopsis of 18 safety studies of the AVA. And if the Committee desires at a future meeting, we could present an in-depth findings. That's all I have, sir.

DR. MODLIN: Thank you. Questions for Dr. Diniega?

(No response)

DR. MODLIN: We appreciate the information on AVA. Those questions occasionally come to all of us from time to time.

The next -- Dixie?

DR. SNIDER: I just want to say that the Department has been working with DOD around supplies of AVA and I made some reference to it yesterday, but I'd also like to recognize DOD again today to make it clear that as they move forward with BioPort and getting more vaccine available, they have an agreement with the Department of Health and Human Services to make a certain amount of that vaccine available to the civilian sector. So that is certainly appreciated by HHS and it is going to present us with some opportunities to address some issues we haven't been able to address related to the ACIP recommendations implementation. So I just wanted to make that clear.

DR. MODLIN: Thanks, Dixie. Dr. Midthun, the FDA update.

DR. MIDTHUN: At the FDA we've had two advisory committees since we were last here at the ACIP. At the advisory committee in November, the vaccines advisory committee was asked to consider what would be efficacy endpoints appropriate for licensure of a human papilloma virus preventive vaccine, and the majority of the individuals at this particular meeting supported use of cervical intraepithelial neoplasia 2 or 3 as a primary endpoint in support of preventive HPV

vaccines. There was also in conjunction, however, with virology with the associated HPV type. There was also discussion of accelerated approval at this particular advisory committee, and most of the individuals there supported use of persistent HPV infection as -- support of an accelerated approval, however, they felt that confirmatory studies should then show an impact on cervical intraepithelial neoplasia 2 or 3 in conjunction with virology and voiced concern that they would be concerned about an accelerated approval if it would interfere with reaching this more definitive endpoint.

At the January advisory committee the vaccines advisory committee was asked to consider the strains for the upcoming influenza vaccine for this next year, and the recommendation was to retain the H1N1 and H3N2 A influenza strains as they were in last year's vaccine, and they deferred the decision on the B strain until the March meeting, which will be March 6th.

I think that's all I have to report, and as Dr. Diniega already indicated, last month we were able to go ahead and approve the supplement to the BioPort anthrax vaccine for their renovated facilities, and also we approved the supplement for an updated package insert. Thank you.

DR. MODLIN: Thanks, Karen. So heads-up to this Committee that HPV vaccine is on the horizon at some point. Yes?

DR. SNIDER: This is Dixie again. Since we do have a little time, I think it might be worthwhile to say a little bit more about the flu decisions. Clearly the H3N2 decision was fairly straightforward, but the issue of H1N1 was a little bit complicated. In the end it was decided to go ahead with the strain from this previous year because the majority of isolates that had been found certainly are like the strain contained in the vaccine.

But there are some disturbing findings, particularly from Asia, with regard to a new H1N1 strain that would not be very well-covered by the current strain in the vaccine. But at this point in time there's not enough information to suggest that there should be a change. And obviously there's an urgency in moving forward with giving direction to the manufacturer.

And the big decision is really tough, although it seems to be moving more in the direction of the Victoria. But as you heard yesterday, completely two different strains circulating, some discussion of a quadravalent vaccine which was I think fairly -- although extensively discussed, fairly quickly dismissed as

something that wasn't really feasible to consider for this year. So it was not a very -- it was not straightforward to make these selections.

DR. MODLIN: Is there a precedent for a quadravalent vaccine in other countries?

DR. MIDTHUN: Yes, there is, in Europe. I think one of the issues, though, is that currently we have 15 micrograms of HA per strain and the issue of bringing in a quadravalent, you would have to grapple with that if you had 15 micrograms per strain, you would now have more antigen in there than in the vaccine that's trivalent. Another issue that was discussed was could we possibly split the 15 micrograms with a given type and have half of -- one, for example, B strain and half with the other B strain. But the difficulty is we really don't have data to address what the immunogenicity would be in that particular scenario. So those were a number of the issues that were discussed.

DR. MODLIN: Thank you. Dr. Carole Heilman, NIH.

DR. HEILMAN: Good morning. I'd like to update you on both plans and ongoing activities with respect to our involvement in smallpox and anthrax vaccines. Yesterday I spoke to you about the status of our dilution studies, but there is still quite a number of

other things that we're doing.

We will be going into a study with those that have previously received vaccines, the seropositives, in quotes, looking again at dilution studies in that population.

We're also working with the pediatric and geriatric communities to develop protocols that are acceptable for looking at Dryvax vaccine in those populations.

We've had some discussions about the need to consider other immunocompromised populations and the problems with -- the potential problems with Dryvax. And in that scenario we're tending to move towards looking at alternative vaccines, such as the various MVAs that are out there.

We do have several companies that are very interested in pursuing this line of -- this pathway with the MVAs and that's our goal right now.

In addition, we have been working with Acambis and CDC. We will not be involved in their straight line licensure requirements, but at their request, we will be trying to do similar kinds of studies in the other populations such as the children and the elderly to expand the data that they have in those groups.

With respect to anthrax, we have been working, as I mentioned several times already, with the DOD, and

in particular two parts of the DOD, the USAMRIID group and the JVAC group, in order to actually get some vialed RPA vaccine to actually test. And they have been fabulous. We ran across a number of pre-clinical and manufacturing data needs that we have been able to identify and actually get the results to, so our plan at this point in time is to be able to file pretty quickly, wait for the additional safety data to come in in pre-clinical, and the protocol is being developed. So with luck, next time we meet here I will be able to tell you that the RPA vaccine trial is underway.

In addition to that, the FY '03 Presidential budget provides for the development and purchasing of RPA and that's one of the line items in our budget. And as a result of that, we have sent out a draft RFP for this particular activity. It's been on our website and we have requested that manufacturers respond to that draft RFP. We've gotten a lot of comments back from the manufacturers and we will be adjusting our approach based on some of the comments we've received from them. So that's where we are.

DR. MODLIN: Thanks, Carole. Questions for Dr. Heilman regarding the recombinant PA vaccine or anything else? Yes, Gus.

DR. BIRKHEAD: Could you say a little bit more about the planned studies in immunocompromised populations?

DR. HEILMAN: What I can tell you is there have been a number of working groups to ask the very difficult question about whether or not people are comfortable about using Dryvax vaccine in immunocompromised, and it's been an interesting set of conversations that have been going on. But suffice it to say at this point in time the leaning is towards no, we cannot do that at this point in time. And so as a result of that, we've been encouraged to think of alternative vaccine approaches and that's where a lot of now the effort is going into MVAs. We have no idea if MVA would work, but the logic behind it is what we're trying to work on.

DR. BIRKHEAD: Sorry, my ignorance is showing. What is MVA?

DR. HEILMAN: I'm sorry, MVA is a modified vaccinia anchor and it's sort of a group of vaccinia vaccines that have been modified so they replicate either once or not at all, but low replicators. And so the possibility of eliciting a sufficient immune response with a low replicator, and low MVAs have been used as vectors for a lot of HIV vaccines, for example, so we know the safety profile of them in that population,

which is good.

DR. MODLIN: Carole, presumably you're considering -- is immunization of immunocompromised patients, it would be post-exposure or post-event immunization rather than pre-exposure --

DR. HEILMAN: Correct.

DR. MODLIN: -- or pre-event, would be the assumption?

DR. HEILMAN: That would be the assumption, correct.

DR. MODLIN: Marty?

DR. MYERS: Related to that, Hal mentioned yesterday the vaccinia immunoglobulin --

DR. MODLIN: Right.

DR. MYERS: -- and estimates of the amount of need and so on that CDC had done is taking into account that in a post-exposure release there might be a number of people that would be undiagnosed and therefore there would be an increased need for that.

DR. MODLIN: Dixie?

DR. SNIDER: I just wanted to ask Carole or Ben if they can say anything about work on some of the other BT -- vaccines against some of the other BT agents, particularly on the A list or B list.

DR. HEILMAN: Carole Heilman. On February 4th and 5th we had a blue ribbon panel meeting to help define the research agenda for the NIH, and as part of that

discussion, we have identified a series of high priority areas that we should be focusing on, particularly in vaccine development. For example, plague is up there. We will be meeting with our collaborators and associates at the DOD to see if we could develop, quite frankly, a joint program for this kind of vaccine development. So there's no real intention to start from the beginning, but there's intention to be able to help -- work with them, bring it along.

DR. DINIEGA: I concur. We are looking at working together on many of the issues. The only area we may differ on is the prioritization for which vaccines to work on, but we have already accelerated our smallpox program, also.

DR. MODLIN: Thank you. The next update will come from National Vaccine Program Office and NVAC. Marty, are you -- you're leading off.

DR. MYERS: I guess I should paraphrase that great quote that -- seeing as how I'm still here, and after last June, I guess that my reports of my leaving NVPO were greatly exaggerated.

(Laughter)

DR. MYERS: But that is in the offing. I think, as everybody is aware, I've been urging the Department to

have the Director of NVPO in Washington and with an office, as well, in Atlanta. The events in September meant that the Director of NVPO has been in Washington since the rotavirus workshop. And just from a personal note, the Myers are back in Atlanta as of about three days ago. However, the location of files, manuscript that Georges Peter is looking for and my slides for this morning are somewhere being irradiated, I suspect.

The plans at NVPO are that I will provide some part-time continuity for NVPO in the short term, and my understanding is that Dr. Art Lawrence, the acting principal Deputy Assistant Secretary for Health and Dixie will assume oversight of NVPO until the new Director is appointed, which is expected to occur, I hope, within the next month or so.

We talked yesterday about vaccine supply, and I alluded to a semantic difference on the whole issue of vaccine availability, of which supply is only one, and we've been talking recently about vaccine availability of some specific other vaccines. One of the things that's been not said, but as you've been hearing I think in all the reports the last day or so, is the extraordinary collaboration that has occurred across agencies, across departments and with vaccine

manufacturers. And I guess I'd like to sort of -- as our interagency vaccine group spokesperson, like to acknowledge the fact that the Department of Defense -- I've met a lot of people I didn't know before. The NIH, FDA, CDC, and specifically the vaccine manufacturers who have played just an extraordinary collaborative role over the last six and a half months and are, to many of us, sort of unsung heroes in some of the processes going on. It's really been an extraordinary period of time. I just wanted to take the opportunity to say that.

NVPO administrates a fund which is called the Interagency Research Program. It is about $6 million. It's also known in shorthand as the unmet needs funding, filling the gaps that occur between funding cycles. I reported on it here last year, as well. Again this year, it's heavily weighted to supporting vaccine safety initiatives. About a third of the funding this year went for vaccine safety issues.

Pandemic influenza has been -- preparedness for the last several years has been a major funding area and that continues to be a major area of funding for NVPO, and adult immunization disparities and adult immunization is another area. This year for the first time a major new area that was identified by NVAC and

supported by the interagency vaccine group was immunization initiatives for adolescents and for pregnant women, and several new areas of emphasis. We had a couple of workshops. Rotavirus is going to be on the report later so I won't say anything about that. We talked about the supply workshop yesterday. Pandemic influenza preparedness is a still-unfinished business but we're very hopeful that the action planned will clear the Department in the near future. There's still some issues that relate to that and the -- with that we hope that the technical documents will be finalized and cleared. I think, as everybody knows, the state and local planning guidelines are on our website. A new version of those will be coming out shortly.

Polio laboratory containment is another initiative the NVPO is managing. Dr. Walt Dowdle is leading that. We're into the inventory establishment period for the potentially contaminated specimens and there will be a meeting convened early in March by the new Assistant Secretary for Health, Dr. Slater, which is bringing together the members of the other Departments in the administration to develop their support in developing inventory, which will be completed by December. And I think as everybody here knows, the intent is first

to create the inventory. The second thing is -- the next stage is to increase the level of biocontainment for potentially contaminated specimens, and then ultimately to increase it yet again.

Two weeks ago, right after the NVAC meeting, the interagency vaccine group, jointly with NVAC, recognized Dr. David Satcher at his reception and recognized him specifically for his contributions to the immunization program first as the Director of CDC and then as the Assistant Secretary for Health and Surgeon General for the immunization programs and specifically for the issues relating to disparities in vaccine delivery.

I think that's all I have to say. Georges is going to give a report from NVAC. Unless there are questions.

DR. PETER: Thank you. As Marty mentioned, the committee met two weeks ago. It was our first face to face meeting in nine months. Our meeting in October had been canceled because of the events that had taken place in September. However, we had had a conference call at which we discussed the IOM report on thimerosal.

At our meeting we began with a unanimous resolution congratulating the New England Patriots as the recently-crowned champions of the National Football League, and I'm sure the ACIP would unanimously pass

a similar resolution.

We also welcomed six new members, including several that are well-known to this Committee -- Drs. Schaffner and Guerra, who was a former member of this Committee.

I will briefly review the topics that we discussed, much of which is similar to the agenda, but with a different perspective that we discuss here. First of all, thimerosal in vaccines, we received an update which you'll be receiving later today from Roger Bernier.

The NVAC issues in the IOM report of last October are different than those that the ACIP faces and are two, one of which is the question of review and assessment of public health policy decisions made under uncertainty. And while all public health decisions are made with a certain degree of uncertainty, these are really issues where great uncertainty is faced and a working group will be formed, but we will wait until we have the new NVPO director with whom I can work.

Secondly, which we have not begun to address, and a very important point that the IOM drew attention to, is the need for research on communication of changes in policy that occur rapidly. And I think this is -- the importance of this issue is repeatedly illustrated by our discussions yesterday on several issues.

The bioterrorism was a major topic of review, including

anthrax and smallpox preparedness, with presentations very similar to those that we have heard here. I think a very important point, though, was made about the need that as we develop the plans for smallpox preparedness and other aspects of bioterrorism that we involve not only the physician, public health and scientific communities, but also the public in order that the public understands the particular strategies that are used and accepts them in order to reduce anxiety and improve compliance. Dr. Modlin will mention later that we are reforming the smallpox NVAC/ACIP working group in order to address ongoing issues related to the discussions from yesterday.

Vaccine supply was discussed in detail yesterday. The workshop recommendations will be discussed with the work group of NVAC and subsequently with NVAC, hopefully next week because the Assistant Secretary for Health has asked for preliminary recommendations on solving this major crisis, which I think is perhaps the greatest crisis we've faced with immunization delivery in at least several decades.

The immunization registries is another challenge. The Healthy People 2010 has as a goal that 95 percent of children under the age of six will be enrolled in registries. Progress has been made in that many of the

programs and projects currently have or are developing programs and are meeting some of the standards that have been established in the NVAC report of several years ago. However, we are far short of the goal of 95 percent. I think between 20 and 25 percent of children are currently enrolled, and the NIP has developed some creative strategies for solving -- for raising compliance. But I think that one of the overriding needs is funding, which is very difficult to obtain in the current fiscal climate. And this is indeed a major challenge.

The standards for child and adolescent immunization practices have been again reviewed and approved by the committee, will be resubmitted to the major partner organizations for their approval, and hopefully issued in major journals -- in Pediatrics and Family Medicine, as well as MMWR, within the next six months. And those should be, when finalized, distributed to those committee.

Those are updates on the standards that were originally issued in 1993 and are a sequel, too, to the standards for adult immunization practices, which have been finalized and are in the course of we're seeking publication now.

One of the other assignments given to the NVAC has been

to make recommendations to the interagency vaccine group on topics for review by the immunization safety review committee. The committee has concluded its review on the role of multiple antigens on immune responsiveness, and I think that will be discussed later today, and our role was to make recommendations on the next topic and our recommendation is that it should be Hepatitis B vaccine and neurological disorders.

The final point I wanted to mention was concern expressed by the committee over a recent ruling by the Center for Medicare and Medicaid Services on compensation for vaccine administration. And Bill Schaffner will be pleased to see that I'm using term compensation and not vaccine administration. The ruling applies to Medicare and reduces reimbursement for vaccine administration or compensation from $10 to I believe around $4. The concern is that this is inconsistent with the standards of adult immunization practices which clearly state the importance of educating vaccine recipients about the risks and benefits of vaccination.

This is also of great concern to pediatricians, because indeed if the same thinking applies, then decreased compensation for pediatricians will lead to decreased

time spent in educating families about vaccine delivery, and again is consistent with the theme that Dr. Myers mentioned yesterday about the under-valuation of immunizations.

Well, one of the aspects that Marty covered was that indeed this last NVAC meeting was his final one, and I think that working with him has been a great pleasure. He has provided intelligence, insight, grace, diplomacy, and I've known Marty for a long time and have been remarkably impressed about his continued growth in diplomacy, and he will indeed be sadly missed.

(Laughter)

DR. PETER: But he is not leaving us. He will continue to be involved for -- although he will no longer be the director of the program. And in his leaving, though, as director, I am reminded of a particular phrase from "The Field of Dreams" which comes to us. Joe was a famous baseball player and when it was discovered that he no longer could play baseball, which -- for reasons very different than those that Marty is leaving, a statement was made by a youngster, "Say it ain't so, Shoeless Joe." Well, we say that to you, Marty, and I think you all join me, as the NVAC members do, in thanking Marty for his service the past four years.

(Applause)

DR. PETER: I'd be glad to answer any questions. Yes?

MR. GRAYDON: Randy Graydon, the Centers for Medicare and Medicaid Services. I think we ought to make it clear that the actual drop in the price -- $10 was actually the recommended reimbursement and not actually what was paid last year. I understand that the average reduction was only about 61 cents on the administration.

DR. PETER: Isn't the ruling for the coming year for significantly less?

MR. GRAYDON: For 2002 --

DR. PETER: Right.

MR. GRAYDON: -- on average about 61 cents for administration, right.

DR. PETER: But I think we need to examine this at NVAC in much greater detail, both the implications and the specifics of what is appropriate compensation to ensure that physicians and other health care providers deliver vaccines. I think it relates to important issues, such as how we deliver influenza vaccine, for example.

DR. MODLIN: Yes, Natalie?

DR. SMITH: Just a comment about bioterrorism. To think we were instrumental in getting the NBT money to

also be -- that we can also use it for flu pandemic preparedness. I mean in California and some other states are actually starting to call it catastrophic event preparedness, and it's great to see some more attention to the flu issue.

DR. PETER: Thank you.

DR. MODLIN: Georges, thanks very much. Randy, I know that the issue regarding compensation for administration has been a big issue in all of the provider community, not just practicing pediatricians and family practitioners, but it's become a bigger issue. I wonder if it wouldn't be a bad idea for us to put this on the agenda, possibly for the June meeting, to discuss in a little bit more detail if then maybe you could help us out working through that.

MR. GRAYDON: I understand Georges is going to extend an invitation to Mr. Scully to actually bring it up in the June meeting of the NVAC.

DR. PETER: That's correct. This will be a major item at our early June meeting. And it's more than simply a presentation by the CMS. I think we need to examine some of the economics.

DR. MODLIN: Terrific. Well, maybe we could have a capsule or summary or a reprise of some sort on the agenda for our meeting, as well. I think it would be

of broad interest.

DR. PETER: And I might add that the new Assistant Secretary of Health, who was the director of the National Vaccine Plan, was appointed in the fall and then confirmed and sworn in two weeks ago, and at her presentation Dr. Slater, formerly of Merck Laboratories, did indeed agree that the committee should invite Mr. Scully to come and talk about this major issue.

I might add, too, that Dr. Myers tells me that she is very committed to the importance of immunizations and I think hopefully will be an ally with the types of activities of ACIP and NVAC undertaking.

DR. MODLIN: Thank you. The next update will be from the Vaccine Injury Compensation Program, Dr. Geoffrey Evans.

DR. EVANS: Good morning. I first would like to welcome John Salamone as a member of the ACIP. John, as Dixie mentioned, was a member of the advisory commission on childhood vaccines, a distinguished member, and John also lives in Vienna, Virginia, which is of Wolf Trap Farm Park fame and John is discovering that being close to Washington has its advantages of being invited to meetings as the consumer representative now, and he should be seeing more of

those invitations, I'm sure.

We've got a little bit more time today, and it's good, because there's been a lot going on with the compensation program, as it turns out.

First of all, just to spend a minute on the monthly statistics which you should have in front of you, we have actually had kind of a bump-up of claims filings, which I will get to actually at the end of this presentation, but about 24 per month from what used to be, a year or so ago, of about eight or ten per month. In terms of new vaccines that have been added to the program, we still have the bolus of 389 Hepatitis B claims that really, for all intents and purposes, are on hold while the board -- over a several-year process or longer -- is going to adjudicate them on a causation basis. And that's going to require testimony in the various areas of conditions that are being alleged. What's going to help that clearly is going to be the next IOP topic -- workshop, which will be Hepatitis B vaccine and neurological disorders, which I believe will be sometime this spring -- late spring.

Claims adjudicated, the only thing of note is that they are the -- pre-date the program. These are vaccines that are administered prior to the opening of the program, are down to nearly zero at this point. And

awards of a billion dollars have been paid to date for both the pre- and post-date of the program and there's now $1.7 billion in the trust fund.

