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PUBLIC HEALTH SERVICE
CENTERS FOR DISEASE CONTROL AND PREVENTION

convenes the

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

VOLUME I - DAY ONE

The verbatim transcript of the ACIP Conference commencing at 8:32 a.m. on Wednesday, October 17th, 2001, at the Marriott Century Center Hotel, Atlanta, Georgia.

C O N T E N T S

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

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P R O C E E D I N G S

8:32 a.m.

DR. MODLIN: Good morning. Could I ask everybody to take their seats, please.

My name is John Modlin. I'd like to welcome everybody to the October meeting of the CDC Advisory Committee on Immunization Practices. I think we'll start by asking those members who are present to introduce themselves, and at the same time divulge whatever conflicts -- financial conflicts of interest they may have.

I want to note that ACIP members who may have a potential conflict of interest should make it known at this time. All members, regardless of a conflict, may participate in discussions of all issues, provided that full disclosure of potential conflict of interest has occurred. However, the persons with a direct conflict may not vote on any issue related to the conflict. Members with financial conflicts of interest must abstain from voting on VFC resolutions, the Vaccines for Children Resolutions. Since a conflict may

appear to be present if such a member is allowed to introduce or second a vote for VFC resolution, the ACIP policy prohibits a member with financial conflicts of interest from introducing or seconding an ACIP vote or a VFC resolution.

I think I'll start to my left, beginning with Dr. Rennels.

DR. RENNELS: Margaret Rennels. I have done vaccine trials with Wyeth Lederle, Merck, Glaxo SmithKline, and Aventis Pasteur.

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

DR. WORD: My name is Bonnie Word. I have no conflicts of interest.

DR. CLOVER: Rick Clover. I, or my department, have potential conflicts of interest with Wyeth Lederle, Glaxo SmithKline, Merck, Pfizer and Bayer.

DR. BROOKS: Dennis Brooks. I have no conflicts of

interest.

DR. MAWLE: Allison Mawle from the National Center for Infectious Diseases.

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

DR. TOMPKINS: Lucy Tompkins, Stanford University. I have no conflicts of interest.

DR. DESEDA: I'm Jaime Deseda from San Juan. I have no conflict of interest.

DR. LEVIN: Myron Levin, University of Colorado School of Medicine. I do research with Merck and with Glaxo SmithKline.

DR. MODLIN: And I have no conflicts of interest. Let me introduce Dr. Melinda Wharton from NIP who has just joined the program. Melinda, welcome.

At this point I would like to turn things over to Dr. Dixie Snider, the Executive Secretary of the Committee, for some housekeeping announcements. Dixie?

DR. SNIDER: Thank you, John, and good morning and welcome everyone. I'd like to ask your help and indulgence today. I just arrived from London last

night and my plane was about five hours late. So if I start to nod off, Paul, just get up and shake me.

I'm pleased today to welcome Dr. Stephan Foster from the University of Tennessee College of Pharmacy, and now I'm not sure whether he pronounces it Stephan or Steven.

DR. FOSTER: It's Steven.

DR. SNIDER: Okay, thank you. Dr. Foster, as I say, is from the University of Tennessee College of Pharmacy and he's the new liaison representative from the American Pharmaceutical Association.

Not attending today, as I understand it, are Dr. Charles Helms, who is an ACIP member; Dr. Kristin Nichols, the ex-officio representative from the Veterans Administration; and Dr. Jim Cheek from the Indian Health Service. I'd like to welcome, though, I think, Dr. Amy Groom -- I don't know if she's here yet -- yes, she's here -- who is representing the Indian Health Service for Dr. Cheek.

For those of you not familiar with the logistics of the Committee, the appointed Committee members and CDC employees who serve as facilitators are seated at this

table. The ex-officio 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 -- for National Immunization Program -- nip/acip. And the ACIP e-mail address, for those of you who don't know, is acip@cdc.gov. And the home page is a good way, probably the best way, to keep up with the latest version of the agenda and the meeting minutes.

I'd like to announce the meeting dates for 2002. They are February 20 and 21, June 19 and 20, and October 16 and 17. That's February 20 and 21, June 19 and 20, and October 16 and 17. The Committee members will find these dates on the green paper in their book, and the dates are also on a handout at the table at the back.

Dinner tonight, for those who are interested, will be at the Longhorn Steak House on North Druid Hills Road, not too far from here. There's a variety of food from which to choose. There's no sign-up sheet for a particular menu, although there is a sign-up sheet to go. There will be individual checks, so you can order directly from the menu. For those who are very

concerned about this point, the Longhorn does have televisions for those who are interested in the playoff game. We do have reservations. So please let Gloria know if you plan to attend.

As most of you know, because you've attended these meetings before, there is a restaurant in the lobby of this hotel. You go out the doors and continue down the hall of the convention center to the lobby of the hotel and turn to the left and the restaurant is on your left. The restaurant has assured us that those dining in the restaurant will be served efficiently.

I do want to take some time to talk about the ACIP Charter and some policies and procedures. The ACIP Charter was amended to add three new members. These new members are not yet appointed. However, because of the increased number of the members of the Committee that is up to 15 -- the quorum for ACIP is now eight and, therefore, it's important that you appointed members present today return from lunch and break in a timely manner to assure a quorum is present at all times. So I'm requesting that members not leave the meeting early and not leave at all unless it's

absolutely necessary.