If I can take a minute to give you a little VICP 101, which will just remind others who haven't heard this a couple of times before, that the way to obtain compensation in the program, it has been -- at least early on as the program progressed -- is by proving a table injury, and that allows you to receive the presumption of causation if the condition occurred in a specific time period that's indicated on the table and there's not greater evidence of an alternative cause.

If that's not the case, if your injury occurred outside those time frames or it's an injury that's not listed on the table, then you have a greater burden of having to prove causation, the same standard that's in civil litigation, but in our program negligence is not part of the burden that you have to prove. And a very small percentage of claims will actually be for children that had pre-existing conditions or adult with pre-existing conditions who then feel that the vaccine made their condition worse.

As I've mentioned before, we have a notice of proposed rule-making that we're putting into final.

This was published in the summer and this would modify the vaccines injury table and its definitional counterpart, the qualification and aids to interpretation. By law there's a 180-day public comment period which ended on the 9th and interestingly there was no written comment and no one attended the hearing. We're trying to get this finished as soon as possible, hopefully for publication later this year. And any time you add a vaccine or a condition to the vaccine injury table, there is eight years of retroactive coverage and a two-year window in which to get those older claims in, and these were the changes that we discussed before, such as adding a second category under rotavirus vaccines. There's a general category that exists today, and a specific category of rhesus rotavirus vaccine will be added with a zero to 30-day onset. At least that is the proposal that was subject to public comment.

And some more technical kinds of changes, including removing polysaccharide HIB vaccine from the table since the statute of limitations is long over and we've never received a claim alleging injury from that vaccine, that the corresponding injury that's in the aids for that vaccine. That's of course the conjugated HIB will remain on the table, and removing

residual seizure disorder from the aids, also, because there's no specific injury listed on the table. And we'll officially be adding the pneumococcal conjugate vaccine. It is now covered by the program. It is listed in a general box category, and once this rule is finalized it will have a separate category.

In terms of legislation, a bill that's been introduced several times in the past in an effort to try to reduce the excise tax from 75 cents to 25 cents for each, quote/unquote, dose of vaccine. So examples being for three antigens, three doses for DTP would be going from $2.25 to $.75 and IPV, which even though it's three antigens, it still stays -- it's still considered one dose and that would go down to a quarter.

This bill has received a lot of support in the past, and it's just a matter of maybe this year finding a vehicle that could get it to go through. But the changes of the trust fund have become increasingly controversial over time. Subject of the GAO report a couple of years ago, in which they did not make a recommendation one way or the other, is whether they should reduce the excise tax.

This past year Representatives Dave Weldon and Jerry Nadler, in an attempt to try to make the program more user-friendly and streamlined, introduced legislation

that would set a proof of standard that's used in the Veteran's claims just as an additional threshold standard, and this is known as the fair -- by using a fair and impartial person on determination as to whether a vaccine possibly caused a condition, not a scientific standard at all. And there were also legislative proposals that were approved by the ACCV and sent to Congress in 1991 by the Shalala administration that would extend the statute of limitations up to six years, but would be based on when the petitioner first knew or reasonably should have known that they had a vaccine injury, which of course could get into a lot of gray areas.

There is also the payment of interim fees and costs to attorneys, compensation of family counseling and establishing guardianships -- trusts, and these were things that the ACCV endorsed unanimously and actually were incorporated in some of that legislation.

More importantly, this past week the chairman of the House Government Reform Committee, Representative Dan Burton, as well as the ranking minority member, Henry Waxman, introduced legislation entitled the National Vaccine Injury Compensation Program Improvement Act of 2002, which incorporates some of the Weldon/Nadler proposals as far as the ACCV, changes the death benefits

upward to reflect inflation and also makes lost earnings more generous. It changes the ACCV member requirement. Currently John Salamone was on, for example, because he was the parent of an injured child. It would allow actually an individual who was injured -- an adult, for example -- to be a member of the commission. Actually this -- I believe, John -- was generated because of suggestions from your group, to be able to have a member who had been affected by the polio vaccine.

One of the worrisome aspects of this legislation is this last one where they would -- and the language is confusing and we're still trying to clarify this, but anyone that wishes to file for a vaccine administered after October 1st, 1988 would have the opportunity to do that, once again, with a two-year window to file. And this would be even if your claim was dismissed before, if you claim was affected by changes to the table and so on. What's not clear to us, among other things, is which table -- there's actually been several iterations of the table, changes over the years -- which table these claims would come under. And this was just introduced and we're just in the process of trying to go through this now.

There's been continued oversight by the government

reform committee. There were hearings actually toward the end of 2001. Essentially you had panels of petitioners and their attorneys that would basically review the experiences they've had with the program, often long delays in getting adjudication and in some cases there were appeals, and HHS and DOJ officials were a part of the second panel. And from the first hearing in '99 came a report that was released in October of 2000 which came up with three main recommendations, the third of which I'd like to discuss now. But basically it would be -- the first one reflects the concern over the modifications to the vaccine injury table particularly that were done in 1995 by removing residual seizure disorder and shock collapse into pertussis vaccine, which has caused a lot of controversy. Also the idea that some of the litigation is protracted and too long. And then finally -- this is very serious concern, I believe -- and that is that we've got to consider what to do for a class of cases that fall into the non-table category. And there's good reasons for that.

The original table, as it was put together, had eight conditions listed for seven vaccines that were being used at that point, seven antigens. But with the addition of five new vaccines over the nineties, only

two conditions have been identified for those five. And that makes sense because if you're going to license a vaccine for general use, which are the vaccines that are covered under the program, it's not likely that there's going to be a serious adverse event that's associated with the vaccine or it wouldn't be licensed. This makes for a difficult burden of proof when you have a situation where nearly all claims are filed that allege non-table conditions and the Hepatitis B claims are an example of that. You have a variety of conditions that are being alleged and I don't think there's one of them that actually alleges anaphylaxis, which is the only condition under Hepatitis B vaccine. So there is the growing call for a more relaxed standard, and in comes the American Academy of Pediatrics, who asked for agenda time at the last ACCV meeting in December to introduce a proposal that they have been working on for some time now. And this is going to get formal action -- receive formal action at the March meeting and will also be discussed at the NVAC meeting in the spring. And the basic approach is based on the Agent Orange Act of 1991, which set up a more relaxed standard for determining which conditions might be related to herbicide exposure, and this is -- the standard, instead of a causation standard, is known

as the positive association standard and there's a standing committee that -- by IOM that was set up. And in our -- the proposal for the compensation program incorporates a lot of that, but sets up what's known as a relationship standard, which would affect non-table claims only. Below a threshold would be then created for allowing compensation and reasonable biological mechanisms would be the -- that and positive association would be the two main things you would have to prove in order to reach the finding of relationship standard being satisfied. And again, the IOM review is our key element. This is in your booklet and there are probably some extra copies at the back. It's an extremely complex proposal. The four pages -- there's the four pages that are -- is the statutory proposal and there's a two-page overview. And I just wanted to at least have the opportunity to introduce the concept today. Obviously it's -- this is embryonic, but it's something that needs to get some consideration, by ACIP, as well. Obviously this will affect some of the ways that we view vaccines. And even though this will not affect the vaccine injury table itself, which is an important distinction -- the table will remain sacrosanct -- it will take the causation standard in order to change that and the things that are reflected

in the IOM reports that have been published in 1991 and 1993, and also it would not affect the vaccine reportable events table or necessarily the vaccine information statements, although if there was a finding of a strong relationship between a vaccine and a condition, certainly that's something that we might think about putting in the vaccine information statements.

The expectations would be that this would be less adversarial, that more claims would be resolved more quickly in the petitioner's favor, and it certainly would be -- consistency in this kind of approach versus having a fair and impartial person standard. A separate committee would be set up. This would involve the immunization safety review committee that has now been reviewing topics, and they would be looking at making determinations of the biological mechanism and positive association, as well as the relevant time frames for onset. And the first task under this contract would be, as I understand it, just to develop the methodology that the court would utilize for topics that are not being covered, that are not going to be reviewed by the IOM.

Finally there would be reports every two years on the alleged relationships. They would be decided by the

Secretary in consultation with the commission, and any person or entity could petition the Secretary to have a topic considered. And as has been called for before, we've been trying to do. There would also be periodic reviews of the vaccine injury table itself every four years.

I just wanted to end by talking a little bit about some litigation that's been cropping up around the country. There've been ads in USA Today and other print media about a class action suit, and this came up at the supply meeting last week. Apparently there have been claims filed within the past 12 to 18 months that allege thimerosal-related injury in just childhood vaccines in general. And there seem to be two types of suits, where you have a specific plaintiff, a specific child who's injured and seeking lifetime of care, but tied into this particular suit is also a companion suit which is a class action suit where you have a handful of people who represent a large group of unnamed individuals. And one class in one of these suits comprises 30 million individuals, as it stated, who say they do not currently have a neurologic injury but are asking for compensation in order to be able to determine future checkups for neurologic injury.

Their position in filing outside the compensation

program is this: that there's a $1,000 requirement for anyone that comes to the program you must have more than $1,000 in damages, so they're claiming less than that because obviously there's no neurological injury that's been -- that's identified at this point; and they are not suing for a vaccine-related injury in the sense that's written under the compensation act, but rather they are claiming that the vaccine with thimerosal is now an adulterant, which would fall outside the compensation act. And the government is taking a much different view of this and is going to be preparing a statement to be filed in some of these state cases disagreeing with that, saying that thimerosal is an integral part of the vaccine and in no way is to be viewed as an adulterant, so these claims should be filed within the program.

Now when I alluded to the increase in claims that the program has received in the past six months, it does appear now that some of this is now spilling over into the compensation program, as it should, and we've actually had 38 claims so far this fiscal year that allege autism. And we've had claims all along that do allege autism, but this is a dramatic change now. And some of the more recent filings now specifically name thimerosal and there's not any particular vaccine in

some of these cases. Some of them just allege MMR, others are just for some of the different vaccines that are covered under the program. So I think I'll stop now and take questions.

DR. MODLIN: Thanks. Paul?

DR. OFFIT: Just a quick question. I have a son who's nine year old, big Sixers fan. What he does is he sits in front of his TV wearing -- during a Sixers game and wears his lucky Alan Iverson T-shirt and swears that every time they win it's because he's wearing that T-shirt. Now I've argued with him that what he really needs to do is he needs to see what happens when the Sixers don't -- you know, when he doesn't wear the T-shirt, do they still win? But he's refused to do that. I just wondered whether or not he's got me now on the positive association standard.

(Laughter)

DR. OFFIT: He believes so. Yes, he believes strongly so.

DR. PETER: But is he a good basketball player?

DR. OFFIT: He is that.

DR. PETER: Maybe he would qualify.

DR. OFFIT: But are we getting away from the notion of control groups. Are we getting away from the scientific method? Are we sort of heading back into

the Dark Ages? I just need to know what to tell him.

DR. MODLIN: Geoff, can you answer?

DR. EVANS: You know, that's a tough one. I think that I would reassure him that there's every reason to believe his shirt is really having an effect.

DR. MODLIN: Myron?

DR. LEVIN: Following up on that, when the Institute of Medicine looks at alleged associations, as I think one of your slides said, what happens with that information? Does that -- how does that filter down to change what happens in your program? Is it meant to be some sort of control about whether or not to wear the T-shirt or what?

DR. EVANS: The way that you're talking about how the scheme would work, how it -- what would happen is that, in contrast to the Agent Orange Act, as I understand it, which is administrative with the Secretary of Veteran's Affairs, takes the results, the categories that the IOM has determined -- there are four of them and it's on your two-page summary -- and then makes the cuts in terms of which will receive benefits and which doesn't. What happens in this situation is some of the categories, the top two categories, the court then would -- those would be compensable, those would be entitled automatically to compensation, assuming some

basic legal requirements were taken care of. So it would be a non-table table. It's not a table injury, but it certainly falls in a class of conditions that would be eligible for compensation.

DR. LEVIN: So I guess what I'm asking is, is this a way of putting some science into the decision-making?

DR. EVANS: This is -- yes. I mean there's a -- there will be a consistent approach, modeled after what is going on in Agent Orange, to the extent that there's a methodology that they create in terms of trying to take the various categories of evidence such as controlled studies, case reports, ecological studies, whatever, and then trying to adopt a different standard and then having a consistent approach from that point on. So I would say -- Walt asked recently how we view certain conditions and how they would probably likely be judged. I think there's a good bet, for example, that since the IOM in its '97 report felt that tetanus-containing vaccines are causally associated with Guillain-Barré Syndrome, that that would be one of the conditions I think that we would find that satisfies the relationship standard without any trouble at all because there is certain compelling evidence as part of that.

DR. MODLIN: Georges, then Bob.

DR. PETER: Myron, I've been a member of the working group of the Academy that made this proposal, and indeed the role of the IOM is indeed to ensure a scientific base for both the table injuries and the non-table injuries. But as Geoff has said, to have a somewhat more relaxed standard, but still to require a scientific basis for compensation.

I think the -- well, I think perhaps a lot more discussion needs to take place before this becomes a law, but I can assure you that the IOM would indeed provide the expertise that's necessary. It also would help because it would provide the court with a set of guidelines from experts on evaluation of these cases rather than individual Special Masters having to make individual decisions. So I think indeed it would enhance the scientific credibility in the long run, as well as hopefully be less adversarial and be -- and some of the parents groups be more satisfied.

I don't know, Jon, whether you want to comment at all or whether -- you probably haven't -- it's unfair to ask you because you may not have seen this proposal yet.

DR. MODLIN: I guess not. Bob?

DR. CHEN: Just a couple of suggestions on additional ways that I observed over the long years in the injury compensation program in terms of how we might improve

it. I think the first item is that -- this excise tax is a bit unusual in that it does really nothing in terms of try to prevent these injuries in the first place. If you read the ideals of Senator Paula Hawkins in the early days in terms of her sponsorship, her intent for this excise tax was as much for preventing future vaccine injuries as it is for treatment of those who are already injured. And I think it would be very nice -- for example, just another analogy, is the airport excise tax is used for improving the runways, radars, et cetera to prevent future problems rather than compensating for just the airplane crash victims. So again, it would be nice to improve the act back towards its original intent.

The second suggestion would be that -- and Georges, I think, will work with you closely on that. I think the proposal is on -- that the AAP has come up with is a helpful one. The one major gap that it has is that fundamentally, if you take a look at the process of the vaccine injury table and how things are added to it and how basically immunization is a dynamic process with new vaccines that are being introduced, and which the only way in which kind of -- these reactions, by and large -- these injuries, by and large, are going to be rare, and the only way you're going to find it is in

the post-marketing setting. And unless the resources are available there to do the actual studies, then the IOM has nothing to evaluate its evidence on. And this has been the record review after review after review. So fundamentally, the problem that we have is unlike the National Transportation Safety Board which, whenever an airplane crashes they have the funding to go out and do the investigation instead of raising the funds with the next appropriation -- next year's appropriation, or even the years after, in order to go out and do the investigation when already much of the evidence is already gone. That is our current situation is that for any particular hot topic, be it thimerosal, be it MMR and autism, we have basically no standing budget to go evaluate it and so that's the same concern that I have that if we even allocate one percent or two percent of the balance of the trust fund and/or if we were proposing a reduction from 75 cents to 50 cents per dose and devoted 25 cents of that to either preventing the future vaccine injuries or to the research, then a lot of this heat which -- attending the multiple ACCV meetings, it seems to me all this is just totally unnecessary. We now have advances in genetics. We have ways to studying this to get at the science. Instead we're going backwards to Agent

Orange, going back to when in fact just presumption and there's absolutely no -- so I think we need to get away from old. We need to move forward. Otherwise, I'll be happy to work with the AAP and others to improve that.

DR. MODLIN: Neal?

DR. HALSEY: Neal Halsey. I would like to express several concerns about the potential relaxation of the standards for compensation, both of the proposals. And there's some specific things that could be addressed with the Academy of Pediatrics one, but I think the establishment of a relationship or an association is so easy for many people to do, and it's unfortunate, but there is a small but growing industry of physicians and scientists who are willing to state that there is a relationship or an association, based upon either their expert opinion or based upon some limited studies that they may have performed, and even inventing some new assays that are being presented to seek compensation which are not based upon good science. And I think you're opening the door enormously to potential claims and compensation against virtually all the things that could be going wrong with people throughout their lives. And I'm not saying that there isn't room for relaxation of the process and improvement of the process. But I think

this is something that should be scrutinized extremely carefully.

There also is a need probably for the NVPO to hold a meeting on causality assessment in vaccine adverse events because there's a lot of misunderstanding over that process. And I think there's actually some misunderstanding that's represented in the Academy proposal, and I think it's too weak with regard to establishment of causality.

DR. MODLIN: Dixie?

DR. SNIDER: Dixie Snider. I guess I would just want to have some input into the process from this perspective. I mean having gone through some of the Agent Orange discussion here at the Agency and many other situations, I understand what -- I think where the Academy's coming from, where the program is coming from, where the parents are coming from and others. And it seems to me that in this whole process it's going to be important for all of us, including the ACIP, to be a little more refined in terms of how we characterize evidence and talk about the strength of evidence because there is -- there are criteria for causal associations and a certain -- there is a spectrum, in that associations can meet all the criteria or a subset of those criteria, or very -- maybe only one, a temporal

association. And it may be that society wishes to compensate people who have an event that is supported only because of a temporal association. It may be that the severe events are unfortunate enough and our society has enough resources that it wishes to compensate the parents and the child so that the child gets taken care of and everyone feels that there's justice.

But there is a danger, as Neal says, I think, in terms of the credibility of the immunization program, a misunderstanding of science and so forth, for people to take that decision as proof of a causal association. So I think it's going to be very important, no matter what's done, to very clearly articulate what's being done and whether that's based on establishment of a causal association or the fact that there are no data, but despite the absence of data society wants to provide compensation, or the data are very limited and only support a temporal association. Again, nevertheless, society wants to -- or doesn't want to, as the case may be. But the communication around this is going to be extremely important. Otherwise there are some potentials for adverse and inappropriate assumption that certain events actually have been proven to be associated with vaccines when in fact they haven't.

DR. EVANS: John --

DR. MODLIN: We had Sam first.

DR. EVANS: -- can I just respond to that a little bit?

DR. MODLIN: Yes.

DR. EVANS: I agree with what Dixie has said, and it does come down to what the original intent was of the program, and at that point there was a decade or so of studies and so on. It's now a dynamic process. We have new vaccines and we're put in a position where we have to reassess what the original intent was and whether we're going to have a compensation program that's only going to compensate five percent of claims. And there's no magic number whether you compensate -- is five percent right or 25 percent or 38 percent? No one knows the answer to that. But if litigation starts to go back to the tort system, then we will have not achieved one of our primary goals. So there's a tension here that's palpable and it's going to be up to us to try to figure out the best way to go forward and not create an unnecessary perception of risk for the vaccines we give.

DR. MODLIN: Sam?

DR. KATZ: As one who's -- Sam Katz. As one who's participated in many Institute of Medicine functions and as a member, I have great confidence in the

Institute of Medicine. And Kathy Stratton will be here this afternoon to talk to us a bit about the most recent report. As many of you know, their immunization review committee has published yesterday their report on immune overload and immune dysfunction as a possible cause of vaccine-related problems. However, I would point out that some of the criteria that were required for membership on these review committees were such that no one sitting in this room or around these tables could have been a member. If you'd ever been a member of the ACIP, of the FDA vaccine committee, of any formal committee that dealt with vaccines -- which hopefully would have brought some of the most knowledgeable people to the table -- you could not become a member of that committee. So it becomes a very, very questionable issue as to how the Institute of Medicine assumes its role in this.

I think they've done a wonderful job so far, and Kathy Stratton, again, will bring this to our attention. But I think there is an element of caution I would express in how the ground rules are established as who will do the Institute of Medicine reviews and what will happen with them.

You know, in my own -- as a pediatrician, I think any child who has any challenge or disability should be

cared for under our health system. Unfortunately, we don't have that sort of health system so we're still faced with these issues. But I wonder if maybe that's the way we should be going in the long run rather than prolonging this adversarial business.

DR. MODLIN: Georges, last word.

DR. PETER: Well, I think all these comments are very helpful, and some of the concerns that have been expressed are addressed in the detailed report that the working group of the Academy prepared, including careful language that states that indeed this positive association does not establish causation. But I think Dixie's point is very, very appropriate and, as Geoff said, this is a complex proposal and I think this discussion has been very, very helpful and indeed it is just a proposal at this point in time. The ACCV has not discussed it in further detail, so I thank all of you for your comments.

And I might add, Sam, you are a member of the Institute of Medicine committee and so -- I mean the Institute of Medicine so that you are a powerful factor perhaps in addressing some of these issues. And I think your comment about the fact that indeed a better system would be if we took care of children with disabilities generally is very appropriate. It's been made to me

as long ago as by Ted Mortimer when we were discussing in the early years about the compensation program. As he said, if only we had a system that took care of these children, we would not have some of these issues that arise where we attempt to compensate simply on the basis of a possible association with the vaccine rather than a more caring, all-encompassing health care system.

DR. MODLIN: Georges, Sam, thanks. Geoff, thanks very much.

DR. EVANS: Thank you.

DR. MODLIN: The next update will be the update from NCID. Alison, are you leading off? I actually would ask if possibly Tim might want to give a minute or two update on the recent HIV meeting.

DR. MAWLE: I'd like to update the Committee a little on some of the work that our influenza branch is doing, the avian influenza viruses that were found in humans in Hong Kong. Since this is a flu and bioterrorism meeting, it seems appropriate to get pandemic flu in there, as well.

I apologize for not having slides, but my laptop refused to turn on this morning, so.

Some of you may have seen the paper that was published in the Journal of Medical Virology from our influenza branch in January of this year describing some of the

sequence data from the H5N1 viruses and the H9N2 viruses that were isolated from humans. I just want to summarize what the paper found and just mention some of the implications of that.

They sequenced 16 H5N1 viruses that came from the 1997 outbreak, two H9N2 viruses that came from the 1999 -- and they also sequenced two human H3N2 viruses that were circulating there in 1997. And their interest was in the non-structural genes from these viruses.

Obviously the first interest was in the H and N genes, but they looked at the six non-structural genes to see what relationships there were between these viruses and what we could learn. In fact, before the H9N2 viruses were described in humans, they'd already looked at the internal genes of the H5N1 and shown that they were in fact of avian origin and most closely related to an H9N2 virus that came from quails. And when they went and looked at the two H9N2 viruses that went into humans, they found they had those very similar internal viruses from the H5N1 viruses.

They looked more closely by doing bootstrap analysis of the internal genes, comparing those human and avian sequences, to sequences for other avian viruses. And that's a fairly complicated analysis, but their bottom line is that they found that all the viruses that went

into humans, and the avian H5N1s that were circulating in the birds in Hong Kong, could be put into one clade. They also found that there were three other clades which were also H9N2, but those were all of avian origin. So the take-home message here is the internal genes of these viruses that went into humans, even over a two-year period and different lineages, were in fact identical. Okay? They're very closely related, and they're not found anywhere else.

And basically they also looked at what the amino acid sequence would come from the -- what would predict from those predicted sequences. They could get obviously very precise amino acids that were associated with those clades. And they also looked at what have been described as human amino acids versus avian amino acids in the influenza virology. It's been an article of faith, if you like, that there are certain amino acid sequences that you find in the internal genes that make it an avian virus or a human virus. When they looked, first of all, at the H3N1 virus -- N2 viruses that were circulating at that same time, they found four amino acids that in fact came from what had been considered the avian lineage. And when they looked at the clades that the -- clades one and clades two from these avian and the avian viruses that had jumped into humans and

true avian viruses, they also found mixed sequences. Some of them were what had been considered avian, some of them had been considered human. So this distinction that's been made between host -- human sequence -- human amino acids and avian amino acids really doesn't hold up and is something that needs to be reviewed and studied more carefully.

So the basic bottom line from these studies has been that the internal genes of the viruses -- the avian viruses that went into humans were very closely related to each other and different from other influenza -- human influenza A viruses. The high degree of similarity between the sequences suggests that there was very little selective pressure applied on those viruses, which is not surprising since there's no evidence at all that they were transmitted from human to human. There appeared to have been multiple transmission from birds to humans. The amino acid residues clearly distinguish them from avian isolates, and we need to re-evaluate what we mean by host-specific amino acid residues.

I think one of the interesting things and the reason I'm bring this paper up is that it gives us some answers about how this -- what is actually meant for an avian virus to go into humans. It's reasonably clear from

the pathogenicity studies that have been done that the H2N2 viruses were very mild, whereas the H5N1 -- there were significant fatalities and it was a much more serious disease. However, it may well be that these internal genes of this particular cluster is what's allowing them to grow well in host cells. And one of the things that the lab's beginning to do is look at these specific -- the amino acid sequences that was unique to these particular internal genes and start to ask questions about what those functions were.

Clearly the ability for an avian virus to grow in human cells has major implications for a virus of pandemic potential.

The other thing that would be really nice to be able to do is to begin to be able to predict what subgroups of avian viruses might be the ones that have more pandemic potential than others. There was a question yesterday about the H5N1 that's currently in Hong Kong that included this -- the slaughter. The internal genes from that virus are different from these, and there is no data right now that suggests that that virus ever went into humans. And there's obviously very good surveillance right now. We think it would have been picked up if anything had happened.

The other thing that's very exciting in the lab that's

being done with these viruses is we have the potential now to mix and match the genes, that the genetics of flu have come a long way. And they're beginning to do studies of mixing the genes from human viruses and avian viruses to look at which ones conferred transmitability. These are in animal studies in both mice and ferrets, with the goal eventually of hopefully being able to predict more precisely what viruses are going to lead to pandemic flu.

DR. MODLIN: Alison, when you say internal genes, I presume you mean genes for internal proteins. Is that the N protein or the --

DR. MAWLE: We're looking at -- that there are six genes, so you've got the matrix protein, the NS protein non-structural proteins, and then the three polymerase proteins.

DR. MODLIN: But the ones that are common for human proteins -- human virus protein sequences are --

DR. MAWLE: The ones that we talk about are the H and the N, those are external proteins.

DR. MODLIN: Right.

DR. MAWLE: So we're talking about all --

DR. MODLIN: But which internal protein are we talking about that is common -- that shows common sequences between human virus and avian virus?

DR. MAWLE: All of them.

DR. MODLIN: All of them.

DR. MAWLE: All that cluster.

DR. MODLIN: All the proteins? Okay. Other questions or comments for Dr. Mawle? Tim, can you give us a one-minute update on the HIV vaccine meeting?

DR. MASTRO: Tim Mastro from the National Center for HIV Prevention, thank you. I'd like to give a brief follow-up to the presentations I made last June on the status of the ongoing HIV/AIDS GP120 phase three HIV vaccine efficacy trials. One's going on in north America among 5,400 people at high risk for HIV infection. The other's going on in Bangkok, Thailand among 2,500 injecting drug users.

Since the last ACIP meeting in late October, the first efficacy analysis for the north American trial was conducted. The data safety monitoring board chaired by Walter Dowdle reviewed the efficacy data at that point and they advised the study to continue until its conclusion, which will be at the end of this year when we expect to then learn the efficacy results in early 2003. They noted there were no safety problems, no evidence of immune enhancement leading to higher incidence in the people getting vaccine. Presumably the trial did not reach its efficacy stopping point,

which would have been a lower confidence bound of 30 percent at a .03 level of efficacy, so we'll know in a year from now how that trial's working, and a year later from the Thai trial.

And just very briefly, last month, related to the possibility of having a partially effective vaccine, CDC convened a consultation on issues related to use of a partially effective vaccine in the United States. We'll be putting the notes together from that and publishing that in Clinical Infectious Diseases hopefully next month.

DR. MODLIN: Thanks, Tim. Any questions for Dr. Mastro?

(No response)

DR. MODLIN: Hearing none, we will take our scheduled break right now. I'm going to ask everybody to please be back at ten past 10:00. We'll start at ten past 10:00. We'll have a 20-minute break.

(Whereupon, a recess was taken from 9:50 a.m. to 10:15 a.m.)

DR. MODLIN: Would you please take your seats so that we can get started.

In October of 1999 the ACIP withdrew its existing recommendation on RotaShield that had been in place for about a year. We did so on the basis of information

that at the time was certainly good information and compelling, but on the other hand, was very preliminary. And we agreed that we would continue to revisit this issue as new information became available and as refinements were made to studies that were underway at that time.

It was about a year ago that Myron Levin joined the Committee, and we threw him a real curve ball in asking him to take on the leadership of the rotavirus working group and to lead the process of re-examination of that decision. We have had some discussions around this at our last couple of meetings, and the plan is today to focus on this in greater detail and Myron is going to take us through the issues.

DR. LEVIN: Thank you, John. So the rhesus -- the rotavirus working group has considered the recommendations for the use of the rhesus rotavirus vaccine and I'm going to use RRV as my symbol for RotaShield, which is really what we're going to be discussing here today.

First I want to give you the order in which we're going to discuss these things. The first issues have to do with events surrounding RotaShield that occurred in 1998 and '99. Then we'll talk a little bit about the interval history since the withdrawal of the ACIP

recommendation for its use. We'll then try to summarize for you the rotavirus working group activities and then summarize some recent meetings, one as recent as last night. We'll then have a discussion and we'll ask the ACIP to vote on what I'm presenting.

And finally I'd like to end up with two additional issues. One is a discussion of potential future research we thought should occur that we identified as important for future decisions about oral rotavirus vaccines.

And finally we want to talk a little bit about the manufacturer's concerns. This particular issue has raised a lot of peripheral issues that had to do with how vaccines come to market, how they're judged and what kind of rules the manufacturer faces as new vaccines might come on line.

Between 1998 and 1999 there was initially a pre-approval meeting and it was discussed how the rotavirus vaccine might be used. At that time a selective recommendation was considered, initially, and that was abandoned, primarily because it was felt that there was insufficient evidence that would allow us to decide how to use it selectively.

In August of 1998 the vaccine was approved by the FDA.

By November of that year it was recommended by the ACIP and that recommendation was published in March of 1999. The AAP, meanwhile, had published their recommendations in December of '98, and both the ACIP and the AAP put into their recommendations warnings at that time with respect to intussusception as a potential adverse event.

At the time that the ACIP recommendation was made, intussusception, IS, was made a unique VAERS code and the vaccine then was distributed. By August of -- well, let me just back up because actually it was distributed right after the recommendation, but by August -- July of 1999 already there were enough potential disturbing observations that led to the CDC to temporarily recommend suspension of the vaccine. And that temporary recommendation was based on VAERS reports up to that time of 15 cases of intussusception. There was data in the post-licensure follow-up from Kaiser-Permanente of additional cases of intussusception, and there were early results -- a similar follow-up in Minnesota -- for cases that eventually became part of the case control study that we're going to talk about. All of these together led to the temporary suspension of the recommendation, and the AAP withdrew its recommendation already by July of

1999.

In October of 1999 Wyeth-Lederle withdrew its vaccine from being available to the public, and I just want to point out to you that that was done prior to the next week when the ACIP met on the 22nd of October, 1999. At that time the intussusception data was presented in its preliminary analysis -- and I want to make that clear -- looking again at the VAERS data that it had accumulated up to that time, the cohort study and a case control study.

These were still in preliminary analysis, and I make that point because the numbers have changed somewhat over time as they have been refined. But I want you to understand that it's been an orderly process of trying to understand what numbers really fit the data that has come in.

The ACIP withdrew its recommendation at that time. When it withdrew its recommendation, it emphasized that that withdrawal was meant to apply to the situation here in the United States, and they felt that the same risk/benefit analysis might not apply to the use of the vaccine in the developing world where the risk and benefit ratio may be quite different.

By the time the vaccine was withdrawn, the following is true: There was approximately a million, perhaps

a little bit more than a million, doses administered, according to the National Immunization Survey. 540,000 age-eligible infants had been vaccinated. This was approximately less than 13 percent of the coverage for the children targeted for the vaccine. In the interval since then, there has been ongoing research in this problem. There is additional work on the epidemiology and the natural history of intussusception, of rotavirus infection, of a potential interaction between the two, finding in general that there is -- that rotavirus is not a common cause of intussusception except maybe the exception being in Japan with one investigator. There's been additional research in the diagnosis and management of intussusception. An animal model has been established to look at virus-induced intussusception, and there's been laboratory and clinical studies of candidate oral vaccines, some of which now are in testing.

I bring these up because these led to large workshops that bear directly on our deliberations today. Early in the year 2000 there was a workshop that was sponsored by the NIH and the National Vaccine Program Office. Then last year in September we had another workshop, the National Vaccine Advisory Committee and NVPO

jointly sponsoring it, and this was summarized for you at our last meeting here by Georges Peter. In Georges' summary he made the following important points: That the case control and case series studies indicated that there was a strong, temporal specific association between RotaShield and intussusception. The workshop at the time, in general, agreed that the population attributable risk was approximately one per 10,000 vaccinees, and this was primarily after the first dose of vaccine.

At the workshop we also heard information based on ecological studies. These ecological studies, they -- it was pointed out no epidemic of intussusception was detected after the use of RotaShield, as one might have expected if this was going to contribute a lot of new cases of intussusception. There were some criticisms of that, that the coverage rate was low, that there was some limited power to detect -- and those studies, by the way, were also in preliminary form and I'm going to tell you more about the subsequent follow-up with them.

But there was this disconnect between a increased risk of intussusception after vaccination and yet not being able to find it with a different kind of study. And in order to explain this, the people who did the

ecological studies suggested that maybe there was a triggering phenomenon. That is that individuals who got intussusception after the RotaShield were really predestined to get intussusception anyway, and that if one were to look further, there would be a compensatory decrease further down the line in the population that would have been vaccinated and that overall it would be a wash, that there would be ultimately no increase rotavirus-induced intussusception -- I'm sorry, no excess of intussusception in vaccinees who received RotaShield. This was discussed at great length and there was data against and for this hypothesis that really was discussed at the workshop.

So with all this information in mind, the working group and I'm going to tell you about their -- its composition -- deliberated on this. You can see here from the slide that the ACIP had six members in the group. There were five members on it from CDC. The FDA had two representatives, HRSA had a representative, the AAP had two representatives at different times. You'll see some names appear in both in two different places because people change hats. Rick Zimmerman, for example, is on both the ACIP and was on the AAFP representation. National Medical Association had a representative. Sam Katz

represented the IDSA and Patricia Fast for NVAC and NVPO.

There were four opportunities for us to work together. There were two teleconferences. There was a meeting before the ACIP meeting in June of last year, and there was a meeting last night. Approximately half of us, if not more, were at the workshop in September to hear the discussions of the issues I've been talking to you about.

I want you to understand what information has been reviewed. There were these articles by Simonsen, which represents the ecological analyses -- and we again heard, by the way, a lot of this information last night as she updated her data. There is an article that talks about the ability or the likelihood that parents would accept a rotavirus vaccine at this time, an important issue. There are articles, as you see, about whether or not there's triggering or whether there might not be triggering. You see information here about seizures with pertussis because that was an instance where triggering has been implicated.

There were a number of letters written, one from the I think he's assistant director of the NIAID. There were letters for and against triggering and ecological studies, as shown here, in the New England Journal and

to Lancet, everybody explaining their position. There was the draft of the last workshop that Georges Peter reported on that everybody got a chance to look at; it has not yet been published. Phil Rhodes had a follow-up, looking for a compensatory decrease in one of these cohort studies. Larry Pickering surveyed pediatricians to see the likelihood of them accepting an oral vaccine at this time, and we have that information. And we asked the manufacturer to give us information on what their concerns were about this deliberation.

There was, you see here, additional pieces of information that really had to do with putting in context the problem we were faced with with a similar context of -- for example here, pertussis and other vaccines where there have been adverse events, and how to weigh -- really it has to do with how to structure a risk benefit analysis.

So I'm going to really focus on our activity in this past month. We had a teleconference on the 7th of February which was preliminary to going over all the information and gave a final opportunity to hear the ecological studies last night, and then allowed us to deliberate further.

We agreed that all the relevant information that I've

shown you had been reviewed, that there was nothing else to be reviewed, and that all of it was sent to the ACIP which must have a lot of paper at home. We then had another presentation last night, as I said, of the ecological data and a discussion of it.

So from those several meetings -- I'm going to sum up both the teleconference meeting and the one last night a number of items were discussed. What about the possibility of a selective recommendation? That had been rejected in the past and it was rejected this time again because we felt we had inadequate information on side effects in the high risk group; who a high risk group would be, after all. Targeting minorities as a high risk group would be difficult politically, and I think we'd have trouble getting caretakers of minority individuals to utilize this vaccine at this time with confidence. We're not sure exactly what the safety profile might be in a selected group and we have a fair understanding -- and manufacturers can correct me -- that there would not be vaccines sufficient -- this wouldn't be a sufficient recommendation for a manufacturer to go forward and provide vaccine.

We talked about a universal recommendation. We agreed, first of all, that having an oral rotavirus vaccine would be valuable for the United States, and

indeed for the rest of the world, and this was -- and almost everyone agreed with this. The feeling was that even if we had the appropriate risk benefit analysis that it would show that it would be valuable, although there was some disagreement. The next bullet is whether or not we have the appropriate risk benefit analysis. Some limitations were mentioned. For example, we don't include in it at the present time the cost of education that will be required to sell -- sell, in quotes -- a new oral rotavirus vaccine. To get people to use it, I guess is what I mean. And we don't have factored in, for example, the number of emergency room visits and workups that might be required because people are now afraid the side effects they're seeing are in fact due to the vaccine, and so forth. And so I think we feel the cost benefit analysis may not yet be adequate.

There was general agreement that there is a attributable risk of about one in 10,000, and we all agreed that the future use of a vaccine such as this will require a strong education program, but we didn't favor a universal recommendation.

We agreed that the vaccine will be -- such a vaccine would be very important and will be in developing countries; that US policy does affect policy in other

countries, but we didn't think that it is the -- would necessarily be the major determinant of whether the vaccine would be used elsewhere. And there are several examples given where our policies differ from those that are used abroad. So that's an issue, but it's an issue that we couldn't solve.

In summary, what the rotavirus working group favored was that there should be no change to the current ACIP policy to withhold a recommendation for the use of RotaShield in children in the United States. There was a minority opinion that a permissive recommendation might be possible.

There were three reasons why that was considered as not the best solution. One is that there -- it's still our understanding that there will be no vaccine available for such a recommendation, and I would be happy to have the representatives of manufacturers correct me or speak to this point when we finish. The second is that it's unlikely that it would be heavily used in the current environment, which you're all familiar with. And the third reason is it would be very hard, in my opinion and in our opinion, for an ACIP to recommend a vaccine that doesn't exist at the present time. It would affect our credibility. So for all those reasons, that remained a minority view, although some

people were enamored of the idea that perhaps that would be one way to move forward with studying that vaccine. So John, maybe now's the time to have a discussion.

DR. MODLIN: Maybe the way to start would be to first ask Mr. Reilly if you'd like to respond for Wyeth.

MR. REILLY: Kevin Reilly for Wyeth. Let me expand a little bit. I agree with what Myron has said and -- but I would like to sort of fill in some of the issues and some of the deliberations we have faced.

First of all, and I think I said it at the last meeting, we at Wyeth will clearly follow the direction of the Committee. We're not trying to set policy. We are trying to follow the direction of the Committee in whatever direction the Committee wants to move if we can feasibly do that.

In terms of a permissive recommendation, I think I would sort of echo and even more strongly raise some of the concerns that were just raised on a permissive recommendation. In our mind, a permissive recommendation would not clear the vaccine, in the public sense. I think if we want to use this rotavirus vaccine and if we feel that it has a cost benefit that makes it useable, in our assessment, the only thing that will do that is a universal use recommendation. I would agree with Myron, in our estimate, if there is

a permissive recommendation, we think the usage -- given the publicity, given the history of this vaccine -- that the usage would be very low. And we do not think it fits into the model of some of the prior ACIP recommendations where a vaccine has started off with a permissive recommendation and then evolved to a universal recommendation after some years of use. We're in the opposite situation. We've had a universal, we're backed off it. We don't see that we're in a normal, typical permissive environment. I would also draw everyone's attention to the discussion we've just had before the break. We live in a very litigious environment. Litigation is an issue that we have to consider as a manufacturer, and I would put our position as a manufacturer or sponsor of a vaccine -- and the difficult position that we would feel that we were in if we were providing a vaccine that has a known trigger or a known side effect, and I think we all are aware of the concerns of the administration of vaccines to healthy infants.

I have said previously, and I would repeat it, we are prepared to reinstitute manufacturing in the face of a universal recommendation because then we know there would be a substantial use of the vaccine. In the face of a permissive, we think it would be very low. It is

three years now since discontinuation and we -- the facilities that we were using for rotavirus vaccine manufacture were moved on to other activities. We do have the ability to reinstate, but it is a significant operational issue and a regulatory issue. Frankly, we would probably have to go back through the FDA again in reinstituting manufacture, which will be a significant task for all of us.

I would touch on the developing countries. Our assessment, and through relative -- I must admit, relatively informal probing and market research that we have done, we also think that it would -- to clear this vaccine for use in the developing countries, the signal that will do it is a universal recommendation, not a permissive. We do not think that that is going to be a trigger -- a signal strong enough to get widespread use in developing countries. And in developing countries we're also faced -- we know the benefits are significantly higher than in the US. No one knows at this stage the other side -- the risk factors of intussusception in developing countries, and the lack of medical treatment. So we treat both side of the equation in developing countries as being very different to the US and a very serious issue.