The ACIP Charter does give the Executive Secretary or designee the authority to temporarily designate ex-officio representatives as voting members, but this only takes place if there are less than eight appointed members not qualified to vote due to a financial conflict of interest, and I prefer not to do that. The ex-officio representatives will be formally requested to vote when that's necessary. And when this occurs, they will be asked to disclose any potential conflicts of interest. So please take note of that. That's not something that we have routinely done in the past.

There are a number of new rules that we're operating under and we apologize, collectively, for the fact that we did not get a full revision of the ACIP policies and procedures out to you in advance. A number of people have been working hard on it, but we still have a bit of work to do.

I mentioned the Charter authorizing 15 members and the new quorum. There will be a consumer representative appointed to the Committee when this is decided.

Many people have indicated some concern about how we

solicit nominees for the Committee. As most of you know, we've contacted people who attend these meetings and we've contacted members and liaisons and so forth. But in the future, in addition -- not instead of, but in addition -- we will be putting a solicitation in the Federal Register for nominees. Individuals who are selected for nomination to the Committee are going to be contacted in advance to determine their willingness to serve. And if they're interested in serving, they will be sent a copy of the policies and procedures document and asked to abide by these policies.

I had a meeting late last week, and I'm happy to say that, as new members come on board, our Committee management office will offer an orientation session now at the ACIP meetings for new members, which is also something we haven't done in the past.

Members of ACIP may, of course, provide technical advice to manufacturers, but we will not grant folks waivers if they participate on a manufacturer's advisory board when the scope of the advice goes beyond technical guidance. In other words, providing technical guidance is fine but providing policy

guidance to a manufacturer will not be -- will make a person ineligible. Also, members will be asked to divest themselves of stock ownership if that's over $5,000 in a particular company. We'll consider waivers on a case-by-case for members who serve on an ad hoc basis for being expert witnesses, for example. Some of the other points, we cannot take a formal vote to recommend a vaccine, of course, prior to licensure by the FDA. We do have changes, as I think all of you know, in the policies and procedures that allow us to meet on an emergency basis because we have had issues that have come up that require our attention other than at scheduled meeting times. And so in the policies and procedures document there are contingency plans so that we can consult with you and have an official ACIP meeting outside the usual meeting times in exceptional circumstances. And we can even do that without prior notification in the Federal Register if that's justified.

ACIP working groups include two or more ACIP members, other CDC staff, FDA staff members when appropriate. They may include ex-officio and liaison

representatives. The folks that serve on working groups will be designated special government employees so that we can share information with that group, proprietary information included, provided people sign the appropriate forms that they will not divulge, obviously, proprietary information, and these are some things that we worked out with the FDA to enhance the ACIP work.

Manufacturers' representatives can serve as consultants to the working group, but they cannot be official members of the working group. So we do want the input from the manufacturers in that regard. We've always held open discussions and we reserve meeting times for official public comment. The Committee, of course, has limited time to conduct business and, therefore, under many circumstances, we schedule formal comment periods during the deliberation of an agenda item. We receive comments during open discussions. I think John has been very good about calling on people from the audience who have something to contribute to a discussion. But at times we do have to limit the amount of time a person can

speak. So if you have comments you wish to make that you know of in advance, we ask you to talk to Gloria to sign up. This is for the public comment period. This is not for comments, of course, around any particular agenda item that we happen to be discussing. It's important for us all to hear your comments. We have a microphone at each end of the Committee tables for members of the audience to use when they want to address the Committee, and I do appreciate folks identifying themselves when they come up to the microphone and speak into the microphone. We do tape these sessions and they're transcribed, and it makes it a lot easier for those who are doing that work if you speak into the microphone.

So with that, let me turn it back over to Dr. Modlin.

DR. MODLIN: Thanks, Dixie. Let me add my personal welcome to Dr. Foster and Dr. Groom. I'd like to just mention that in the back of the Committee's folders there are a number of information pieces and updates that have been published in the MMWR since our June meeting. It includes the smallpox statement, which will be of interest to some.

I want to mention that the flu working group will meet for lunch today in the restaurant and the Harmonized Schedule working group will meet at the hotel restaurant at 7:00 a.m. tomorrow morning for a breakfast meeting. And I guess there will be an area set aside for each of these meetings.

Let me just reiterate, Dixie asked to have everyone who speaks into the microphone to first of all identify themselves and to speak directly into the microphone, if you would.

Before beginning with the first agenda item, I'm going to ask the liaison and ex-officio members seated around the second table, inside table, to identify themselves and their affiliations. We'll begin with Dr. Katz.

DR. KATZ: I'm Sam Katz from Duke University, here representing the Infectious Disease Society of America.

DR. PETER: I'm Georges Peter from the Brown Medical School, and I'm the liaison representative from the National Vaccine Advisory Group.

DR. MAHONEY: Good morning. Martin Mahoney with the American Academy of Family Physicians.

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

DR. ABRAMSON: Jon Abramson with Wake Forest University School of Medicine representing the American Academy of Pediatrics.