DR. MODLIN: Thanks, Mr. Reilly. Jon or Gary of the

AAP, I wonder if you'd like to -- this would be an appropriate time just to give us your opinion and as to whether or not that has changed or evolved in any way over the last six to 12 months or longer.

DR. ABRAMSON: This is Jon Abramson for the AAP. No, I do not see any movement towards changing our current recommendation.

DR. MODLIN: Rick?

DR. CLOVER: Rick Clover from the AAP. I'm the same, we don't see any movement toward change of our current recommendation.

DR. MODLIN: I certainly think we probably should open this up for discussion -- for general discussion, so if there are others who have thoughts or opinions or questions about the process, the data. We've got everybody here in the room. Rick?

DR. ZIMMERMAN: Rick Zimmerman. I just think Myron deserves credit for doing an incredible job of really bringing this together and obviously different points of view and a lot of data, so I think he deserves our thanks for that.

DR. MODLIN: Lucy?

DR. TOMPKINS: I just -- Lucy Tompkins. Just regarding some information, Myron. I believe I read that there are studies going on now in some developing

countries on a vaccine for rotavirus. Is that correct? Where there will be a risk benefit calculation?

DR. LEVIN: I know there are studies going on, but I thought they were in developed countries. If someone knows about studies in developing countries, if they could speak up.

DR. MODLIN: I wonder if anybody from either Merck or Smith Kline.

DR. LEVIN: Here's Tom Vernon.

DR. MODLIN: Tom?

MR. VERNON: Thank you. I am Tom Vernon from the Merck vaccine division. I did want to comment by way of an optimistic note. I am convinced that rotavirus will be back to this Committee. It may be the GSK vaccine, it may be ours, or very likely both.

We are quite pleased with our clinical trial as it is now going forward, a very satisfactory enrollment rate, and that enrollment is in the first world and shortly will be expanded in the third world, as a matter of fact. And so I trust that those of you who will still be on the Committee when the issue comes back are prepared to -- and I believe you will be looking at a vaccine which has proven out very, very well in the trials.

I also trust that my colleagues won't mind my mentioning one number, and that is in the trial so far -- and we have had a case of intussusception. It occurred four months after the third dose. And whether those doses were the vaccine or the placebo, of course, we don't know.

In short, we are optimistic as we go forward. We're pleased with the enrollment as it is now occurring. Finally, I would add my thanks and congratulations to Myron Levin for the way in which the rotavirus work group has carried forward. Thank you.

DR. MODLIN: Thanks, Tom. Barbara?

MS. HOUK: Barbara Houk from GlaxoSmithKline. I just wanted to mention that we do have clinical trials ongoing outside the US in both developed and developing countries. To date we have limited experience in making any strong safety comments, but we do plan to go forward with expanding trials in developing countries in the near future.

DR. MODLIN: Thank you. Dr. Kapikian or Dave Morens or anyone from NIH, would you -- we'd certainly welcome comments or thoughts if you'd like to address the group.

DR. KAPIKIAN: I'd just like to make one comment about the permissive recommendation, also thank Myron for

the intensive work he's been doing in this Committee, and that is that I know the comments about permissive recommendation or what's been stated here. But a vote by the ACIP for a permissive recommendation would send a powerful message to the developing countries that would have a profound effect on the survival of millions of infants in the developing world, because developing countries will not use a vaccine essentially banned in the United States.

I've been approached by various foundations in the last few years, and also by members of a country -- a developing county where they have an excellent record for vaccine production, who have asked about the availability of the four rotavirus strains in RotaShield in order to make it for the developing world and make it under conditions where the price would be very low. But with our connection, of course, that these strains were committed to Wyeth Laboratories, I always said we had to wait in order to see what was going to happen to this issue.

Now that it appears that Wyeth has indicated that it's not interested in this permissive recommendation, the NIH can now, we think, make the four rotavirus strains in RotaShield available to these foundations and also to the country that has an excellent record in making

this vaccine for production in developing countries and for use in those countries at a low price. However, as I said before, developing countries will not use the rotavirus vaccine because it is still essentially banned in the United States.

My final point is that a permissive recommendation from this Committee, although it's not practical from the standpoint of availability of a vaccine because, as we've learned today from Mr. Reilly, no vaccine will become available under these circumstances. But a permissive recommendation would have a tremendous effect in the developing countries of the world where it's estimated 2,000 infants die every day from rotavirus diarrhea, because it would free up this vaccine for production in the third world inexpensively for use where it's needed most. And believe me, I know I've had discussions with people here and outside at the meetings I've attended in Geneva and different places, they say why don't the developing countries use the vaccine from the risk benefit question? The benefit is so much greater than the risk. But as some of you in the room have been to these same meetings, there is no way that we'll use a vaccine that is essentially banned in the United States. And I think a message from this Committee of a permissive

recommendation, in theory, would free up these strains to be made in developing countries and would make this vaccine available for use where it's really needed, and these foundations and the developing county where this could be made is a real fact and it could move forward. But without a positive comment -- and the comment that was made in the original withdrawal where you all said the right decision in October of 1999 should not bear in developing countries carried absolutely no weight at the meetings in Geneva. They said but it's not can't be given. But at least a permissive recommendation, although the vaccine's not available, would say it could be given if it were available. That would have a tremendous weight and we might save 800,000 lives this year instead of waiting five years for new vaccine to come down the line. Thanks a lot.

DR. MODLIN: Al, thank you. I think everybody in the room certainly knows that Dr. Kapikian is a real pioneer in the development of vaccines for rotavirus disease and indeed understanding rotavirus disease and is the creator of this very innovative vaccine that we're discussing today.

Bob Chen?

DR. CHEN: I wonder if there is a bit -- one bit of evidence that was presented at the NVPO meeting in

September that may lead us a way out of this impasse between developed versus developing countries. And again, this -- it's just a hypothesis, but I think it's worth exploring. What was striking was that the Cubans did a study of OPV and intussusception on a whole different topic that we won't go into in great detail, but the only bit that I want to highlight is that in contrast to the US where we see absolutely no seasonality whatsoever with intussusception -- be it New York, be it in the HMOs, just totally flat -- in Cuba -- which is not that far away and hygienically perhaps better than most developing countries, and one would classify perhaps even not a developing country there was a marked seasonality. It looked just like a rotavirus epidemic curve, a volcano that peaks in April of each year and falls back down.

Now what is the significance of that? Well, that suggests to me that the epidemiology of intussusception in developed versus developing countries is very different. Then what's the next step from that? Well, if we think of intussusception as more or less a sentinel event for antigenic stimulation of the gut from various enteric infections, that may start to give us a clue. We acknowledge that the gut of the infant in developed

versus developing countries is very different, that the range of GI infections in the very clean environment in the US is very different than that that might be in a tropical setting, and such the risk for intussusception after rotavirus vaccine may in fact be very different in the two settings.

Now there's one other situation where this seems to be the case, at least in terms of my personal experience. Back in the 1980s before acceptance of AFP as the marker for success of polio eradication program, they asked me to review the epidemiology of Guillain-Barré syndrome in developed versus developing countries because of our virus studies in association with the flu vaccine, and it was striking to us that GBS in developed countries is by and large a disease of the elderly, people in the 50 and 65 years of age, probably semi-immunocompromised. Whereas GBS, as well as other AFP in developing countries, is a disease of children less than ten. And the way to explain that, given what we now know about potential infectious triggers of GBS, that might be why the GBS has asymmetry in developed versus developing countries.

So it's still just a hint, but I think it's something that's worthy and I'm very pleased that Barbara Houk mentioned that in their studies they're looking in both

developed and developing countries for their vaccine because I think at the end of the day it might be a way to solve this conundrum, and that is in fact intussusception may be a very different risk factor in the two settings.

DR. MODLIN: Dr. Morens?

DR. MORENS: David Morens, NIH. I wanted to ask Mr. Reilly, I think I understood your position and comments about the undesirability of a permissive recommendation. But I wondered whether you'd comment on whether there are any situations under a permissive recommendation in which you might be willing to reconsider making the vaccine?

MR. REILLY: I'm not sure I really -- I'm sorry, Kevin Reilly from Wyeth. I'm not sure I really understand the question. I'm not quite sure what's being asked.

DR. MORENS: Well, what I meant to say is you've indicated that a permissive recommendation from ACIP would be undesirable and that it would be very difficult you don't think the vaccine would work under a permissive recommendation. But what I'm asking you is if there were some sort of permissive recommendation, are there any circumstances under a variety of permissive recommendation in which Wyeth would reconsider making the vaccine, even though the use

might be very low?

MR. REILLY: I'm still not sure I clearly understand what's being asked. All I can do is repeat what I said a little bit earlier on. I think given the circumstances of this vaccine, given the history and the publicity that was -- surrounded the withdrawal and the commentary on the vaccine at that time, I think a permissive recommendation in the United States would have very low usage, very low pick-up by the parents and practitioners and not achieve any of the positive issues of validating this vaccine for use in developing countries and use overseas.

DR. MODLIN: Roger?

MR. GLASS: Yeah, John, I just want to make two observations.

UNIDENTIFIED SPEAKER: Name, please?

MR. GLASS: Yeah, Roger Glass from NCID. I wanted to make several observations. I think we first came to this Committee in October of 1995 with the first discussion of rotavirus and its importance in the world and United States. And that began a dialogue with ACIP over three years, in which everyone embraced the idea that this was clearly an important vaccine for the United States and for the world.

The events with intussusception were really a shock and

disheartening, but I was quite heartened to hear -- to see that both Glaxo Smith Kline and Merck are moving ahead, both in testing their vaccines in the US and developing countries. So I think that's a clear indication that we will be back to talk about rotavirus and perhaps to have a vaccine in the near future. But I really want to underscore that throughout this difficult period, I think the leadership, John, of you and Myron to get the working group together and to consolidate opinions and air them fully is really one of the positive events that's come. And I think that open discussion over two years, however difficult it has been, underscores the wonderful work that you both have done and I wanted to say that on behalf of the working group. Thank you.

DR. MODLIN: Thanks, Roger. Other thoughts, comments, questions? Dr. Deseda?

DR. DESEDA: I just wanted to make a few points. One of them is the fact that there's been so many changes in the last year or year and a half in terms of the risk associated to the vaccine, like one out of 2,500 to one to 10,000. That is -- definitely sheds new light on the subject, and I'm in favor of a permissive recommendation because I think it's a step in the right direction. And like other people have said,

eventually we're going to be facing the same problem where the other drug companies or any other manufacturer. And in at least where I come from, when we discussed this in a number of meetings, the way a lot of pediatricians see this -- which surprised me initially -- is that if there is a vaccine where there is a risk of intussusception associated within the next two or three weeks, this period of alertness or concern is -- they see this as a positive thing in the sense that everybody will be thinking about intussusception. I understand that this would also include a lot of expenses in workups. But still, you can see it's an attractive side-effect of the use of the vaccine. But what I find very hard to understand is how a drug company -- essentially looking for an economic venture using the vaccine in this country, where there is probably much more profit than using it in third world countries where it's needed -- how can they be so insensitive in the sense of completely opposing a permissive recommendation?

DR. MODLIN: I think maybe this is a good time to begin to focus in on this question. Let me ask if there are other members of the Committee -- voting members, if they -- if there are other members who would support a permissive recommendation; and if so, why. And, I'm

not asking for a vote, but maybe I could press you on this issue a bit in terms of a permissive recommendation. You would be in favor of that, even if it appears that it's unlikely that the vaccine would be produced and distributed in this country -- in the United States?

Other comments or questions? Rick?

DR. ZIMMERMAN: I think two comments -- Rick Zimmerman. I think two comments that bear following up on. One is a note that has been made several times and in somewhat different contexts, so that we started out with a universal recommendation. We then went against a universal -- we withdrew that recommendation. And so it makes it very difficult to do anything. And in hindsight, which is obviously much better than -- it might have been better for us to have started with permissive, to have gathered the data. And I don't know what the decision would have been if we had started permissive and it's kind of hard to know.

But it's -- as we think about the future, we may not want to jump to a universal recommendation quite so quickly, to allow a time when there is -- with the next vaccine -- some permissive use, allow more data to be gathered on adverse reactions in a large population

through VAERS, and then move toward a universal instead of making the jump as quickly as we did.

DR. MODLIN: Well, just to press you a bit on that, I remember us being very much part of the process from 1995, as --

DR. ZIMMERMAN: Sure.

DR. MODLIN: -- Roger mentioned. This Committee was looking at the possibility of preventing 50,000 hospitalizations due to infant diarrhea in this country and so that a -- the prospect of a universal recommendation was very attractive at the time.

DR. ZIMMERMAN: It was. It was to me, too.

DR. MODLIN: Paul?

DR. OFFIT: I think that offering a permissive recommendation as a means of gaining more safety data is problematic in the sense that I think that pediatricians and family practitioners look to Committees like ours or the AAP to send a clear and definitive message about whether or not we think a vaccine should be used. When we say to them, you know, use it if you will, I think we wouldn't be in a position to gain a lot of safety data because I think it wouldn't be used. So I think we're going to have to make a decision with the next vaccines whether or not we think the pre-licensure data are sufficient to at least put

us on a level of comfort regarding those vaccines. That's the way it's going to have to work.

DR. MODLIN: Dr. Fedson?

DR. FEDSON: David Fedson, Aventis Pasteur MST. I'd just like to ask a question that really reflects a personal opinion and not that of my company. It seems to me that the crucial question here is whether or not there is a market for the Wyeth-Lederle product, and obviously -- for very good reasons -- there seems not to be in the United States or perhaps other developed countries. But if a market could be guaranteed for that vaccine that was sufficiently attractive from the company point of view, then there would be another basis for Wyeth-Lederle to reconsider going back into production, and that would seem to me to come from the international community, the Children's Vaccine Fund, the Global Alliance for Vaccine Immunization, and so the question really should not be one so much about the notion of whether a permissive recommendation by this Committee would persuade the world, but what the world would want if a company would produce the vaccine. And I think that that's the kind of question that really can and should be asked, and I think that would provide a definitive answer. I don't think that the ACIP needs to regard itself as the arbiter of whether the world

will or will not use a vaccine. There are certainly vaccine recommendations in many countries, developed and developing, which are at great odds with the recommendations that come out of this Committee and that will continue to exist.

DR. MODLIN: Good point. Thank you. Other comments? Gus?

DR. BIRKHEAD: I was just going to say that -- Gus Birkhead -- that I think it's not realistic or practical for this group to have a permissive recommendation, given our scope of our responsibility. But I am very sensitive to this issue of the influence of the recommendations here internationally, and I wonder if it's possible that we could have some statement that risk/benefit of the vaccine is not sufficiently small in the United States, but depending on the circumstances, may be -- something that says that we recognize that there may be situations where it could be used.

DR. MODLIN: I would point out --

DR. BIRKHEAD: That may be beyond our scope, but --

DR. MODLIN: It's not, and in fact we've already made such a statement with the -- at the time the original recommendation was withdrawn in October of '99. It may very well be that first you'd want to review the

language of that and see if you'd want to change it in any way. Paul?

DR. OFFIT: I have a question actually for Karen. I mean it seems to me that the FDA is a body who is responsible in large part for determining whether or not vaccines are safe. The RotaShield vaccine now has been licensed and there are now new data that have been generated post-licensure. Let me ask an impossible question for you. If these data were now submitted to you pre-licensure, would you license this vaccine?

(Laughter)

DR. MIDTHUN: Paul, that is an impossible question, but I guess what I can say is that most certainly for vaccines in general, there are always new data that become available post-licensure. And getting back to one thing that Geoff Evans said earlier, for example, for new vaccines that get licensed, we don't have table events. But that's not to say that there aren't serious adverse events that later on are identified with a vaccine. Usually these are very rare events. That's why we don't see them in the initial licensure application, because those typically will involve -- maybe even a large study would involve tens of thousands. For example, Prevenar had 40,000 infants, 20,000 roughly of whom received the vaccine, and that

was a large study. So there's always new information that you expect to become available. And the way we deal with that is we're constantly evaluating it. We will update package inserts to reflect new information. And so it's always a process that's in flux.

And I guess I'd just like to comment on something that someone else mentioned with regard to do you come out with a permissive or with a universal recommendation. This was something that was actually discussed at a vaccine safety workshop that was held in November of 2000 because the issue that arose there was that it really is very difficult, oftentimes ever, to have what you would like to have in terms of the information at the time of licensure. You always want to know more. And one of the things that was discussed at that meeting was perhaps there ought to be consideration of a transition between the time of licensure and actually coming out with a universal recommendation so that one does have a mechanism to gather additional data, maybe through the large post-marketing studies. But it's always difficult, Paul.

But certainly there are new events that are identified with vaccines and those end up in the label. I mean obviously vaccine is associated with paralytic polio.

It was something that was in the OPV label. Clearly that was a very, very serious adverse event. It was rare, but it was very serious and it was there. And that vaccine obviously continued to be used for some period of time until the decision was that there should be a transition to IPV.

DR. MODLIN: Thanks, Karen. It raises some other issues, but we probably ought to continue to focus on this. Dixie?

DR. SNIDER: I just think on this issue that -- and it holds, of course, for every issue -- that just as a pragmatic matter to remind everyone that the ACIP recommendations are made to the Secretary -- the Assistant Secretary for Health and the Director of CDC, who then have to accept those recommendations. And so as a practical matter, there's also the issue of, should you decide you wanted a permissive recommendation, you would be making it to those individuals and you would have the burden of -- to prove to those people that that was a rational decision for them to accept.

DR. MODLIN: Good point. Yes?

DR. WARD: Dick Ward from Children's Hospital in Cincinnati. One issue I just wanted to raise, and maybe it's a question and maybe it's a comment, but the having made a recommendation for a vaccine and then

having to have withdrawn that universal recommendation, the concern that we all face is what's going to happen with the next two now? It's already been pointed out there's a good chance that two more will be back here within some time.

The two companies that have developed these vaccines clearly both believe that there's a reasonable chance that theirs -- their vaccine will not cause intussusception or they would not have gone forward. However, because it's now one in 10,000 is the numbers that are believed to be caused by the tetravalent rhesus vaccine, that it's going to be extremely difficult to establish that either of these vaccines is not going to cause any intussusception. So my concern is, when these two vaccines do get reviewed by this Committee in the future that the bar will not be set so high that there will be no chance of -- no matter how many children are evaluated pre-licensure, that the bar will be set so high that you'll never be able to truly give a universal recommendation.

DR. MODLIN: Dr. Ward, you raise an issue that actually we'd planned to discuss as soon as we finished making a decision specifically on this issue. I know that Myron is planning on addressing that. Maybe we should move on. Is there anyone else who wishes to comment

specifically on the issue of withdrawing the recommendation or reinstituting it?

If not, Myron, I wonder if the question really should be before the Committee as to whether or not to accept the recommendation of the working group, which is to make no change?

DR. LEVIN: Yeah, our feeling was to ask this question of the group: Do you want to alter your current recommendation concerning the use of RotaShield in the United States?

DR. MODLIN: I do think we need to vote on this issue, and I guess the question would be -- perhaps the motion, if I can make it, may be do we wish to continue our current policy or not? In other words, to make no change to the withdrawal of the recommendation that was made by this Committee in October of '99. Is that clear?

I'll propose that. Could I have a second?

DR. ZIMMERMAN: Second.

DR. MODLIN: Seconded by Dr. Zimmerman. Okay, those who are conflicted with Wyeth, with Merck and with Smith Kline may not vote, and those individuals are Dr. Pennels and Dr. Offit.

DR. LEVIN: And myself. I'm conflicted --

DR. MODLIN: And Dr. Levin. So we still have a

quorum, I believe, so those in favor of that motion? Those in favor would be Dr. Smith, Dr. Zimmerman, Dr. Tompkins, Mr. Salamone, Dr. Brooks, Dr. Birkhead, Dr. Ward and Dr. Modlin. Those opposed? Dr. Deseda. Those abstaining? Dr. Rennels, Dr. Offit and Dr. Levin. Thank you.

Myron, why don't we go ahead with the other question that you posed to us?

DR. LEVIN: So that the next issue that we -- and actually have been considering all along -- is what other information might be needed if we were to consider this issue again or an issue related to other potential oral rotavirus vaccines? And you've already heard optimism that there will be such vaccines available. The information I'm going to relay to you came not only from the members of the working group, but also from a lot of input from manufacturers and from other individuals that we've consulted. Specifically, in order to get the proper cost benefit analysis, we feel that we need better information on rotavirus morbidity, hospitalization and mortality, stratified, for example, by age, by region of the country or in fact the world, and maybe by type of rotavirus that's causing the infection. We need better information on intussusception, again stratified by risk factors such

as those that are shown. We would like to have better methods for early diagnosis of intussusception and treatment. We saw some information on this at the last workshop. It really wasn't ready for prime time, but it would be nice to have a way of quickly determining that intussusception is present in a child and maybe dealing with it sooner.

We would like to have more information on how the animal models could be used, both to study intussusception and, perhaps more important, to see if they would provide some sort of correlate of safety so that we could test the new candidate vaccines.

We would also like to have correlates, whether they be clinical or virological, for a vaccine's likelihood to cause complications. Some individuals felt that maybe alternate approaches, such as a vaccine or virus-like particles in an oral vaccine might be another way to go and might, for some reason, be safer.

We would like to know more about whether or not the benefits and limitations of oral rehydration are as advertised. For example, even though these work, are they used adequately? Could we use them better and is there a population of children that you can't use them in readily? You don't have that information.

Clearly we would like to see what happened with the

large clinical trials that you've heard about that are ongoing, and maybe this is going to be the real solution. And by sufficiently large, I mean of the size that are already underway.

We need reliable information, and I think the information we have is just preliminary, on whether or not the oral rotavirus vaccine of any kind would be accepted by care givers and by professionals who would use them.

And I think a lot of people have made this point, and I think Dr. Ward was hinting at it, and you'll see that the manufacturers are concerned about this. Can we create a public health forum that will weigh the risks and benefits, cost effectiveness, of any candidate oral vaccines and weigh them against other strategies and, in essence, create an environment where we know what would be acceptable. And maybe I should just stop there for a moment, John, and say that there are a lot of Federal agencies that have differing constituents, different sets of rules about how they evaluate this information. And I think it often makes a playing field that's difficult for the manufacturers to know exactly who to turn to from what and who's going to trump whom.

So what we really need is to create an environment --

I hate to use the word committee. Create a process by which we could have different groups represented that could all deal with this question in a forthright way and put in place a way of systematically trying to answer this question.

Now we may not come up with the final answer. I don't think it's the ACIP's job alone. I think we should participate, but I think we need to work with others to try to answer this critical question as to what would be acceptable, not only for this vaccine but for vaccines in general.

DR. MODLIN: Since the FDA is such an important part of this thinking, this process, I guess I would ask Karen as to whether or not this sort of a public discussion around this issue would be helpful to the agency in terms of trying to get an understanding of what we, as a group representing children in this country, would accept as a -- would accept as a risk benefit for a valuable vaccine in terms that does have rare but important side effects.

DR. MIDTHUN: I think certainly we would all benefit from public considerations of some of these very important issues. I think that I really have to go back and get some further input, though, because I think one of the issues we of course consider is for -- when

we approve a product is for the individual, what is that risk benefit. And this is a much broader view, which is more -- on a societal basis, what kinds of things do we want to consider. So I think that's really -- is a very big question and I really need to do a little more homework on that.

DR. MODLIN: Marty?

DR. MYERS: I don't want to speak for Georges, but I think this is central to the issue that he was talking about, the new working group that he's going to chair with NVAC on making decisions in uncertainty and with engagement of consumer groups and other parties. Maybe Georges would comment, but I think this is the type of discussion that should occur there.

DR. PETER: Thanks, Marty. As you leave me, you're suggesting I take on this assignment. No, I think this is an appropriate topic to discuss. I'm not sure how readily answerable it can be because, as you said, Myron, the different groups have different constituencies. And really the question you're asking is what level of risk we're willing to accept. And Dr. Salisbury, who is with us, discussed eloquently at the workshop this very issue, and I don't think we know. But I think we should perhaps have some further discussions, even if we can't come to an agreement,

because this question will be critically important for when indeed the candidate vaccines are presented. The broader issue, though, of acceptance of risk is a very difficult one. A very rare risk that leads to a fatal disease will not be as well accepted as, for example, a relatively more common risk that has less complications, so -- and I think one of the points that Tom Sari made at the workshop was that intussusception, even though it may be a rare complication, is a major problem for pediatricians in a rural practice. So the implications are much greater than simply a febrile seizure following pertussis vaccine. I only cite those points to indicate the complexity of the decision-making process.

Good point, though, that Marty makes about our work group will really be how we have established policy in the past in the face of uncertainty, and can we make suggestions. And one of the suggestions might be a forum to discuss these kind of issues as you have --

DR. LEVIN: Can I just answer that, John, in that I think what you're touching on touches on the issue of education that we're going to bring up. I think it will be very important for the public and for the practicing physicians to hear that we have a group that has grappled with this problem, even if we don't have

the answer, so that when the educational program comes into being, it's in the context of having been well thought out as to what the problems are. Those that we can answer, we will; those that we can't, at least we can speak forthrightly about.

DR. MODLIN: Good point. Dixie?

DR. SNIDER: Dixie Snider. Yet I think that this is quite a broad issue in thinking about the discussions we had yesterday when Hal was talking about smallpox vaccine. We run into some of the same problems. How do we engage the public in some kind of dialogue? So it's not just childhood vaccines, but it runs the gamut. And there are some people from other disciplines who've actually published some textbooks on how to engage the public effectively in controversial issues. I guess what I'm saying is that they're not necessarily represented in the vaccine community that we have normally tapped into, but I think now is the time to tap into some of those people who have studied these issues of how to engage the public effectively around some controversial decisions.

DR. PETER: Dixie, if I could add one other comment, which is I think the NVAC, in its discussions of the smallpox preparedness plan, was very cognizant of the particular point you made. I mean the smallpox

decisions that are made are associated with controversy and we do need to engage the public and we do need to have better mechanisms if indeed our decisions are going to be accepted. So I very much welcome that suggestion, Dixie. I think it's most appropriate.

DR. MODLIN: Geoff?

DR. EVANS: Going along with the idea of engaging the public, in bullet number two I think it's also important that we have empirical research on how people view risk and make risk decisions, and that the public and parents be part of that bullet.

DR. MODLIN: Bob Chen?

DR. CHEN: I just wanted to address really more the first point. I think fundamentally we are in a dilemma in that historically events as rare as one in 100,000, be it GBS after swine flu vaccine or acute encephalopathy after whole cell pertussis vaccine, at the end of the day were not acceptable in the US context. And yet obviously the pre-licensure clinical trials will never be -- I don't think we, at this point, have the logistics of the cost to be able to afford to do that. So then our challenge is would a -- is there a transient phase of some type that we can get at, and on top of that, is there a methodological way to make

sure that we could actually detect something that we weren't looking for before. And in the rotavirus example, we were actually very fortunate that the pre-licensure trials did tip us off that intussusception may be a problem and there was some specific coded added on that.

But the larger question is if we weren't so lucky, could we still detect a potential problem? And we've been working with our methodologist, both internally at CDC and FDA, to see if we could use some of our data mining tools out there and from our group has actually demonstrated recently that as early as December of 1998, even before the first report of intussusception came into VAERS in February of '99, and definitely way before when the MMWR article came out in July of '99, it is now possible to detect a signal. So hopefully in future we'll be able to give a presentation to the group, at least providing some assurance that we may have a reasonable early detection system even for unknown events.

DR. MODLIN: Thanks, Bob. Myron, do we have anything else?

DR. LEVIN: Yes. I wanted to move on to, I think, equally important issue is how the manufacturers view this. And the manufacturers of the current vaccines

in trial were the one who were contacted, and I'm summing up here for you what I saw in their letters. There was of course the concern that there would be a low profit from a domestic use of the rotavirus vaccine, not -- for two reasons. One is the large size of the trials that will be required, and I think you heard numbers yesterday from somebody quoting I think from Aviron that of the hundreds of millions -- it was excess of $700 million -- and how does one recoup the cost of doing a trial. And that trial, certainly the Aviron trial of the cold adapted flu vaccine is nowhere near as large as that is being planned here, at least by Merck. That's what I know about. So that's one issue, the high development cost.

We've already heard from people, including Mr. Reilly, that the slow uptake -- that uptake will probably be slow in the permissive setting. But even with the universal setting recommendation, for the same reasons probably, there are lingering safety concerns. There are many physicians -- and we've heard this from other sources -- who don't consider this a serious problem. Not everybody agrees that we have a need here, and there are many physicians who feel they can handle it adequately with oral rehydration. And indeed, many physicians don't even know they're

dealing with rotavirus and it's a diagnosis that's not always etiologically confirmed. But for all those reasons, the uptake would probably be slow initially, and that would feed into the fears about what profit may come from it.

Everyone agrees with this issue: In order for the company to do a risk assessment of a potential vaccine, they need to know the answer to this question, and we've just been talking about it. What risk of vaccine-attributable intussusception would be offset by prevention of rotavirus and death, in our opinion and in the government's opinion and in the public's opinion? And we have to somehow help to frame the answer to that question so they can go forward in their planning.

These are the actions that industry would like to see undertaken. We've talked about some of them. They want also more accurate evaluation of rotavirus disease burden for, again, the risk benefit analysis. They want better definition of intussusception risk factors and approved diagnosis and treatment to limit the adverse events. They say that they want a universal recommendation for any rotavirus vaccine that has an acceptable risk. And they point out very clearly that there will be an important education

program required, both by the government and perhaps by professional societies to foster the acceptance of any license and a recommended rotavirus vaccine that comes on line. It's just going to be hard, I think, to start a new rotavirus vaccine up.

And then some of the -- and this is the last slide -- they want to make sure that the vaccine is included in VFC and the VIC programs. And then they had two other concerns, and actually Rick, you touched on one of them. I think they're concerned that there may be a permissive recommendation made before a universal. I understand why you want it, but you can understand why they would be concerned that it would happen. And then the question was posed: If one vaccine is licensed and a second good vaccine is available, must it jump through the same hoops, the same size trial, to be licensed, as well, or will there be some way of coming on line short of that?

So that concludes the manufacturers' concerns, although I'd like to hear more from the manufacturers if I've either misspoken or left out some concerns that were relayed to me.

DR. MODLIN: Mr. Reilly?

MR. REILLY: Kevin Reilly. I'll make a couple of general comments. We weren't one of the companies

responding because we don't have a second vaccine in clinical development at this stage. But I think I would make a comment more on the first slide and pick up on the investment issue.

Clearly the companies that are in vaccine development and vaccine supply now are committed to that business. This is also picking up a little bit on the themes of discussion yesterday. We believe we are strongly committed. We take risks. Basically the business we're in is taking research and development risks and we -- sometimes it's difficult, but this is the job we do and -- I'm trying to think of better words, but we're comfortable with it, even though it's a pretty uncomfortable place to be sometime. So I don't want to give the Committee the impression that these R&D investment risks are a burden on us beyond what we're capable of handling and beyond what we're committed to. I think we do have -- in general we do have a very difficult situation now in rotavirus because the side effect quantification in RotaShield product now has created a hurdle for new products, and that is a serious concern for all of the companies involved in clinical research in vaccines. And one of the things that we're debating and one of the things we're struggling with is if this is a new parameter or new hurdle, what is

the size of clinical trials that are going to be needed in future for new vaccines. And I think that's probably one of the major fallouts or one of the major implications of the decision on the RRV decision. I think the other thought that I was also speculating on as Myron was talking, we also have a conundrum that ACIP is the recommending body for the US and that's its mandate and that's its direction. But it is also a global reference body and that is, as vaccines become more global -- and in fact the pressure on manufacturers and some of the international agencies is to introduce vaccines around the world faster than they have been historically -- then the role of critical reference points from advisory committees becomes a big issue.

DR. MODLIN: Thank you. Other responses from any of the other manufacturers or anyone else at this point?

DR. PETER: John?

DR. MODLIN: Yes, Georges?

DR. PETER: If discussion is concluded, I am incredibly impressed by Myron's presentation of the work of the working group. And I think that the working group's conclusions, particularly the latter half with respect to the needs, really indicates that the workshop that NVPO and NVAC conducted in September was successful in bringing forth these issues. And I

think a sequel to the paper that I'm supposed to eventually get published -- I have written it but I haven't finished it yet on the workshop --

DR. MODLIN: We're all like that, Georges.

DR. PETER: -- is that indeed I think the wisdom of this work group's deliberations should indeed be written as an ACIP statement, or even if it isn't an ACIP statement, written as an independent paper because I think it identifies issues that need greater dissemination with the public. I mean I tried to write notes down, but to have a document would be very helpful for our future discussions and we shouldn't lose sight of that point. So I wondered if that would be a consideration the Committee might --

DR. MODLIN: I think we can certainly find a way to disseminate the work product here effectively. I'm not certain that through an MMWR update is the appropriate way to go. It's something -- maybe we need to have some discussion, but it's an excellent point. I think maybe also in terms of bringing things to an appropriate close, I'd like to add my own personal thanks to the efforts that Myron has put in. He's obviously taken this on with a great deal of energy and sensitivity and thought. Thank you.

And I guess maybe also wind things up, just to recognize

that this is not by any means the end of the story and this is something that we will continuously have before the Committee on an ongoing basis and look forward to doing so.

DR. LEVIN: Just two things. I want to thank the members of the working group, who were very helpful to me, especially to Trudy Murphy who really helped put things together. And secondly, I guess I would propose that the working group not be disbanded -- just stop working -- but that there will be a time -- there will be a time when all of the work that's been done will be useful in evaluating, I hope, the vaccines such as the one that Tom Vernon spoke about.

DR. MODLIN: Thanks, Myron. Let's move on to the next item on the agenda, which is an update on thimerosal. And I believe that Roger Bernier will be leading this.

DR. BERNIER: The purpose of the presentation this morning is to update the Committee on the progress that has been made in transitioning the supply of vaccines in the United States towards a thimerosal-free vaccine supply, and also to get a sense from the Committee whether or not the Committee feels that any more needs to be done at this time to bring about the closure to this transition.

To try to help the Committee recapture where we've been

with this, there is a table that was handed out that should have been put on your -- in front of you last night and you should have it still there. It's a two-page table and the top of it reads Chronology of Thimerosal-Related Events on Four Fronts from July, 1999 to February, 2002. There are some on the back table for those of you who haven't gotten it.

And what I'd like to do is jump ahead and direct your attention to the second page of this table, which was my way of trying to summarize everything that's gone on, more or less anchored by the events at the ACIP meeting during this two-year period. And if you would look at that, the first time that we really had an adequate supply of thimerosal-free vaccines -- that is HIB, Hep B or DTaP, which is what you see in the fourth column, it's -- on the first page, those are all no's, but in March of 2001, for the first time, we achieved a situation where we had at least two of those three products. And in June of that year the ACIP considered whether or not it wanted to make any change in its policies regarding the use of thimerosal-containing vaccines. And the decision at that time was not to make any change. The policy had been not to express a preference. And even though we achieved this -- two vaccines for each of the three -- HIB, Hep B and DTaP

there still was a feeling we did not need to express a preference.

The situation was altered somewhat in October of 2001 when the IOM report was issued and the IOM actually took a position different from the ACIP and recommended that the use of thimerosal-free vaccines be the norm, if the supply was adequate. At that time the supply did appear to be adequate, at least for DTaP. But if you'll notice, I have put, in the last column, the yes in quotation marks because there was some question about the adequacy of the supply.

In October, 2001, at about the same time, the ACIP -- or I should say an ad hoc group, not the Committee itself but an ad hoc group -- drafted a joint statement of -- a preliminary joint statement that did include a recommendation to cease use of thimerosal-containing vaccines by March 31st, 2002. However, that draft statement by the ad hoc group was postponed. Because if you'll notice, in the last column, the DTaP supply situation changed while this joint statement was being considered, so that by December of 2001, what had previously been a yes in quotation marks for the DTaP supply became a no. And so at that time the proposed joint statement by the ad hoc group was basically deep sixed and postponed and it was no longer on the table.

And that's the situation that we're in today, in February, 2002. I think you'll hear or have heard that we're still not in a normal situation for the DTaP supply. And what you will hear from Dean Mason is now an update on some additional data of what is remaining in the pipeline for HIB, Hep B and DTaP in particular. And the question that we will ask, to get a sense of the Committee, after the presentation, while there still is a supply shortage for DTaP, there is not a supply shortage for Hepatitis B and for HIB, and so conceivably the Committee might want to do something in regard to Hepatitis B and HIB; i.e., there could be actions taken or recommendations made to potentially hasten the closure of the transition for those two because there's not the same supply concerns. That is, you may want to think about that or not, depending after you hear the data from Dean. So Dean will make the presentation and then I'll get back up and perhaps, John, we could have a discussion of it then.

MR. MASON: Thank you, Roger. To go right into the presentation -- I call this the evaluation of the evaporation of thimerosal-containing vaccines, and I know that it doesn't really go up into the sky like water does, but I think that clearly it's our intent to exhaust the T-containing inventories as quickly as

possible.

A quick reminder that there has been significant progress made over the past couple of years with respect to the conversion or the replacement of T-containing vaccines used in the pediatric schedule, with thimerosal -- non-thimerosal preservative-containing vaccines. And this table illustrates those embolden in dark are the six vaccines for which they have been transferred from the left side of the table, the T-containing side, if you will, to the preservative-free side of the table.

Several notations or cautions. This reflects products for which we have a CDC contract. They do not reference all licensed products in the United States market and there are several other limitations. For example, the Td, we do not presently have a contract for this product. It does contain thimerosal. And influenza vaccine, we have two of the three companies listed here. We did not have the third company with a contract this year with CDC so they're not listed.

Our objective was to evaluate the amount of thimerosal preservative-containing vaccines in provider inventories, looking at points in time, comparing September the 20th of last year and about five months later, February the 20th of this year. This was a

convenient sample of providers who happened to be receiving site visits from public health officials in different parts of the country in these two periods of time. It's a cross-sectional survey. We did physical inventory counts in the provider refrigerators for all DTaP, HIB and Hepatitis B-containing products. The thimerosal classification, we wrote down lot numbers. We sent the lot numbers to the vaccine manufacturers. They cross-checked against their records and verified which were T-containing and which were non-T-containing vaccines -- with much thanks to the persons who were involved from the manufacturers' perspective in that endeavor.

So in terms of being able to actually catalog or categorize or describe the products, we were quite successful we think. We identified the status of 96.5 percent of the products inventoried in September, and we identified -- in February almost all of the product that was inventoried we were able to determine its thimerosal classification status. For September this involved 16 states and three cities. February, even more expansive, 25 states and five urban areas. The sites visited in September were 225, and that was expanded to 447 in February of 2002.

Perhaps this is the most important slide. It shows the decline in thimerosal-containing inventories, the top box being the accumulation -- the total of all of the subsequent boxes. For all doses, the percent of decline on these inventories was from 56 percent to 1.9 percent. The total doses in September that were T-containing were 3537 of the 68,000 figure and the figure for February, the T-containing total was less, though the number of doses inventoried was much greater, 2796 of 449,000. You will notice that the preponderance of T-containing product is in the DTaP/HIB combination. Still I'd point out it's only 721 doses that we inventoried among these 447 sites all over the country. But nonetheless, this product is licensed for fourth dose. It's not what we consider to be for the youngest children or the infants, so the frequency of its use and the reason that it remains in rather proportionate amounts in provider inventories is because of the lack of demand as a part of the routine schedule and the fact that it's not been necessarily adversely affected by the shortages that we've experienced in the public sector.

And then of course the Hepatitis B vaccine, you'll notice an increase there, 7.5 percent as opposed to 4.9

percent of the last survey. We believe that most, if not all, of this product is Merck product and we need to do some more evaluation to determine the proportion of this product that is pediatric versus adolescent versus adult. Our impression is most of this is pediatric, but that's something that we can't formally report on today, keeping in mind that the pediatric dosage is a ten microgram and the adolescent and adult dosage is a five microgram.

The message here is that you can see the decline from 16 percent to less than 2 percent in the period of approximately five months.

We undertook at the time of the visits to provider offices in cooperation or the legwork -- and all the credit really goes to the states and to local health departments that agreed, on a rather short notice, to help us collect this information -- the results of 447 interviews was that 83.5 percent of the providers reported they had no thimerosal preservative-containing vaccines in stock at any time since October of last year.

I should also mention that the respondents may not always be the doctor who is the main care provider. It could be a office clerk, it could be a nurse on the front line or it could be the medical physician within that

clinic practice. That's not information that we documented.

Only 25 percent responded that they were aware of the voluntary exchange programs. I believe at the last ACIP, if I recall, both Glaxo and Merck had indicated that they were prepared to exchange T-containing -- I believe Hepatitis B vaccines, at least -- with providers. They were prepared to exchange the T-free for that T-containing, but in the respondents, one-fourth indicated they were aware of such a program. Only 2.9, almost 3 percent, indicated they actually exchanged product. The reasons given for not exchanging, they were not aware of the program, they had no T-containing vaccine in inventory, it wasn't worth the effort, and they would wait until it expires which to me indicates they probably weren't planning to use it; they'll wait till it expires, then exchange it. There were other reasons given; these were the most common.

So some observations to this is that the provider inventories is small and it continues to decrease. The T-containing preservative pediatric vaccine inventory is mostly comprised of Hepatitis B and DTaP/HIB. You noticed on that previous slide there was zero percent of DTaP that was found to be

T-containing, so 91 percent of the T-containing is comprised of these two products, with a reminder that the DTaP/HIB is only licensed for the fourth dose. The less than one percent of all DTaP vaccines inventoried in provider offices contained T-preservative. I was thinking it was zero, but let me go back and look real quick. Yeah, we did -- six-tenths of one percent was documented to -- and our judgment on that, because you know of our shortages and so forth, it's likely that those that still have it are doctors who have very low volume and just don't rotate their stock or have a significant demand for product.