DR. OVERTURF: Gary Overturf from the University of New Mexico representing the American Academy of Pediatrics.

DR. SANTOS: Jose Ignacio Santos with the Ministry of Health, National Immunization Council, Mexico.

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

DR. NEUZIL: Kathy Neuzil from the University of Washington representing the American College of Physicians.

DR. WILSON: David Wilson from the University of North Dakota representing the American Medical Association.

DR. SIEGEL: Jane Siegel, University of Texas, Southwestern Medical Center, representing the Healthcare Infection Control Practices Advisory Committee.

DR. MARCHESSAULT: Victor Marchessault from the University of Ottawa representing the Canadian National Advisory Committee on Immunization.

DR. FRANCE: Eric France from Kaiser Permanente Colorado representing the American Association of Health Plans.

DR. FOSTER: Again, Steve Foster from the University of Tennessee College of Pharmacy representing the American Pharmaceutical Association.

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

DR. REILLY: Kevin Reilly, Wyeth Lilly Vaccines, representing vaccine manufacturers.

DR. SALISBURY: David Salisbury, Department of Health from London and United Kingdom, where I head the immunization program.

DR. GRAYDON: Randy Graydon representing the Centers for Medicare and Medicaid Services.

STEVE SEPE: Steve Sepe, National Vaccine Program Office, sitting in for Dr. Myers.

DR. GROOM: Amy Groom, here for Jim Cheek,

representing the Indian Health Service.

DR. DINEAGA: Ben Dineaga, Department of Defense, Health Affairs.

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

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

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

DR. MODLIN: Thank you. The first week of September, the National Vaccine Program Office and NVAC sponsored a three-day workshop on rotavirus vaccines and intussusception. We had a number of members of our rotavirus working group attended that meeting and we're going to start off -- the first item on the agenda will be a report on that meeting and then some subsequent discussion about where the ACIP would like to take the rotavirus and intussusception issues next. And we'll start off with Dr. Myron Levin, who is the chair of the working group. Myron?

DR. LEVIN: Thank you, John. Good morning, everybody.

So as John mentioned, the Rotavirus Working Group, which had its first organizational meeting in conjunction with the last ACIP meeting, decided at that time that it would base its activity on the meeting that John just described, which was entitled "Intussusception, Rotavirus, and Oral Vaccines." It was held on September 5th through the 7th in Arlington, Virginia.

We felt that it wouldn't make sense to independently collect the same kind of information that was presented and analyzed, in a very comprehensive manner, by a group of national and international collaborators. So we chose instead to base our activity on that and to present information today as shown on this overhead. Dr. Georges Peter, who was -- who is the rappateur from that meeting -- will take 20 minutes or so to present what were the most relevant and important observations and conclusions from the meeting. We've allowed ten minutes for discussion at this meeting, and then Dr. Sam Katz will lead a discussion of potential decisions that the ACIP might make. So that's a change from your program in that there will be some discussion in

addition to the informational meeting. So Georges?

DR. PETER: Do I have a pointer here? Thank you. Well, thank you, Myron. In early September, indeed, we held a three-day workshop sponsored by the National Vaccine Advisory Committee and the National Vaccine Program Office to review the association of intussusception, rotavirus, and oral vaccines. And I might add that the original purpose of the meeting was to discuss the implications of the finding for development of future vaccines. But in so doing, we realized that we could not do so without fully examining the association of intussusception and rotavirus. The discussion indeed focused on RotaShield, but had important implications for vaccine policy, in general. For example, what is an acceptable risk for any vaccine and how do we manage risk, two very important topics. The purpose for today's presentation is to review the data that's relevant to your discussions. The NVAC will consider the findings, but in a different context; namely, how do we foster public/private sector collaboration in the development of new vaccines. The topics for the meeting are listed here. I believe

you may have, or you should have, copies of the agenda from the meeting. But the three days were divided into a number of sessions which are outlined here, and I will only cover a few of these in detail. And the most important ones, from the perspective of the ACIP, are the discussion of the RotaShield experience and, secondly, the attributable risk of intussusception, and third is how we assess and manage risk in the context of this particular problem.

Now, the background information is well-known to most of you. Both the national and international burden of rotavirus disease were again summarized. The rate of hospitalization varies from one in 16 in Venezuela to one in 77 in the United States, still indicating a considerable burden of disease in terms of morbidity in this county. Worldwide, the mortality has decreased over the past 15 years, but is still appreciable and still indicates the importance of prevention of disease.

Following the initial rotavirus workshop in January of 2000, which this meeting -- our meeting was a sequel to, both the World Health Organization and GAVI had

meetings on the same subject and concluded, as we would expect, that rotavirus vaccine remains international priority and that the problems with RotaShield should not inhibit the further research on this important prevention.

The next topic was intussusception, and our knowledge of intussusception is limited. It was at the time of the meeting and still remains so. The epidemiology, the causes, the pathophysiology, and the pathogenesis remain poorly understood. And I think this lack of knowledge of the epidemiology of intussusception has greatly complicated assessment of the risk of intussusception in association with RotaShield.

Several points of note, of possible relevance to these discussions, are as follows: first, the incidence of intussusception appears to vary from county to country, with a -- relatively low in the United States -- I'm talking now about intussusception independent of vaccine -- and maybe higher in the developing world, although to what extent this is factored by the decreased detection in the developing world is unclear.

Secondly is most studies fail to show an association between natural rotavirus disease, gastroenteritis, and the development of intussusception; i.e., the rotavirus does not appear to be a significant cause, with one exception, is studies in the late 1970's in Japan in which an association was found or increased recognition of rotavirus in patients with intussusception, leading to the speculation that possibly certain strains of rotavirus might be able to cause intussusception. If so, then perhaps the vaccine strain was able to do so.

Thirdly is the incidents of intussusception in the United States appears to be declining.

And finally, the epidemiology of intussusception, that is based upon hospital discharge data, does have major pitfalls that need to be taken into account and investigators have seriously considered. Two, in particular, were noted in a presentation from Dr. Mary Staat at Cincinnati Children's Hospital. One is the miscoding that takes place and, secondly, is the variation in hospital practice. For those of you that aren't pediatricians, the management can vary from

hospitalization of two or three days to a short stay, and one of the problems is that many children may not be hospitalized -- considered as hospitalization because they were only short-stay.

These were only a few of the findings that related to intussusception. For example, an animal model does exist which shows that rotavirus may be a cofactor, at least in mirroring disease. The CDC pathological study of the cases of intussusception associated with rotavirus has not been of much help in determining the pathogenesis of this complication of RotaShield vaccination. That study is limited by a small number of specimens.

The particularly relevant discussion for today's meeting concerns the second day's discussions was the RotaShield experience, pre-licensure trials, which this group is very familiar with, vaccine distribution, and then the studies of intussusception, which I'll spend some time reviewing. And then secondly was the assessing the attributable risk of intussusception from RotaShield following those studies.

The studies that were presented were basically six or seven, depending on how you consider the CDC study, as one or two, and the first study you I believe have been sent, as ACIP members, was by Trudy Murphy and colleagues here at CDC, published in the New England Journal of Medicine. The second is also from investigators at CDC and colleagues in the vaccine data safety link is the -- by Kramarz, the Retrospective Longitudinal Cohort Study published in the Pediatric Infectious Disease Journal; a study in pediatrics from New York State, an ecological study by Chang and colleagues; the study from the NIC investigators at the National Institutes of Allergy and Infectious Diseases, Dr. Lone Simonsen and her colleagues, which is an ecological study and it's just been published in Lancet this week with an accompanying editorial. The fourth -- the fifth study is a manuscript and it's basically by Verstraeten, et al. It's an assessment of the efficacy of VAERS in detecting cases. In essence, 47 percent of cases were detected by VAERS in that study, but I don't think that's relevant to our discussions today. And then finally, the follow-up of

the Kramarz study, the CDC vaccine data safety link group, which is now in progress.

And of these studies, you have the data from almost all these studies, with two exceptions. One is the data is in your material for this study, like the follow-up study is not included. And secondly, and important to note, is that the Simonsen study that is published is a ten-state analysis. Those investigators have undertaken a more extended study with 21 states, and those findings you do not have the data for, although the findings provide similar conclusions.

Let me briefly review some of these studies. First, the case control study by Trudy Murphy and her colleagues -- And I should say at the beginning, I apologize for any inaccuracies in presentation of epidemiological studies by investigators who are in the audience, and I'm sure you'll understand. But the Murphy, et al., study was a case finding of hospitalized patients from 19 states which encompass I believe a large number of recipients of rotavirus vaccine with validation of the cases, four controls which were matched, and the case definition was hospitalization

with radiographic, surgical, or autopsy-confirmed diagnosis.

Also included was a case series study with the same case finding and case definition. Each subject served as his own control, and in this study the evaluation of whether most cases of intussusception occurred shortly after vaccination or whether they were more uniformly distributed through time was determined. And it shows the data from the case series and the case control, and you can see that the incidence risk ratio and the odds ratio were elevated. I don't have the confidence limits here, but the elevation was significant for the three- and seven-day interval after rotavirus vaccine, and eight to 14 days, and after 21 -- after the 15 to 21 days, the findings were -- showed no difference. Now, an important point to recognize is that after three weeks in the Murphy, et al. study, the risk did decrease to less than one. And Trudy, in her presentation -- or at least the materials that she submitted to Marty Myers and I for preparation of our eventual written summary -- noted that the low odds rate following the 21-day interval could be explained as follows.

Infants with markers of higher socioeconomic status were more likely to have received rotavirus vaccine and to have lower baseline risk of intussusception than infants who did not receive RotaShield. Their findings, therefore, they concluded, did not support the concept of a compensatory decrease or a temporal shift.

And the conclusions in the publications by Dr. Murphy and her colleagues are as follows. The study provides evidence of a causal association between RotaShield and intussusception which is strong, temporal, and specific. The risk of intussusception was increased in the three- to seven- and eight-day windows after doses one and three to seven-day period after dose two. And the overall attributable risk was one excess case for every 4,679 to 9,470 infants vaccinated, which is a lower risk than the original estimates of one in 2,500 to one in 5,000 two years ago.