And finally, if it's judged that the Hepatitis B vaccines, other efforts should be made. Perhaps one consideration of the ACIP for strategy would be to accelerate the Hepatitis B vaccine stock depletion by offering to exchange in a more systematic way.

That concludes my presentation. I'll turn it back over to Dr. Bernier.

One more thing, acknowledgements to Dr. Jeannie Santoli, Shannon Stokley and Lisa Galloway for the tremendous efforts in data preparation, data collection and data analysis. Thank you.

DR. BERNIER: John, since a lot of this information literally was being brought to analysis just in the last

couple of days and even last night and probably still this morning is when Dean got these slides finished, and some of them have just been -- some of us have just been talking about the numbers. Our goal this morning is really just to get a sense of the Committee. If the sense is we don't have to do anything more, everything's fine, that'll be it. If the sense of the Committee is that something more should be done, then we may have to work up some additional options for you. Dean presented one or two just briefly, but we're not prepared with a set of slides with options and so forth. We first need to get a sense of the Committee.

DR. MODLIN: I think it's -- Roger, you clearly laid out the issues before us. I would remind the Committee that, to my knowledge, we have not ever expressed a preference for non-thimerosal-containing vaccines beyond the neonatal period, and if I understand it, the question is now at this point, very late stage in the game, do we want to parse out Hepatitis B and HIB vaccines of the very small remaining stocks that are there to do so.

DR. BERNIER: Yeah, and in fact, John, it's probably not HIB because HIB is down -- I forget, Dean, what your number was. It really --

DR. MODLIN: Under one percent.

DR. BERNIER: It really comes down to whether any more needs to be done around Hepatitis B.

DR. MODLIN: Hepatitis B. Natalie?

DR. SMITH: A comment. I think there's been tremendous progress -- it's been remarkable -- in removing thimerosal from the vaccines. And obviously the theoretical concern was over cumulative doses -- anyway, it's my understanding -- and not individual vaccine, per se. I'm wondering if there are any outliers that would have a whole bunch of vaccine so that some kids may be getting -- it doesn't sound like it. It sounds -- I've heard there's some variations around the country, but I just wondered if there's some practices that might have, you know, a fair amount of thimerosal vaccine they're administering.

DR. BERNIER: You mean outliers in terms of the supply that they have? Yes, Dean didn't get a chance to say that and he may want to get back up, but we did look at this, obviously, by where these sites were. And it turned out that the vast majority of this Hepatitis B vaccine, if I understand correctly, is in one location. So this is not a widespread problem, and obviously this is a convenient sample, so we can't say that most of the remaining Hep B in the country is in this one location. But we do know that perhaps, if I get this

right, Dean, as much as 90 percent or more of the Hepatitis B is in one particular area. So we can think about -- well, we don't know. We haven't sampled every single one, so there may well be other places where it's also clustered like this. But it doesn't appear to be a homogenous distribution.

DR. MODLIN: Gus?

DR. BIRKHEAD: Is there any information on the expiration of the lots containing thimerosal? Is that coming up imminently in the near future or is it years away before all those lots expire?

DR. BERNIER: I think it's fairly imminent for the DTaP and HIB products. Because it was a late shipment on that Hepatitis B vaccine that you're seeing, that one may extend into 2003. I don't have the exact date, but it's not -- we're not looking at something that's three, four, five years away. We're looking at most of this for HIB and DTaP, which is -- it's almost virtually gone, so it's not even worth talking about that. But perhaps Merck would have some idea when the last Hepatitis B was shipped out. My recollection from when we talked about this -- and Dean, you can help me out -- I think it was -- probably would have expired sometime in 2003.

DR. MODLIN: Tom, maybe you could clarify -- be helpful

with the thinking that this is Dean's impression that most of these doses are pediatric doses, the ten microgram doses. I thought that when we talked about this on the phone that there was a slightly longer shelf life for those doses, but maybe you have better information.

MR. VERNON: We are talking about the five microgram dose, the pediatric dose, of the Merck vaccine. The last shipment of the vial of a five microgram dose, which constitutes well over 95 percent of the total shipment, occurred in May of the year 2000. The last of the syringe containing five micrograms was distributed -- again constituting less than five percent, and the figure that sticks in my mind is 1.2 percent of the total amount we shipped -- was in October of 2001. I would have to speculate that it is the remainder of those syringe five micrograms that were found, and did not hear whether there was any visual inspection as to whether it was vials or syringes. Now, those syringes were shipped primarily with the intention that they would be used in clinic situations such as school-based clinics and the like. I wish I knew more certainly whether there was any likelihood that those syringe doses were used in the newborn, which is, after all, the age group in which concern was

expressed. Unfortunately, I can't answer that question.

But if this Committee believes that it would be useful to do a further retrieval in this circumstance, it is definitely something that I will take back to the company and have them consider. I do want you to consider the down side of still another message about thimerosal at this point in time in our history of discussion of the possible but not yet proven down sides of the use of this preservative.

DR. MODLIN: Thanks, Tom. Paul?

DR. OFFIT: This is a question for Bob Chen. Bob, we were presented a while ago with preliminary data looking at the relative capacity of thimerosal, at the level contained in vaccines, to do harm. Are there other studies that are in the works or more definitive studies that we'll be seeing?

DR. CHEN: I don't know where Bill Thompson and -- is Bill still here? Must have just stepped out. We are in the process of planning several studies and Bill has been coordinating them. The first set of studies take a look back in the VST cohort and we're trying to look at bringing the kids in for a standardized battery of neurodevelopmental tests, lasting probably somewhere between two and three hours for that battery, and the

folks doing the assessment will be blinded to their thimerosal exposure history. So that, we feel, is the single best way to be able to get at that.

We have funding planned for this fiscal year and there's some kind of fine details related to that, but we have started. We have funded a pilot study in terms of looking at all the statistical issues, as well as the logistical issues of informed consent, as well as the logistics of actually administering which battery of tests, et cetera. And so that -- the planning phase is well underway. The actual study phase remains to be looked at.

We have also planned a case-control study of autism related to thimerosal exposure, and the methodology there would be similar to what was used in the first real public health surveillance study of autism in the US, which uses school children evaluation -- the records -- with a panel of experts who are -- in terms of diagnosing autism and onset of autism, so we're planning to do the same with the VST sites, copying their charts and having the same panel making the diagnosis of whether they're autistic cases or not, and again do the linkage to the thimerosal exposure.

There's a range of other studies underway, some of them funded by NIH -- and Carole Heilman may want to comment

about them -- as well as studies funded by the FDA. And I believe in the UK Liz Miller has a similar initial at least kind of automated screening look at thimerosal exposure and automated outcomes, as well. So those are the various studies that I'm aware of that's underway.

DR. MODLIN: Stan?

DR. PLOTKIN: I would like to call the Committee's attention to a phenomenon that seems to be what I might call a creeping scarlet letter. That is to say the original concern about thimerosal was that there was a possible accumulation in some children. That is that some children might be receiving more than a threshold of absolute safety set down by one organization. Now we appear to be moving to what I think is a new toxicological principle, that no matter how much of a trace a child receives, that might be dangerous.

I don't think -- whether there is science to support the idea of the association of let's say autism with thimerosal when the thimerosal quantity is large, whether there is science to support that is debatable. I think it could be said that there is no science at all to argue that trace amounts of thimerosal are dangerous. And what we're talking about here is the

child possibly receiving one vaccine containing thimerosal.

DR. MODLIN: Dr. Salisbury?

DR. CHEN: Let me just comment. Stan, let me see if I understand your comment. In our studies we have to look at children with both high and low exposure and then hopefully one will see whether there's a difference in outcomes and be able to say whether the hypothesis is of any concern or not.

DR. PLOTKIN: I'm not arguing against your studies, Bob, but those are studies that are retrospective concerning children who may have received 200 micrograms or slightly more of thimerosal. What I'm pointing out is the situation now is that -- what is it, 12.5 micrograms in the Hep B?

DR. PLOTKIN: So we're talking about a much different situation.

DR. CHEN: Sure, in terms of the current exposure. In fact, that's the -- a natural experiment that -- at least in terms of the autism study -- that is -- as well as the neurodevelopment. By doing these studies now, we establish a baseline for kids who were exposed before and now that we have removed thimerosal we can repeat the study three or four years down the road when they're of an age for a reasonable assessment to look at the

same issue.

DR. MODLIN: Dr. Salisbury, last comment.

DR. SALISBURY: David Salisbury, thank you, Chairman. I'm aware of three studies in the UK, one of which is funded by the Medical Research Council, which is a case-controlled study where the endpoint is autism, but all of the immunization details of all of the children will be recorded, so this is information that can be used for this purpose.

However, there are two specific studies that have been set up to look at thimerosal and vaccines. The first is funded by WHO, and that is using the general practice research database, and that one is not yet concluded.

The third study is one funded by my own department and this is a very large cohort study based in Bristol, where there are a group of children who are being followed from birth and all life events are recorded, both relevant to the child and also number of life events relevant to the mother. That study is completed. I know the outcome. I'm sorry that at this moment I can't share it with you. But that will be available I hope fairly soon.

DR. MODLIN: Well, we look forward to hearing it, perhaps next time.

DR. SALISBURY: Next time.

DR. MODLIN: Next time. Let me ask if there's anyone on the Committee that would like to go ahead and at this point express a preference or an end date for the last remaining doses of thimerosal-containing vaccine, and Hepatitis B vaccine primarily?

(No response)

DR. MODLIN: I think that's your answer, Roger. Thank you --

DR. BERNIER: Thank you.

DR. MODLIN: -- very much. We will take our lunch break. I'd like to ask everybody to try to be back at 12:50. Since we're on time, I'd like gain a little bit of time because there are some people who have airplane flights, so at 12:50 we'll start.

(Whereupon, a luncheon recess was taken from 12:00 p.m. to 12:50 p.m.)

DR. MODLIN: Could I ask everyone to please be seated? I think we have close to a quorum of the full Committee, the voting Committee.

There's a change in the sequence we'll have for the remainder of the meeting. I'm not sure I fully understand all of it, but what I've been told is that Dr. Offit will be going first, so Paul, why don't you go ahead and start -- and Dr. Offit's going to give us some information -- scientific background information

on, quote, antigen overload. First of all, he's going to tell us what it is.

DR. OFFIT: I was asked by Melinda Wharton and the CDC to address this issue: Do the many vaccines that children get in the first two years of life overwhelm the infant's immune system? What I'm going to focus on, because it's a large question, is specifically what is the infant's immunologic capacity.

Now the data that I'm going to present are in part contained in an article that we published in Pediatrics in January of this year, and that article was co-authored with Jessica Quarles, Michael Gerber, Chuck Hackett, Ed Marcuse, Bruce Gellin and Sarah Landry.

I think the reason this has become an issue is that times have changed. If you look 100 years ago, we had only one vaccine -- although when you look at this slide now, maybe times haven't changed as much as we thought. But there was only one vaccine, the smallpox vaccine, and so children, by two years of age, could receive as much as one shot or one shot at a time.

Sixty years later in 1960 we added the diphtheria, tetanus and whole cell pertussis vaccines, as well as the inactivated polio vaccine, and now it was possible for children to receive eight shots by two years of age

and two shots at one time.

By 1980 we had changed from the inactivated polio vaccine to the oral polio vaccine, as well as added the combination measles, mumps and rubella vaccines, so now children could receive five shots by two years of age and as many as two shots at one time.

And now in the year 2000 or at the beginning of the 21st century, we have added the varicella vaccine, the conjugated pneumococcal vaccine, the Hepatitis B and hemophilus influenza B vaccines, so children can potentially receive as many as 20 shots by two years of age and five shots at one time.

As a possible consequence of these trends, a recent national survey that was conducted by Bruce Gellin and his colleagues and published in The Journal of Pediatrics found that 23 percent of parents questioned the number of vaccines given to their children, and 25 percent of the parents were concerned that too many vaccines might weaken the immune system.

The first point I want to make is that although we have 11 vaccines today compared to one vaccine 100 years ago, there really are arguably fewer antigens in vaccines today than then. The smallpox vaccine, which is actually the largest of the mammalian viruses, contains about 198 virus structural and non-structural

proteins. Smallpox, interestingly, is the only virus that can be seen by light microscopy. It's that big. If you look in 1960, we added the diphtheria toxoid, which was a single protein; the tetanus toxoid, again a single protein. We had added the whole cell pertussis vaccine -- and I guess the data that I'm using are those that were most recently published on the Tacoma 1 strain of pertussis by Sanger in Mill Hill -- and one would, based on the sequence analysis, estimate about 3,000 proteins that are coded for by the pertussis genome. And the polio contained -- vaccine contained three strains, each of which contained five proteins, so about 3200 proteins. What this tells you is something that you already knew is that bacteria are much bigger than viruses.

If you look in 1980, what we had done is we had added the measles -- we had gone from the inactivated polio to the oral polio vaccine, but again about 15 proteins. The measles vaccine contains ten structural and non-structural proteins, the mumps nine and the rubella five.

But by the year 2000, aside from eliminating the smallpox vaccine, which we -- what we had done is, because of advances in protein chemistry and protein purification, we now had an acellular pertussis

vaccine and therefore had a dramatic reduction in the number of proteins that were contained in that vaccine so that it now, when you compare what was true 100 years ago of approximately 200 antigenic components -- meaning proteins and polysaccharides that were contained in vaccines -- we now had about 125. The HIB vaccine is listed as two because we had both the carrier protein as well as the HIB polysaccharide. The varicella vaccine now takes over as our largest of the viral vaccines, containing between 68 and 70 structural and non-structural proteins. The Hepatitis B is a single protein, the Hepatitis B surface antigen, and pneumococcus contains seven polysaccharide-types in the carrier protein.

Now what I want to do is try and get at the issue of immunologic capacity. And although I don't think there -- there isn't a single answer to this question, what I'm going to try and do is go through two separate approaches to answer that question, and then discuss what I think are the strengths and limitations of those two approaches.

The analysis is going to center on the number of antibodies or the diversity of antibodies, how many antibodies do we have to bind to each of these different immunologic components, so this is -- for those of you

who took immunology may remember -- is an antibody molecule. And it contains, as you can see in green, the heavy chain and then in yellow a light chain. I'm going to teach you everything I remember about B cell immunology from a course I took ten years ago in five minutes because it's what I remember.

Now both the heavy and the light chain contain -- and it's shown here in red -- a variable region. Now that variable region is what is the part of the antibody that binds then to a protein or polysaccharide. And the diversity of that binding is determined by the genes. There are essentially four hypermutable regions that are contained in that -- in the genes that code for variable regions, that allow for that variability or that diversity. And I'm going to go through that just briefly so you can see where this comes from.

So four hypermutable regions, three of them are defined by the genes shown up here at the top under sort of germline DNA. You can see the heavy chain contains variables, shown as V; diverse, shown as D; and joining regions shown as J. And the light chain contains both variable and joining regions. But the point here is that we have a number of different genes contained within each of those regions that allows for diversity. In other words, the -- we have many different

combinations of these genes that allow for diversity, and that is called combinatorial diversity.

The other region, which is not clearly shown here but is located between the variable and the joining genes, is called the junctional regions, and that is to say that there are also options that the gene has -- genes have in terms of how they are combined, and that's termed junctional diversity.

Now if you add combinatorial and junctional diversity of antibody genes, you can account for about ten to the ninth to ten to the 11th different antibody specificities. This is -- the work was done by Susunu Tonagala, for which she won a Nobel Prize in the late 1980s. And if you then take this number and go back to what was our original analysis of the number of proteins and polysaccharides contained in vaccines, and if you assume about ten antigens -- and I'm defining antigens broadly as a protein or polysaccharide -- per vaccine, which is about right. Remember, we said 11 vaccines, about 125 antigens, so that's about right. And you assume ten epitopes per antigen, which I think is about right. And theoretically one could respond to about ten to the 7th, which is 10 million, to ten to the 9th vaccines, which is a billion.

Now I think this is an impractical calculation for two

major reasons. The first is that newborns have less than ten to the tenth B cells in their whole body, so it's not -- that's not -- they don't -- they couldn't possibly make this number of antibodies. And the second, I think more importantly, is if you give a child a vaccine, you will start to detect an immune response in about a week. It's not possible for a single B cell to divide and produce enough antibodies within a week's time to detect that as antibodies, either in a binding assay or in a neutralizing assay. So I think it's just an overestimation of the number of vaccines to which a child can respond.

There's another way of looking at this, and it's an approach I think is really interesting and fun, and it was one set forth by Rod -- or by Mel Cohn and Rod Langman, who are immunologists who work at U. Cal. San Diego. It was published in Immunologic Reviews and they called this the protection, the unit of humoral immunity selected by evolution. It's a great paper if you have time to sort through this roughly 140 pages. But I'm going to make it easy for you because I'm going to do it in like three slides.

They make the following assumptions, all of which are backed up by I think clear scientific evidence. The first is that an antibody concentration of roughly ten

nanograms per ML is likely to be an effective concentration of antibody directed against a single epitope. An epitope is just an immunologically distinct region of a protein or polysaccharide that is recognized by an antibody molecule.

The generation of ten nanograms per ML requires about 17,000 B cells per ML of blood. A single B cell clone takes about three-quarters of a day to divide and therefore will reach 1,000 cells in about seven days, which is what I love about this analysis because I think it's physiologic. That's when we start to see responses.

If we again assume, as we said before, that each vaccine contains about ten antigens and each antigen contains about ten epitopes, then we're saying there are roughly 100 epitopes per vaccine. We know also that -- and this is actually a number that's remarkably true across pretty much all mammalian species -- is that approximately ten to the 7th B cells are present per ML of blood.

If we divide then that ten to the 7th circulating B cells per ML by the 100 epitopes per vaccine, then each person can respond to about 100,000 different vaccines at the same time. Therefore, the 11 or 12 vaccines given to infants in the first years of life will use up -- and

I put that in quotes -- about .01 percent of the immune system.

Now I think that when people see the number ten to the 5th; i.e., 100,000 vaccines, it conjures up an image which is -- I mean at the very least -- frightening and certainly, at least to my wife, absurd. But I'd like to say that I don't think that -- I think that traditionally infants and children and adolescents and adults commonly encounter thousands of antigens all the time. And I'm going to sort of try and go through that analysis so you can understand that, so I don't think it's so absurd.

When children are in the womb they are in a sterile environment. As they pass through the birth canal and then ultimately enter the world, they will immediately be confronted with thousands of different bacteria, bacteria that line the nose, that line the back of the throat, that line the intestine, that live on the skin, that are inhaled in dust. And they will very quickly start to make an immune response to those bacteria. I mean there's a number of studies that show that as early as really within a few days of life, neonates will start to make a vigorous secretory IgA response, an antibody that is found principally at mucosal surfaces. And they make them for a reason. They make those

antibodies because only by making antibodies are they able to keep these organisms. And we certainly all know children who have agammaglobulinemia are at much greater risk for invasive bacterial infection than are those who don't.

In addition, if you look at adult humans, we are traditionally colonized with in the vicinity of ten to the 12th to ten to the 13th bacteria. Think about that. That's a trillion to ten trillion bacteria. That is more by orders of magnitude than the number of cells we have in our body. So you could argue we're composed really of more of them than we are of us, and we make a vigorous immune response to these bacteria. You know, all one has to do is look at nasal-associated lymphoid tissue in the back of the nose or gut-associated lymphoid tissue, specifically patch, and you can see that we're constantly generating these germinal center responses; i.e., making antibodies. And an adult human will make about five grams of secretory immunoglobulin a day, which is I think just a phenomenal commitment to -- of the host to a single protein type.

So I think we are constantly exposed to just thousands of different antigens all the time. Our focus on I think vaccines is because we see that. But I think

if -- we see the child lie on the table and get those vaccines. But I think if parents want to be even more scared, they could just take a swab of a child's mouth and look at it under the microscope because it's teeming with bacteria.

I think this latter analysis also is limited in a number of ways and I'd like to just go through that briefly. I have chosen to focus on only B cell responses and not cellular -- specifically cytotoxic T cell responses. First, young infants are not very good at making T cell independent B cell responses so I'm really talking about T cell dependent responses, and actually that's an advantage of vaccines. By converting agents like hemophilus influenza B or streptococcus pneumonia, by taking those polysaccharides and linking them to a harmless protein and inducing a protective response, we're actually creating with vaccines something that's better in inducing immunity than natural infection. And I chose humoral immunity because I think, although cytotoxic T cells are an important effector function in ameliorating acute infection, I think as a general rule they're less important than are antibodies in protecting against reinfection, which is really what we're talking about with vaccines.