The second study is the managed care study by Kramarz and colleagues in which they utilized ten large managed-care organizations. Cases were validated, which include both hospitalized and non-hospitalized

cases. Controls were unvaccinated members of the cohort and those outside the risk windows. And the case definition was radiographic, surgical, or autopsy-confirmed diagnosis.

And in these ten managed-care organizations, 61,000 vaccinees were in the encatchment population and 463 total infants.

The relative risks are consistent with those in the Trudy Murphy, et al. study, markedly elevated in the three- to seven-day period of time.

The conclusions of these investigators was the risk of intussusception was increased in the three- to seven-day period after dose one. The overall vaccine attributable risk was one case for every 11,703 infants vaccinated. The biological plausibility of association is supported by the correlation between period of highest risk three to seven days after one, and the period of vaccine virus replication in the intestines.

The third study that I want to spend some time on is the study that was just published in Lancet by Lone Simonsen and her colleagues, and this presentation is

on their ten-state analysis. They have also done a 21-state analysis, which is a larger population, and it made some adjustments, but the overall conclusions remain the same.

The case finding was hospital discharge diagnoses in ten states, no controls, and the case definition was hospitalization with discharge diagnosis of intussusception.

The results are as follows. In this period of time, prior to vaccination, approximately 2,600 infants were hospitalized for intussusception, and the incident decreased from 4.7 to 3.1 cases among infants 45 to 210 days old. The incidence of intussusception during a nine-month period when vaccine was administered in the ten states was compared with the incidence during the same time period of the previous year, and an increase -- this should be one percent among infants. And I apologize, Lone, I believe it's one percent in your paper. I don't know how one case ended up. An increase in hospitalization for intussusception among infants in this group was offset by a decrease among older infants, suggesting but not proving a temporal

shift and a possible triggering mechanism. And the conclusions of this group were that the -- were indeed that fact. The annual incidence of intussusception declined continuously during the period prior. Is this a change in the true -- Is this a true decrease or a change in management. The overall vaccine attributable risk is lower than the CDC estimate. This figure is lower -- considerably lower than that in the 21-state study, and in the 21-state study a larger population was involved. Secondly is that this initial figure is based upon a vaccine coverage of 28 percent; whereas, in the 21-state, the coverage was consistent with the NIS survey of 12.8 percent and gives a risk of one -- 18,000 to 33,000, I believe.

The final study that I want to spend a few moments on is the follow-up study from CDC. You have the study plan, but you do not have the data. This data was presented by Phil Rhodes, and I want you -- the important column here is on the right, which shows the relative risk, and shows in follow-up and the number of cases is very small, as you can see here, of cases.

So, therefore, the conclusions and the findings are very preliminary but, again, showing a marked increase in the three to seven-day period of time, but with no compensatory drop. The findings therefore do not support the concept of a triggering mechanism; namely, equal risk in vaccinated and unvaccinated infants three weeks post-vaccination.

Now, the next issue was assessing attributable risk, and a number of epidemiologists provided expert review of the strengths and limitations of the different studies, which differed, as you can tell, in their methodology from the retrospective cohort to the ecological study. And I don't want to comment on these strengths and limitations except to say that the value of ecological studies was debated and discussed at length by the epidemiologists and the statisticians in the office.

Following this session, a round table discussion of experts occurred, attempting to come to consensus on the population-attributable risk of intussusception following rotavirus vaccine. And the conclusions of this group -- which included Dr. John LaMontaine of the

NIH, Walter Orenstein, Jim Schlesselman, Alex Walker was the moderator, and also Jean Shapiro -- was as follows. The causal association of RotaShield and intussusception was strong, temporal, and specific. No question about the association. An epidemic of intussusception did not follow the introduction of RotaShield. However, the coverage was only 12.8 percent, varying from zero to 27 percent in different states; and i.e., was less than the original estimates. Third is the population-attributable risk by this group was estimated to be one in 10,000 children, ranging from one in 5,000 to a high of one in -- to a low of one in 12,000, which is lower than the initial estimate.

The significant question of whether rotavirus was a trigger for intussusception with post-vaccination increase followed by compensatory decrease was discussed at length. The conclusion of the panel -- and here I believe I'm quoting -- was an intriguing but unproven hypothesis.

The next session related to the question: Are other oral vaccines associated with intussusception,

specifically, oral polio vaccine? And some initial studies did show an association of OPV with intussusception, but other studies did not. An expert panel convened at CDC a year ago last June. At least a majority of the panelists concluded that the data was sufficient to exclude a causal association between OPV and intussusception.

The very interesting session was the session on Friday morning of this three-day meeting, with six presenters Dr. Salisbury, Dr. Marcuse, Dr. Saari, Dr. Jacob, Dr. Weijer, and Dr. Norman Baylor. Dr. Salisbury, who's here -- and I must admit I have some reluctance about in any way attempting to capture his words, given his way with words -- he termed his presentation as that of an outsider, and he noted that the perception of risk by the public is as important as the demonstrated risk. And while perceptions are not necessarily correct, they can be very influential. He also made the point that the perception is very much influenced by not only the media, but also by health professionals, and indeed they are members of the public. He noted the importance of communication of risk and reviewed with

us the program in the United Kingdom to -- on risk communication that exists. And indeed, it is a challenge.