The analysis also does not consider a number of

features. One is that I assumed all -- or Drs. Langman and Cohn assumed all epitopes to be the same. That's not true. There are certainly immunodominant epitopes. We know that when we immunize, for example, children with Hepatitis B surface antigen containing vaccine that some children, despite getting three doses or four doses or five doses, don't make a very good immune response to Hepatitis B. Part of the reason for that is that we, as an outbred population, have different major histocompatibility complex proteins, some of which are better able to present specific antigens than others. And I think in part that's what you see with an inability to respond to Hepatitis B, for example.

The other thing that's not considered is once a cell B cell switches from a naive cell to a memory cell, it's taken out of the pool of cells then that can respond to new antigens, and that was not considered in that analysis.

And lastly, and I think frankly most importantly, is that I assumed a sort of a static immune system. That's clearly not true, and I think the best evidence for that is a wonderful paper that was published by David Ho in Nature in 1995. And what he did was he looked at how many naive lymphocytes could be generated

in this population of people who were stressed by their infection with Human Immunodeficiency Virus, an infection which was attaching to, entering and replicating in CD4-positive cells. So he could see sort of -- he had much better sense of what were new naive CD4 cells that were generated. And what he did -- so it's a wonderful analysis, but what he found was that patients could produce about two times ten to the 9th naive CD4-positive T cells each day. That's amazing. I mean that -- what that means is that's about 20,000 CD4-positive cells per second or five -- for an adult human, about five CD4-positive cells per ML of blood per second. So I think vaccines, for all practical purposes, would never use up the immune system.

So I'll summarize then by stating that current studies do not support the hypothesis that multiple vaccines either overwhelm or use up the immune system. On the contrary, young infants have an enormous capacity to respond to multiple vaccines, as well as the many other challenges present in the environment. Thanks.

DR. MODLIN: Paul, that was a wonderful presentation, and I think entertaining as well as enlightening. I guess my first question would be how does one take this and translate it for someone who is in your office and

says the reason my child has autism is because of antigen overload involving the GI tract?

DR. OFFIT: Well, I find what's -- when parents call me about this or when reporters call me about this is that I think the most persuasive story is the one about children entering into a world replete with bacteria to which they make an immune response. And what you can do is I think you can create the correct image, which is that we are just bombarded with this tremendous number of huge antigens like -- like bacteria, which are just -- make -- or contain a large number of both structural and non-structural protein, as compared to the vaccines which are really -- I think to say a drop in the ocean I think probably overstates really how one compares to the other. That seems effective.

DR. MODLIN: Myron?

DR. LEVIN: Can't we say that we're designed to respond to multiple antigens, so we don't have a problem with it.

DR. MODLIN: Uh-huh, it's a good point. Other comments or questions?

(No response)

DR. MODLIN: Paul, thanks very much. I think the next item on the agenda is Dr. Bellini. Is that correct?

DR. OFFIT: I think it's Kathleen.

DR. MODLIN: How did we --

DR. OFFIT: I think it's Kathleen.

DR. MODLIN: Is it Kathleen Stratton? I beg your pardon. There's been several iterations given to me. Dr. Kathleen Stratton from the Institute of Medicine is going to give us an update on the very recent IOM review of the vaccine safety committee on the issue of multiple antigens that was just released this morning, I believe -- or late yesterday afternoon.

DR. STRATTON: There are copies -- or at least I gave Gloria copies of the Executive Summary of the report that are probably in the back. The report was released to the pubic yesterday at 4:00 p.m. and there has been some coverage in the paper today about this.

As you know, this was the third of the nine topics that have come in front of the immunization safety review committee and we had the meeting in November and the report was released.

Just as a reminder to those of you who may not remember, the committee was asked to do several things. It was asked to do what we're calling the scientific assessment, which includes conclusions both about causality, in the strict sense of the word, a causality assessment, as well as a description of the biologic evidence, the biologic mechanisms evidence that might

play with respect to any given safety hypothesis. In addition, the committee was asked by the sponsors, CDC/NIH -- was also asked to look at the significance of the issue to the public, to society, the public significance. And by that we mean the burden of the adverse event, the burden of the vaccine-preventable diseases which could rise if immunization rates were to fall due to concerns about the vaccine, as well as just how salient it is to the public and how much concern there seems to be about it.

You've heard from Paul and you've heard many times the reference to Bruce Gellin and his colleagues' paper that 20 -- roughly a quarter -- percent of parents surveyed really do believe that too many vaccines are bad for the immune system.

Okay, here's the nice graphic that I wanted to show you. It's even nicer in the book because it's professionally drawn. This is my PowerPoint presentation.

The data that flows into a causality argument are epidemiologic data primarily, occasionally clinical data from controlled epidemiologic studies. We also do a review of biologic mechanisms, what's previously referred to by IOM committees, including the first two reports in Immunization Safety Review, as the biologic plausibility that the event could occur.

As the report describes, we've decided to go a step further in how we talk about the biologic evidence that flows into the scientific assessment and that we're going to refer to it hereforth not as biologic plausibility, but as biologic mechanisms -- evidence for biologic mechanisms. And briefly, the reason for that is that there was a lot of confusion in people who read our previous reports from the early nineties, as well as the two reports from this committee, about what biologic plausibility means, what does the word plausible mean? And it has been in fact probably misinterpreted about what that means. It also has a history of meaning the consideration that you give when using the Bradford Hill criteria for in a causality assessment as to whether or not there's biologic evidence that would support a statistical association that has already been documented. And that is the history of the Surgeon General's report and the Bradford Hill criteria from the early sixties. And in fact the review of biologic mechanisms currently with this committee and with many of us when we talk about adverse events is to be used for other reasons than just confirming sort of the face validity of an observed statistical association. And so the word plausible, due to its history and due to its meaning in the English

language outside of vaccine safety concerns, was problematic.

It does not mean that the committee is thinking about biologic evidence any differently. We're just describing in a way that we hope is more clear. Anyway, biologic mechanisms can come from theory, experimental evidence or human evidence. The significance assessment I've already referred to. And as I've said, the committee was then asked to make recommendations for the appropriate -- if that's the word to use -- public health response for the safety concern, policy review, policy analysis, research and communications.

So the interagency group who gives the committee the general topic to be reviewed wanted the committee to address this question that Paul started to talk about, which is do too many immunizations overwhelm the infant's immune system. And so we certainly had to define both the exposure and the outcome. It was a pretty vague concept. And so multiple immunizations, if you're thinking about an adverse event on the body, is really not a serious adverse event on the body. It's not how many sticks you get, how many needles you get, but rather it had more to do with sort of the antigen load and whether the immune system is capable

of responding to it in the most appropriate way. So a single dose of vaccine can contain multiple strains of a single organism, such as the IPV or the OPV; antigens of multiple diseases, such as measles, mumps and rubella or I suppose the DTaP and the HIB. And individual doses of several separate vaccines could be administered at a single health care visit or there's repeat doses. So we use all of these kinds of definitions in the studies that we looked at in the epidemiologic evidence to represent multiple immunization, if it was more than one strain of an infectious disease or vaccines directed against more than one disease in one shot, such as the DTP vaccine, or multiple vaccines given at a time.

Immune system dysfunction -- I'll show you a little slide in a minute, a theory of this, and many of you know this immunology much better than I and certainly the Committee understands it better than I, so hopefully some of this will be self-obvious to many of you.

But the three types of immune dysfunction that the committee felt were reasonable to be -- for which there was a theory that there could be an effect of infectious agents would be -- and therefore vaccines that act similarly in many cases -- would be a risk of infection,

heterologous infections, risk for infections other than those the vaccines are directed against; a risk for allergic diseases such as asthma; a risk for autoimmune disease such as type 1 diabetes. The committee chose asthma and diabetes as the prototypics for the allergic disease and the autoimmune diseases for two reasons. One is there actually are -- there are data about the effects of immunizations on asthma and on type 1 diabetes, so it was an outcome for which there was literature to be reviewed. And also because they're very serious conditions, of course, on a population level and on an individual level, asthma and type 1 diabetes, and these are both concerns that people who are very wary about the safety of childhood vaccines often mention in their concerns. And it really of course is not possible with the -- and they occur in children, which of course is the focus of our project of this particular review was the multiple immunizations received in infancy and whether that's a bad thing for the developing immune system. So infant diseases were obviously the diseases we would look at most.

Just briefly, and I'm not going to go through all of these studies, but to show you sort of the breadth of the studies that were considered, when the committee

looked at the risk for heterologous infections and the controlled studies, there were seven controlled studies, so there was a body of literature. And they looked at a variety of vaccines and on the far right you can see a brief summary of the contribution that these would have made to the causality argument. These are described in much more detail with a much more elaborate table in the text of the report.

For type 1 diabetes, to show you the amount of studies that we have, there were five controlled studies that were of relevance to this particular question. And for allergic diseases there were another five. And I think it was actually with diabetes there were two analyses and two different studies within one published study, so it actually was one more than it would have appeared.

So the very first conclusion that the committee needed to come to was the causality assessment. And for the association between multiple immunizations in infancy and an increased risk for heterologous infections and for an increased risk of type 1 diabetes, the committee concluded that the epidemiologic evidence favors rejection of a causal relationship between multiple immunizations received in infancy and these two types of immune disorders or immune dysfunctions that have

been hypothesized.

When it came to the question of an increased risk for allergic disease -- and asthma was the outcome for most of these studies, although they also looked at other, more minor manifestations of allergic disease -- the committee felt that the epidemiologic evidence was on balance and adequate to accept or reject the causal relationship between the multiple immunizations and this particular outcome. And this is sort of the summary table of those studies, so in fact there were some studies that found -- that had a significant finding for an increased risk of allergic disorder, and there were some that had a non-significant but positive association for allergic disorders. On balance, the committee felt that all the studies had serious enough flaw -- besides the fact that some found an association and some didn't, on balance there were significant limitations and flaws in all of the studies that it really was unable to come to a conclusion on causality for this condition.

Now as some of you may know, the committee was asked at its very first meeting by the sponsors that when the committee had to come up with an inadequate to accept or reject causality assessment, whether or not they could at least indicate how they -- a leaning or a

likelihood, I think was the word that CDC used. Because of the problem that still being able to say we don't know, we don't believe that the data are conclusive, is often hard to explain and not helpful. And the fact of the matter is, the committee spent a long time discussing these particular data, trying to be more helpful, and they honestly couldn't. The really felt that this was a straight down the middle, we really cannot -- not only can we not find for causality, we couldn't find for or against, one way or another. So we regret that this remains an unhelpful conclusion to you, but it was discussed at great length.

With regard to biologic mechanisms, I mentioned it briefly, the way the committee's decided to describe these is whether or not the biologic argument exists in theory only. That of course assumes that there's a pathway that can be hypothesized by which the vaccine could cause the adverse event, but doesn't violate known biologic or physiologic or physical principles. So in fact there could be theories put forth that we wouldn't actually call theories because they're not meaningful theories because they seem to violate what is currently known about certain pathophysiology or biologic principles.

The level of evidence would be experimental evidence,

such as that from in vitro studies or animal models, or human clinical data -- not human epidemiological data, just to be clear. For example, if there's evidence that wild type infection can cause the adverse event, that's pretty strong evidence that there's a mechanism coming from this in human -- a related relevant mechanism exists in human. Or other vaccines cause the adverse event by a pathway that seems to be relevant to all other vaccines. And so it's that kind of an understanding.

The committee then decided that it would review -- that it would summarize its review of the biologic evidence as being either weak, moderate or strong, and clearly that is still a summary judgment call about the weight of the evidence, as is a causality assessment. There's no magic number in a causality assessment of how many studies you need or how many participants you need to find for or against causality. The same is true here. So there is, in both cases, obviously with all expert reviews like this, a level of judgment where the committee's trying to be much more explicit in terms of how it reviewed the data and where it came down on these specific issues.

And we hope that this has been more -- that this will be more helpful. And we certainly would appreciate

hearing about that because we have a unique opportunity with this project to increase the communicability of our reports, since we do them over and over again. And you may not believe it, but we take very seriously everything we hear about the report and we try to make them better, more transparent and more useful.

If Paul had ten minutes of immunology, I've had none, but the committee has had a lot. And so here is, on their behalf, a cartoon. And it is just a cartoon and the risk of putting something up like this is that there's never enough arrows to really show exactly what happens. But in terms of -- this is for the biologic mechanisms arguments I'm going to be showing you, and basically you can start off and there's not a pointer, but at the top -- the rectangles are sort of encounters with the infection or the vaccine and the white boxes are immunologic mechanisms that might come into play that lead to the immune dysfunctions, which are the dark ovals. And as you can see, you can basically have off to your left encounter with a microbe or a vaccine or a vaccine component a relative accentuation of TH2 responses to various environmental antigens which could lead to allergic disease. You could have going straight down TH1 and other beneficial responses which could either lead to the resolution of the acute

disease, or if normal regulatory overriding -- if these normal immunoregulatory mechanisms are overridden or inadequate for some reason, you can lead to three main pathways by which you can get autoimmune disease, and particularly molecular mimicry bystander activation or non-specific polyclonal and T cell activation. And so it's the allergic disease and the autoimmune disease that we were primarily looking at.

And I should point out that there's only molecular mimicry as a mechanism by which these can happen that require specificity between the vaccine antigen and the outcome. The other ones are a more non-specific pathway. And that's about everything I know about this particular slide.

With regard to autoimmune disease, the committee came up with these several pathways and summarized the data. There is a theoretical argument to be made that molecular mimicry -- that when you give a vaccine you could have molecular mimicry and you could end up an immune disease. There was no evidence found that actually directly demonstrated that that occurs with vaccines, so that remains theoretical only that this is a mechanism by which autoimmune disease could happen. By our standard, the data are weak. The committee felt that there were data that this mechanism

could come into play in response to vaccines. And as I recall, the evidence was from VCG and from whole cell pertussis, as well as from pertussis infection. And the BCG data, I should say that in the reviews for causality the effects of BCG were not considered because it's not a vaccine used in this country. But with regard to biologic mechanisms as a way by which this could happen, data about BCG were deemed to be relevant.

A loss of protection induced by homologous infection, there's a long discussion of hygiene hypothesis and these sorts of things in the report. And although the hygiene hypothesis, which is the next one, was considered to be a very strong hypothesis for what it was originally proposed, when it comes to vaccines and that vaccines could cause autoimmune disease via mechanisms related to the hygiene hypothesis was also theoretical only.

Collectively, however, because there is evidence that the committee believed that bystander effects could occur in response to vaccines collectively, there was weak evidence for biologic mechanisms related to an effect of multiple immunizations on autoimmune disease.

With regard to disease again there was weak evidence

about bystander effects. The hygiene hypothesis and a direct role for vaccines in the hygiene hypothesis was theoretical only. Collectively there is some evidence, it's more than theoretical, that makes it weak that a mechanism could exist by which vaccine could cause allergic disease.

With regard to the risk for heterologous infections, the discussion was carrier-induced epitope suppression in competition for antigen presentation, and the data here were believed to be strong for biologic mechanisms by which this could happen. And because I knew Paul was talking about this, I didn't put in the slide about antigen overload in the generic capacity of the infant immune system, but we were aware of the data that Paul reviewed at the time of our meeting, and the paper came out before our report was released. And in fact, the committee absolutely agreed that there is a generic argument to be made that the infant immune system definitely has the capacity to respond to antigens -- the inherent capacity to respond to them, and that didn't seem to be much of a question and that's discussed in the report and I just didn't make a slide because I knew Paul was preceding me -- or hoping he was going to precede me instead of come after.

As you remember on the first slide, the committee was asked to make conclusions about what is the significance of this particular issue at some population-based level. And the committee thought a lot about Dr. Gellin's survey and thought about the fact that more and more vaccines will be introduced to the immunization schedule or to the immunization offerings in some way. In the future clearly there will be more vaccines licensed and that the concern will remain that there are just too many immunizations. And so because it has been and probably will continue to be of societal concern because of parental worries about the vaccines, because of the potential health burdens of these immune dysfunction diseases, and the vaccine-preventable diseases which could go up if fears about vaccines cause people not to be immunized, and because of the future challenges for immunization policy-making -- as we'll get to in just a second -- so this is a significant issue even if the epidemiologic evidence was at least able to reject a causal relation for two of the immune dysfunctions, it is and is going to continue to be a question for society. That includes all of us in this room, as well as the parents. So the committee was asked to make recommendation on policy analysis, policy review, research and

communications. The committee was quite taken by a paper I'm sure that you all know by Drs. Feudtner and Marcuse, and in light of the fact that there will be more vaccines being considered for use in children, the committee hopes that the approach laid out by Feudtner and Marcuse remains of interest and of discussion to state, Federal and national, actually, vaccine policy makers, and that they continue the discussion that was started by Drs. Feudtner and Marcuse as you proceed to get ready for more immunizations added to the vaccine schedule. It primarily focused on the challenges that will be posed by the use of new vaccines, although theoretically one could look back on some of the decisions made in the past -- and I know that some of you have -- taking into consideration the kind of things that Ed presented in his paper and that's a full range of perspectives about the benefits, risks and implications. The committee hopes that part of that is a discussion of state mandates for vaccine use. This does not mean in any way the committee doesn't understand that state mandates are extremely important. Of course they are. The NVAC -- the NVPO, rather, and the NVAC have started -- has started an initiative and I believe they've had one of their three meetings. Unfortunately September 11th led to the

postponing of two of them, but the committee thought it was a very positive step whereby there'd start to be regional meetings about the different types of recommendations that could be made and hope that that continues. This is an attempt to applaud what you've done so far and to hope that it continues, this sort of effort, whether it's the NVPO effort or some other kind of effort, as well as exploring the merits of how you accommodate requests for alternative vaccine dosing schedules. This doesn't say that they should be accommodated, it doesn't say how they should be accommodated, it just said as you continue to prepare yourself for new vaccines added to the schedule, it's just a reality that people are going to ask you if there's alternative ways other than the ACIP schedule for how to get their vaccines. And you need to start talking about it. It doesn't say that you -- I mean the committee doesn't have a view about whether you should or shouldn't, but your constituencies, your public health nurses and your public health doctors and your physicians are going to get these requests, and they probably need help in terms of thinking about how to think about it, how to talk about it and how to communicate about the benefits and risks of deviating from recommended schedules.

The committee did not recommend a policy review of either the schedule or the licensure of any of the vaccines on the basis of concerns about immune dysfunction.

The committee did make some calls for epidemiologic and basic science research, and I won't go into them in great detail. The committee did not call for a major new initiative and randomized controlled trials on the effects of the vaccine schedule on allergy. The gist of these recommendations is to leverage existing studies and existing knowledge as best as you can, like including immunization history and studies of diabetes such as being done in the Daisy study, which is the -- I forget what the acronym stands for now already, but it's the diabetes study that's being done I think out of Colorado -- explore the use of existing cohorts. I mean really just leverage as best you can existing studies and existing knowledge to keep trying to understand better vaccine reaction.

There's some basic science research. We applaud the continuing research on the development of the immune system and identifying genetic variability as a better way to understand genetic susceptibility, and I know that's part of what Bob was alluding to earlier this Bob Chen I think earlier -- and things like that and

so it was really sort of an encouragement of all these different approaches and hoping they keep continuing because ultimately maybe we'll have much better sense and more data.

The committee did make a recommendation about communication, and it recommended that an appropriate panel of multi-disciplinary experts be convened by the Department to develop a research strategy to better understand why people believe what they believe about vaccines in order to craft better and more effective risk benefit communication strategies. So I think that the Gellin survey -- and Bruce says this all the time himself -- was a good start, but just a start. So now we know that in 1999 25 percent of parents believed this, but that doesn't get at why do they believe that and what are the reasons they believe that and what do they need to know to feel more comfortable about vaccines. And so it's an encouragement to go the next step beyond surveys and focus groups and to develop a research strategy so that eventually you'll have a better understanding of how people make decisions about vaccines and why they worry about the things that they do so that you can do a responsible and effective job at communicating the risk and benefits of the vaccines.

And for those of you who want to know how to get in touch with me, there it is, and I'll stop now.

DR. MODLIN: Dr. Stratton, thank you. You've summarized a long and comprehensive report in a very concise way.

We do have a few minutes for discussion if there are questions or comments, beginning with Jon Abramson.

DR. ABRAMSON: Well, hi. Did the committee consider the issue, that is repeatedly raised as we consider more and more universal vaccination with influenza, of yearly vaccination with a -- a couple of street strains that you vary every year a small amount or a moderate amount? Did it actually think about that issue and come to a conclusion?

DR. STRATTON: Not specifically, and -- I mean generically that still counts as multiple immunizations during infancy, and certainly the mechanisms, the biologic mechanisms that were laid out would generically come into play. But because there weren't data about that issue published for the causality assessment, that particular question wasn't reviewed. Is that what you're asking, Dr. Abramson?

DR. ABRAMSON: Yes.

DR. MODLIN: Dr. Pickering?

DR. PICKERING: Larry Pickering. Thank you for the

nice review. I've got a mechanistic question about the disparity between the heterologous infections. In the causality area you stated there were seven infections, I believe six of which were no effect and one was questionable with regard to study design so that there was no association.