He also asked the question of what risk we would have tolerated or -- and accepted to continue to recommend RotaShield and, if so, for what reasons.

Dr. Marcuse provided the different perspectives. The various policy options include, for vaccine utilization, elective usage, selective recommendations of high risk group, universal recommendation, and a universal recommendation with a mandate. Dr. Marcuse then reviewed with us the various factors that one would need to consider, as well as the different perspectives.

I think, though, a very important presentation was by Tom -- Dr. Tom Saari, a member of the Red Book Committee and a pediatrician with many years of experience in pediatrics and infectious diseases in Wisconsin. And he has done a number of surveys of the views of pediatricians, including one on rotavirus vaccine, and he made the point that physicians have a community but not a national perspective, analogous to Tip O'Neill's

comments that all politics are local. And from a pediatrician's viewpoint and practice, the community, not the national, benefits and costs are a very important issue. Issues that a practitioner would consider include their own experience with a particular type of adverse event and disease, vaccine costs, and which importance of which differs considerably in different states, depending on whether they're universal purchase or not, and then anxiety in parents. And he noted that anxiety in parents is, indeed, a very important factor because it can lead to increased phone calls, greater number of medical visits, and unanticipated use of medical resources. A key problem in the assessment of risk is that an adverse event following a vaccination from a pediatrician's perspective may require the involvement of specialty services, such as in the case of intussusception where a pediatric surgeon and radiologist may be required. And those specialists may not be available in many rural, under-served communities.

In comparison, the complication of febrile convulsions

is one that pediatricians are very familiar with and, therefore, much less of a concern than perhaps would be the case with intussusception.

I don't have time really to discuss the presentations of the others, but I think Dr. Saari's and Dr. Salisbury's presentations were especially telling.

My own conclusions were, number one, is that when one assesses risk and benefit with rotavirus vaccine, a variety of different perspectives -- from that of the public, national and international perspective to the community -- no consensus on the acceptable risk was reached by this group. The decisions are complex and necessitate, though, professional and public acceptance when a vaccine is recommended. Industry perspective is very important, since we need manufacturers. And then, very importantly, and I think we've learned in the last ten years, is the very great importance of risk communication, which is, indeed, highlighted by the problem of intussusception and other problems with which we've dealt.

The final session related to the future. We heard presentations from two manufacturers who have vaccine

trials with candidate vaccines and we also know about a third trial in India that may start but, indeed, that's not the issue for the ACIP today. The issue is -- for you concerns the current -- currently still-licensed RotaShield vaccine.

I might add, too, and I meant to mention this in my earlier comments with respect to this question of whether a temporal shift in intussusception occurred from the vaccine, i.e., with a compensatory decrease. The question -- one of the questions, to me, is if indeed -- Let's just assume for a moment that, indeed, that's the case, that intussusception is a trigger -- I mean, the vaccine is a trigger to intussusception. Would that, indeed, have made a different recommendation from ACIP? Well, that's just one of several questions, and Dr. Katz will now, I believe, present specific questions to the ACIP. And I guess -- I guess we have time for discussion now.

DR. MODLIN: Georges has done a beautiful job of summarizing three days of discussion, condensing it into 20 minutes. I think we do have some time for -- let's do open it up for questions and comments,

specifically regarding the information that Georges has presented and the events that occurred at the meeting. I think many of the members are actually quite -- are certainly very familiar with this and -- Myron, did you have a comment?

DR. LEVIN: No, I don't.

DR. MODLIN: Oh, okay. Any discussion?

(NO RESPONSE)

DR. MODLIN: Remarkable.

DR. PETER: Your silence is overwhelming.

DR. MODLIN: Well, fine. Obviously, there are very important public policy implications. Sam is going to lead us in a discussion of those. Sam?

DR. KATZ: Thank you very much, John. First of all, I must thank Georges, because he was very kind in making available to me, in advance, his 15-page summary which is not in its final form but which I'm certain you will all see eventually.

Secondly, I need to thank Myron Levin, who was very helpful in preparing the overheads that I will show you now. I should point out that

this -- what I will discuss briefly is the result of

several conference calls, and the conference calls including -- included most members of the working group: John Modlin, Trudy Murphy, Peggy Rennels, Myron Levin, Paul Offit, Kathy Carbone, Geoff Evans, Bob Chen. There may have been others, I'm not sure. I didn't write down the names of who was on the calls, but as you look at the members of the working group, nearly all of the members were able to attend the conference calls.

One point that Georges didn't make that I found interesting in his presentation from the meeting is that there is one country that apparently has a viable rotavirus vaccine being used, and that's the People's Republic of China, where they're using a vaccine that's prepared from a lamb strain of rotavirus.

If Myron will help me, we'll go ahead. The questions really that we present to you in the time that's allotted, I doubt that we can handle, except that I think they're important for consideration.

First of all, does the ACIP wish to reconsider its decision to withdraw the recommendation for universal use of RotaShield in the U.S.? Do you want to consider

it at this meeting? Do you want to postpone consideration to February? Or do you think there's some other meeting which would be appropriate for such a discussion?

Next is what information does the ACIP require from the working group in order to prepare for a vote in February, if that is your decision? To await further discussion, further publication, availability of Georges Peter's summary, or whatever other information may be forthcoming, perhaps from Dr. Rhodes' study? What other information would be helpful to you if you want to take a vote in February? Information that is pending obviously is Georges' written report from the September three-day meeting, a final analysis of the extended follow-up study that Dr. Rhodes is conducting, background materials on the strengths as well as the limitations of various study designs used to assess the risk of intussusception. We would like to have an update of pending -- of potential predictors of vaccine safety. Dr. Offit and some of his colleagues at the University of Pennsylvania have developed some animal models, muri

[phonetic] models, as I remember. There are studies of imaging being done during rotavirus infection, looking at lymph nodes in the mesentery and in the intraperitoneal cavity, looking at the potential increase in mucosal thickening of the recipient of infection, and looking at vaccine in the same way. There's information pending also regarding other studies. There are two other products under investigation, one interim data from the Merck study, Glaxo Smith-Kline also has a vaccine under study. What information would we want from the manufacturers? What information, as Georges very appropriately pointed out, from Tom Saari? What about the physician? And of course, what about the parent? And I think that, in particular, I was pleased that he stressed what David Salisbury had said. I found that most appropriate, not just for rotavirus vaccine, but for the entire vaccine establishment as we are today, as we consider other issues. I think public confidence and the public perception of how we make our decisions, why we make them and what these are, are critical to where we will go.

In some ways, some people think well, now anthrax and smallpox have restored public confidence in vaccines. I'm not sure that's quite correct. It has restored public interest in vaccines, perhaps, but I think it makes even more critical how we go about our decisions, how we go about informing the public, informing health care workers, informing legislators, and informing the media.

And then another one is: Does the ACIP want to provide guidance to manufacturers, not just for future rotavirus vaccines, but for all vaccines as to what would be acceptable for universal use in the United States? Rotavirus may serve as a prototype in this regard, but I think this is an issue that becomes increasingly important. And if so, what is the appropriate forum for such a discussion? We are but one group, and I think we sometimes forget, with all the liaison groups that surround us, that the Food and Drug Administration, through its committee, so-called VRBPAC, Virus and Related Biological Products Advisory Committee -- I always have a hard time remembering what that acronym is, Karen. Did I get it correct?

DR. MIDTHUN: Not quite, it's the Vaccines and Related Biological --

DR. KATZ: Vaccines and -- I'm prejudiced for viruses, I'm sorry. Vaccines and Related Biological Products Advisory Committee, the National Vaccine Program Office, the National Vaccine Advisory Committee. And I think we are sometimes confused by the purview of each of these. If we are, can you imagine what the public is? And if we don't all speak with one voice and with agreement about critical issues -- and in this one, obviously it's rotavirus and intussusception -- then I think we will totally lose public confidence. And once again, I'm glad that David Salisbury is here because I think he can give us some very good examples with -- for MMR and autism in the United Kingdom and how that scenario has been played out.

Well, with that, then I'd conclude my remarks and turn it over to our Chairman to lead a discussion in what time we have left. Thank you.

DR. MODLIN: Sam, thanks very much. Sam has very nicely focused the issues before us and, in some respects, tossed the hot potato back in our direction.

Let me open this issue up for discussion. And I certainly -- I think anyone is welcome to ask questions about the proceedings of the meeting, about scientific issues or whatever, but I do very quickly want to begin to focus down on the questions that Sam has posed for us. I think, obviously, the most important for us today is: Would we, as a committee, be willing to reconsider our recommendation to -- or our recommendation withdrawing the recommendation back in October of 1999.

Let's open it up for general discussion, and then we'll begin to focus in on the Committee. Natalie?

DR. SMITH: Yeah. Sam, you talked about several studies that are ongoing or information that will be forthcoming. What's the time line for those?

DR. KATZ: I'm sorry, what was the --

DR. SMITH: About information that will be forthcoming

DR. KATZ: I didn't hear the question.

DR. SMITH: What is the time line for when we might have

DR. KATZ: Well, it's interesting you asked the

question, Natalie, because in the material I received it said that Phil Rhodes' study would be done in March of 2001, but it's now October and I don't know. Is there any -- I can't answer your question. Is there anyone here who --

DR. MODLIN: Melinda --

DR. KATZ: -- can help?

DR. MODLIN: -- or Trudy? Bob?

DR. CHEN: Phil's not here, but basically what happened was that, as you -- many of you may know, we had to expand beyond the VSD sites where we had the built-in infrastructure to managed-care organizations that are not in the business of doing research. And so once the acute publicity is out, it then requires convincing regular practitioners that are willing to abstract their charts and send it in for xeroxing, et cetera, et cetera. I think we are making good progress in terms of pulling in those. I expect by February we should have those results by then.

DR. MODLIN: Okay. Dennis?

DR. BROOKS: I have two questions. The first one is, you mentioned the Chinese have the rotavirus vaccine,

and even though it's a different type of rotavirus vaccine, is there any data related to intussusception on that type of vaccine?