DR. STRATTON: Right.

DR. PICKERING: Then under the biological mechanisms you said there was strong evidence for existence of biological mechanisms by which multiple infections could possibly influence individual risk for the heterologous infections, and that's based on I guess both epitope suppression and antigen competition. But the studies there, as I read them, are few, so is that based on basically the number of studies, the quality of studies, different epitopes and how can you help me differentiate or equate the disparity between the causality and the biological mechanism comments?

DR. STRATTON: That's tough, and I don't know I'm going to be able to do it justice. One could glibly say that of course isolated biologic findings don't necessarily end up panning out in population-based epidemiologic studies and that this is probably not the only case where you could come up with good evidence that mechanisms could happen but in fact in a population

level -- or even in an individual human, a level that doesn't happen. Epidemiologic studies are what they are is all I can say. There does not seem to be increased risk for these invasive -- particularly the invasive, very serious conditions. I think it's only an apparent contradiction, but one that -- you know, as scientists we all understand that sometimes the evidence that something could occur through biologic mechanisms and not occurring due to other reasons. I don't think I'm -- is that helping you at all? It's not helping me, I just realized.

DR. MODLIN: Larry, it's John.

DR. STRATTON: Maybe John could answer.

DR. MODLIN: I'm just wondering if this is a situation where we have some clinical data that, at least for children who received the old polysaccharide H flu vaccine and maybe even the current conjugated H flu vaccines that there is some small increased risk of disease in the immediate post --

DR. ABRAMSON: Well, actually --

DR. PICKERING: That's homologous.

DR. STRATTON: That's homologous.

DR. PICKERING: This is heterologous and I agree, John, I understand that there are data with H flu there may have been in the three or four days afterwards, but

the heterologous is the question that I raised.

DR. MODLIN: You're right.

DR. STRATTON: But I think in most -- and as I understand, and again I'm sorry if I'm not in total command of this particular piece of the data, but I believe it primarily comes from the MMR -- the evidence of the MMR and varicella interactions. It was that -- now Dr. Modlin, you are nodding your head when I said that the evidence was strong and now you're frowning, so perhaps --

DR. MODLIN: That's right. That's right.

DR. STRATTON: Can I come back to you on that one?

DR. MODLIN: MMR and varicella is a different issue. MMR and varicella I think is basically an interference issue.

DR. MYERS: But I think hemophilus and E. coli K1 would be a mechanism that would be possible --

DR. STRATTON: Right.

DR. MYERS: -- but in fact there's new evidence to suggest that it occurs. And those are the two points I think --

DR. STRATTON: I think that's another good example.

DR. SALISBURY: David Salisbury. Kathleen, just to pick up that last point, I do recall telling you before your committee started work that there was work

completed in the United Kingdom looking at heterologous invasive disease following administration of MMR, but I don't see any reference to that having been considered in the report. That wasn't actually the point that I wanted to raise. What I really wanted to say was I found myself getting a bit confused about the charge that the committee was given when you came to looking at biological mechanisms, because I understood that the purpose was to look at multiple immunizations.

DR. STRATTON: Uh-huh.

DR. SALISBURY: But most of what you told us in the biological mechanisms was not specific at all to multiple immunizations. It was actually specific to single immunizations and they were mechanisms postulated for each vaccine in turn. And I wondered how the committee has moved from consideration of suppression and competition that relates to single vaccines to the actual charge which was the biological mechanisms for multiple vaccines.

DR. STRATTON: So you're questioning -- you're specifically questioning the heterologous.

DR. SALISBURY: No. You were not asked to look at issues to do with single vaccines such as epitope suppression and competition. You were actually

charged to look at multiple vaccines in this regard. And I wondered how you had actually made the jump from what you were reporting to us, which was to do with single vaccines, to the actual charge which was to look at multiple vaccines.

DR. STRATTON: I think that some of the data on that reviewed were actually were for multiple immunizations and it may exist for single immunizations, as well, I don't actually know that. But there were evidence that a multiple immunization, such as an MMR or something -- that there were data that those mechanisms did in fact -- could in fact come into play. The causality data were always on multiple -- or were definitely always on multiple and the mechanisms --

DR. MODLIN: Thanks. Neal?

DR. HALSEY: Neal Halsey. My point is similar, but it has to do with autoimmunity rather than the heterologous in that as I read the conclusions -- and I haven't read the entire report yet -- I mean they did come to the conclusion that there were biologic mechanisms where multiple immunizations could theoretically predispose to autoimmunity. I am concerned about some of that because of the large amount of public concern about autoimmune diseases and so

forth.

One thing that's not understood very well by many individuals and by many physicians is that in the response to any infectious agent there is often an autoimmune response of some type that is regulated by the host. And I hope that that's in the full report. And so that autoimmune responses are actually very common in the way in which we deal with infectious agents of all types. And so I'm not quite sure that I understand that conclusion in that certainly there are biologic mechanisms for exposure to any infectious agent to theoretically predispose to an autoimmune response. But separating an autoimmune response from autoimmune disease is critical with regard to conclusions.

DR. STRATTON: I think that the issue of an autoimmune mechanism response to infectious diseases is covered in there, but that is not directly relevant to the multiple immunization. So it's there as background for why it is that one might worry about it, and that was separated out from the evidence that a vaccine actually can lead to various steps along the way for an autoimmune -- it could ultimately result in an autoimmune disease. And it's probably why it is viewed as weak, because it's mechanisms that an

autoimmune process could take place after vaccines, but not strong that the autoimmune disease actually takes place. So I think it is in there, Neal, in the full discussion of that.

DR. HALSEY: Could I make a recommendation to the IOM, and that is mirroring the recommendation that you've made to the agencies about exploring how to help the public understand some of the issues with what the public perceptions are. I would encourage you to conduct some small studies amongst physicians and other health care providers in terms of how they interpret some of the conclusions of the IOM and what they mean, and are those interpretations consistent with what your intent was.

DR. STRATTON: I think that's a great idea, Neal. And as a matter of fact, the committee requested at the last NVAC meeting that it be allowed to do one of its sessions on cross-cutting issues, one of which was are we being understood and are we communicating properly. And it's my understanding that the -- I don't know whether the interagency group has actually approved whether or not that we could spend some of our time and our effort doing exactly that, though I am fully in support of your suggestion. And any way that you or anybody here could help us think about that would be welcome.

DR. MODLIN: Natalie, very quick.

DR. SMITH: Very quickly, I just wanted to echo what Neal just said, and an exciting piece of this new process, as I understood it, was the communications piece. And I think it will be useful. I realize most of the focus is on communicating with providers and other professionals and you have disseminated the reports widely, but messages for the public, as well, because since you're so important, especially as an independent panel.

DR. STRATTON: Right.

DR. SNIDER: And Kathleen, my understanding is that the context of this is that -- sorry, Dixie Snider. That we're giving all these multiple antigens and in that context are we seeing any adverse events of this nature. But the other piece of it is not really articulated, which is if we were to abandon immunization altogether and let all the natural infections occur, presumably some of them might result in these adverse health consequences to an even larger extent. And that's not really a piece of what you were asked to do, but in the interpretation of it by the general public, it seems to me that also needs to be brought into the discussion, or at least into consideration.

DR. STRATTON: Right. I mean I think we certainly do always talk about that, about how the vaccine-preventable diseases could go up if immunization rates fall and how unfortunate that would be. So I think it's not ignoring that. I think, for example, the press coverage that came out today about this particular report in fact sort of talks about that a little bit, that the known benefits of the vaccine are very real.

DR. SNIDER: But I was going beyond the vaccine-preventable diseases to even saying that we don't know about some of the other complications of the infections themselves. In other words, the infections themselves may, in some people, cause autoimmune diseases, but we don't know about that.

DR. MODLIN: Dr. Stratton, thank you very, very much for coming down to bring us up to date on this very nice report. And I think all of us look forward to reading it more thoroughly and I'm sure there are number of questions and issues that will come up in the next days and weeks.

Since it's likely that we're going to lose our quorum by 2:30, I think we probably should move on. And the last item on the agenda is labeled as an update on MMR and I understand that Walt is going to introduce the

issues and that we have a couple of other participants.

DR. ORENSTEIN: This Committee has reviewed the issue of MMR and autism several times and there have been some very comprehensive reviews, independently, by both the American Academy of Pediatrics and the Institute of Medicine, and all the groups have concluded that there should be no change in our present schedule, which is reliance on MMR. And in fact in the 2001 harmonized schedule that was just issued, MMR is all that appears on the schedule. There is no mention of single antigen in a sequential kind of schedule.

There have been preliminary review of some data from the UK and Ireland by both the IOM and the AAP in their reports. However, recently there has been a publication by Uhlmann, et al -- which is in your packet in The Journal of Clinical Pathology reporting that in 75 of 91 children with autism and ileal nodular hyperplasia they were able to detect fragments of measles virus genomes compared to five of 70 controls, and we'll go over that in more detail. This paper has raised quite a storm within the UK about changing policy or providing choice, and David Salisbury will cover that in a little bit of time. We felt the need to reinforce our policy and I -- while not in your notebooks, I think it was handed out yesterday, I've

sent a letter to Sir Liam Donaldson, the Chief Medical Officer, reaffirming our policy, which reliance on MMR and talking about not only some of our concerns with the scientific validity of this report, but also concerns of potential real harm by dropping immunization rates and increasing susceptibility time and potentially even tragically ironically increasing the rate of autism since rubella vaccine is really our first anti-autism vaccine since congenital rubella is one of the few known causes of autism.

Since that time there has been a letter from Congressman Weldon to the American Academy of Pediatrics urging them, based on this new information, to -- or this new publication of information, to urge pediatricians to offer a choice of single antigens, and I presume that is likely to occur to us and may come from various sources.

So we thought that it would be useful to get a sense of the Committee about our current policy and so what we'd like to do is have Bill Bellini initially review the study and give a critique. Then David Salisbury will give us some information about what's going on in the United Kingdom, as well as some further scientific critique. And then I would turn it over to you, John, to gauge a sense of the Committee.

DR. BELLINI: Thanks. As Walt said, I've been asked to review this paper by Uhlmann and -- out of O'Leary's group and the title of the paper is Potential viral pathogenic mechanism for new variant inflammatory bowel disease. And essentially I put the author's conclusion up here. It says that the data confirm an association between the presence of measles virus and gut pathology in children with developmental disorders.

This paper is written fairly skillfully in some respects in that it has a departure from the original hypotheses and actually with some supporting data that was presented to Representative Burton's committee about two years ago. It nevertheless uses the same techniques and technology to examine similar groups of individuals with developmental disorder.

There are some problem areas in the paper. The first is that the actual cases -- they are inadequately described with respect to the type of developmental disorder being examined. The reasons for why these children were biopsied aren't clearly defined.

Again, although not touched upon in this paper, one of the issues that has surfaced prior to this paper was relationship to MMR vaccination, there is no vaccination status actually listed here and whether or

not these children have had wild type infection is also not mentioned.

The controls -- they selected, so they say, developmentally normal individuals. But some of the controls have been diagnosed with Crohn's disease and with ulcerative colitis. And essentially these two diseases, in previous publications, have been identified or associated with measles in the gut, as well. And so it makes one wonder where, now they're being used as controls, whether or not these have been pre-screened in prior experiments that actually have turned up negative in those studies and now used as controls in the current study.

The mean age of the cases -- actually the range of the age of the cases was between I believe one year -- excuse me, three years and 15 years. And of the controls, I believe from zero to 17 years. The mean age of the cases was listed at seven years of age, and there was no mean age mentioned for the controls. And this is important, as you might recognize, depending upon if that mean age is shifted far toward the older individual it may actually affect the result of the time the antigens may be resident in the gut.

Another problem area was that there was no mention of the investigators or the technicians or technologists

being blinded as to whether specimens were from cases or controls. And there's no mention of possible contamination of specimens during collection, processing or transport, keeping in mind that virtually all these specimens came from a single laboratory that was working on measles for some time. As far as the molecular techniques are concerned, this is probably the top of the molecular capabilities that we have right now for identification of genomes in cells. Certainly the TaqMan reverse transcriptase PCR is a very new and actually very good technique. It can be very sensitive down to single copy of viral or other types of genomes present within a cell, and it can allow for quantitation. In other words, actually give you some idea of the total copy number present within a group of cells or an extracted RNA mix. When used in conjunction with in situ RT-PCR, which is actually just in cell RT-PCR, one can amplify in a single cell that single gene product that, during the process of this particular technique you preserve morphology of the cell and you also preserve surface markers so that you can now not only tell that there yes, there is RNA against this particular entity in there, but now we can tell what cell it is and, by specific markers, specifically the type of cell.

Now as I've stated here, these methods are complementary and when used in concert they provide a convincing argument for the presence of whatever gene in question you have. For the current paper the authors use both the hemagglutinin and fusion gene primers. Now these are the glycoproteins, the surface glycoproteins, so the virus in which antibody is made. Nevertheless, these are the primers they choose to probe for in that real time PCR, the one that'll give you the actual number of copies of RNA. This is sort of curious because the N gene primers, the first gene in the gene order of virus in this particular group of viruses, is the one most commonly and most abundantly read in the messenger RNA. And so looking for the H and F, which are further downstream on the RNA, would mean that they're looking for a genetic product that was actually less frequent than the nucleoprotein gene product, which would have been N. So that was sort of curious.

And secondly, they do copy number calculations, and when you read through the methods, they sort of walk you through what they did, but there are no data. There are no standard curves that are supplied for you to make a decision whether or not they have their system working properly. And secondly, only ranges of copy

numbers are given and one of the ranges I remember reading from the paper was they could detect down to one copy and up to 300,000 copies.

I don't want to belabor this point, but I want you to understand that this particular figure, which is figure 3 if you're following in the paper, states that this is a demonstration of the specificity of their primers. In other words, if they have F gene primers that they're actually amplifying the fusion gene product or H gene product. And the way you do that is to -- okay, the top panel is an agarose gel and what they do is they amplify the appropriate gene products from either controls like Vero cells that are infected with measles and this lane is an SSV-derived RNA that's been amplified. And these four are actual specimens from what they say are affected patients. This last lane here in lane seven is a control, and the whole process is again repeated for the hemagglutinin gene primers on the other half of the panel.

The first thing I want to point out is that any time you put RNA into such a reaction, like a PCR reaction, you're going to get bands because if it hasn't got anything specific to latch onto, it latches onto other things that will eventually go ahead and give rise to some sort of product. You can see here all the smear

that you get on a gel of this type, probably because there's nothing in here to amplify specifically. That's sort of an aside.

Anyway, what they do to prove to you that these are -- there are specific primers and they're actually amplifying the genes that they say they are is then blot these DNAs onto another kind of filter and then probe them with a probe that lies between the two primers. And what you see immediately is this is their F gene probe and it doesn't at all mimic the intensity of staining of DNA that they see from any of the other sources, either of the controls here -- which should be just burning a hole through here -- and then their actual patients. There is one, for example, that looks specific. But again, without seeing sort of a whole picture, I can't really say. The hemagglutinin gene I'll say is that it actually looks pretty good and that's certainly the kind of response that you would see to intensity of staining of DNA like this should actually be probe intensity like this (indicating). But again, going through and trying to see what else is present, we really can't say -- in terms of intensity what the degree of difference would be here.

I brought along an example of sort of what we see when we actually do dilutions of -- this is measles

nucleoprotein -- into either 200 copies -- excuse me, 100 copies, 1,000 copies, 10,000 copies and 100,000 copies. You can see the probe intensity just dies off, as does the band intensity here (indicating). But you can again see that we can detect down to 100 copies or so of DNA and there's absolutely no staining available on the gel. This kind of diminution you don't see in that report.

As far as their in situ RT-PCR is concerned, not all the specimens were looked at. Only about 56 or 57 were looked at. Instead of using F gene and H gene primers and probes for the in situ RT-PCR, they went to N gene probe titrations, which makes no sense at all because if you're going to try and prove to your audience that the actual RNAs that you're seeing in your TaqMan PCR are actually reflected in the cell, then why switch and go to nucleoprotein primers? And again, only the N gene probes are used and thus the confirmation of the presence of the F and H gene sequences by independent method wasn't mentioned. And so either they weren't attempted or they weren't successful, I don't know which.

Finally, if you were wanting to see some sequence evidence that this actually was either vaccine or wild type measles involved, you wouldn't be able to get it

from the actual H gene or F gene regions that they chose to amplify because they're not robust enough regions to tell the difference between wild type and vaccine areas of the genome. They would be able, however, to amplify the nucleoprotein genes and have that information if they chose to use them in their correct context here. And why they haven't, I'm not real sure. In summary, I think that from the beginning of the title of this paper to the conclusions there's a gross overstatement of the results. And secondly, I think the authors have not given us the opportunity to analyze their data. Thank you.

DR. MODLIN: Thanks, Dr. Bellini. I know there are probably questions for Dr. Bellini, but in order to accomplish what Walt would like us to do, so I'm going to go on and ask that -- ask Dr. David Salisbury to briefly comment on the current situation and the scientific review of the allegations within the UK. And then maybe if there is time and there are questions for Dr. Bellini, we can return to them. David?

DR. SALISBURY: Well, thank you, John. It's David Salisbury. In the time available I think it really is impossible for me to tell you all that has gone on over the last few months, other than to say that we have, day and night, dealt with allegations based on this

paper, based on other work, based on endless numbers of unique reports of children with autism whose disease came on magically overnight after they'd had MMR being given great prominence within newspapers and on the media -- and on the television, for instance.

So we have been having an extremely difficult time dealing with many, many issues on many fronts. The paper itself was leaked and reported on a television program and that led to it being published on the Internet the day after, whereas it was actually scheduled to be published I believe in April. We also got a number of reviews of the paper, and the reviews are broadly in line with those that you've heard from Bill.

Some of the reviewers raised some other questions. For example, I believe that the control strain of measles virus that was used for the internal control within these tests is a laboratory-derived vaccine strain and therefore the possibility that the case samples are contaminated would give you exactly the same result if you chose to interpret it that way. So there are a number of methodological failures that were brought to our attention. And there are a number of design failures in the way the experiment has been set up that, for example, make it impossible for you to draw

conclusions as to which factor is the operant factor leading to the conclusions that were drawn.

I think it's worth picking up Congressman Weldon's point because it came out of this paper, and a couple of days after the paper was released, Dr. Wakefield, on the radio, was challenged about the cases within his study. And he did admit that not all of the cases had actually had MMR vaccine, but some of the cases had had single measles vaccine.

If that is correct, then it rather takes the ground away from suggesting that it would be better to replace MMR with separate vaccines, because clearly some of his cases had never been anywhere near MMR, but had only had single measles vaccine.

As a result of all of this, the chief medical officer has written to Dr. Wakefield and asked him a series of questions that will perhaps help all of us understand some of the difficulties that we face. For example, how you can have controls within your study with Crohn's disease, when only a couple of years ago you were announcing that such patients would have had measles virus in their intestine. And we have asked him a number of questions, both relating to his current research and his previous result, without which it becomes -- without which being answered satisfactorily

it becomes very difficult to accept that there is a serious concern about this vaccine.

We have also asked him to confirm the arrangements whereby we can collect his samples and the raw data so that this can be independently reviewed. And I think that many people have commented on exactly the point that Bill has alluded to, that it is impossible to draw any conclusions because the data you want is not there and the data that is there is not necessarily the information that you want within the paper.

I can only tell you that as of about mid-day your time there had been no answer from him on the questions that he has been asked.

DR. MODLIN: David, thank you. In the interest of time, we can come back to it in a second, but Walt has asked me to ask the Committee if, based on the information that we now have, if there is any interest in altering our recommendation on use of MMR as a combined vaccine and a permissive recommendation for a single antigen. I think the silence is deafening. I hope that's all the feedback that you need, Walt. Do you need anything more formal?

DR. ORENSTEIN: No, that's fine.

DR. MODLIN: Okay. I'm sure there is interest in both of these last presentations. However, a number of us

are going to try to make tight airline schedules, so we do have public comment left over, but my last comment notwithstanding, does anybody wish to make public comment at this point?

(No response)

DR. MODLIN: If not, we'll call this meeting to a close. I thank everyone for their presentation. We'll see you in June.

(Meeting adjourned at 2:20 p.m.)

C E R T I F I C A T E

G E O R G I A)

DEKALB COUNTY)

I, Steven Ray Green, being a Certified Court Reporter in and for the State of Georgia, do hereby certify that the foregoing, consisting 232 pages, was reduced to typewriting by me personally or under my supervision and is a true, complete, and correct transcript of the aforesaid proceedings reported by me.

I further certify that I am not related to, employed by, or attorney or counsel for any parties, attorneys, or counsel involved herein; nor am I financially interested in this matter.

WITNESS MY HAND AND OFFICIAL SEAL, this ____ day of March, 2002.

_____
STEVEN RAY GREEN, CCR-CVR-CM
CCR NO. B-2102

[SEAL]