The second is, there was very -- this summer I attended various -- various forums that essentially talked about public confidence in vaccines. And I am somewhat concerned that if we do -- I mean, I think the discussion is relevant, but if we do consider reconsidering this vote, it could destroy some of the public confidence in ACIP, particularly since this was quite a media event when we did decide not to promote RotaShield anymore.

DR. MODLIN: Paul, maybe you could answer Dennis' question, or maybe Roger. I -- either one. Paul?

DR. OFFIT: I can answer the first one, the China question.

DR. MODLIN: Yes.

DR. OFFIT: I mean, to my knowledge, the strain that's being used in China, there are no data, to my knowledge, about -- as to whether or not that strain induces intussusception, but it should be kept in mind that intussusception in China is very --

DR. MODLIN: I'm not sure your mike is on.

DR. OFFIT: Can you hear me? Intussusception in China is very much different than it is in the United States and that the incidence is about nine times greater than -- or seven times greater than that that occurs in this county, and it does have a seasonal association. It's primarily a winter disease in China which, you know, begs the question as to whether or not natural rotavirus infection, you know, may be a cause of intussusception in China, in which case the vaccine may actually prevent it. So -- but, you know, the real answer to your question is, I think there are no data yet.

DR. MODLIN: Roger Glass, do you have anything to add?

DR. GLASS: No.

DR. MODLIN: Okay, thanks. Georges?

DR. PETER: I think -- Is this on? One question is, what would Wyeth require to re-market the vaccine? Peter Paradiso may be here and Kevin Reilly, and perhaps you should comment. Peter did give some comments, but I certainly don't want to speak for you.

DR. REILLY: All right. We've actually made public statements before, primarily in the international

arena where there's still a very strong interest in rotavirus vaccine. But specifically to RotaShield itself, we would be prepared to go back into production of RotaShield if there was a universal recommendation and a need for it in the U.S. So we would be prepared to -- clearly, we haven't been manufacturing it over the last two years when there's no demand for it, but we -- as was mentioned earlier, we're still licensed. We still have production facilities. It would take us some -- a little bit of time to get back up -- geared back up but, yeah, but we are prepared to go back into it, in the light of a universal recommendation.

DR. MODLIN: Maybe this would be an appropriate time to ask Jon Abramson and Gary Overturf where the Academy would be with us at this point and the what-if's, what if the Committee were to reconsider and to even withdraw its withdrawal.

DR. ABRAMSON: I mean, specific for the RotaShield --

DR. MODLIN: Yes.

DR. ABRAMSON: -- vaccine, I think the Committee on Infectious Disease and the American Academy of Pediatrics would not be willing to recommend it

universally.

DR. MODLIN: Paul?

DR. OFFIT: Yeah. Just -- I think one thing that Sam said, it really puts the finger right on it. I think it's really important is that -- I mean, rotavirus disease is not a big killer in the United States. About 20 to 40 children die, but worldwide it is a big killer. And so we're left with a vaccine that does have a rare -- is clearly a rare cause of intussusception. And although there would obviously be more hospitalizations from disease than from intussusception, and probably more deaths from disease than intussusception, I think it -- we are entering sort of a new paradigm which is what level of serious side effects are we willing to accept for diseases that are not themselves big killers in this country, but rather are high causes of morbidity. I mean, you could argue that influenza in a young child is going to be, at some level, part of that discussion, also. But that's at the heart of it. And I think, Dennis, when you expressed sort of concern that, you know, we lose -- may lose public trust if we have that discussion, I

think it's important -- and as I said a year ago -- to at least have the discussion, because -- because -- in terms of what are the -- what are reasonable risks associated with the benefits for these kinds of diseases. Because you know, children will get hospitalized by this disease and they will be -- some will be killed by this disease in this country. And so we have to have that discussion. I mean, I think we owe it to all the children in this country to have that discussion because there are children that die from rotavirus disease. And so -- so I don't think we're hurting the public's trust by having that discussion. I think we have to be willing to have that kind of discussion because it's not going to go away. I mean, whether it's the next rotavirus vaccine or any next vaccine, if the incidence is one in 100,000, or one in 500,000, or one in a million, you know, there has to be a level at which we, you know, consider the benefits to clearly outweigh the risks. So it's a good discussion to have.

DR. BROOKS: Yeah. I wasn't against having the discussion as much as I wanted people to be aware that

there were a lot of concerns about public trust, and people voiced them quite a bit this summer when I was at the various forums.

DR. MODLIN: Dixie?

DR. SNIDER: Thank you, John. Dixie Snider. I just wanted to point out a couple of things for consideration. One is the fact that the FDA has consulted its Vaccine and Related Biological Products Advisory Committee about upcoming or ongoing rotavirus vaccine studies. And in some respects, a de facto decision has been made with regard to what would be acceptable because you have to approve protocols that have a certain sample size and, therefore, they have the ability to detect at a certain level and, of course, the inability to detect at a level that would be lower. So, in some ways, I guess we've already started down the road of having to make a decision again.

Regardless of what we decide about RotaShield, decisions about rotavirus vaccines are going to come on the table.

And then there's the issue of when you make a recommendation, what kind of recommendation? Kevin

Reilly talked about a universal recommendation as something that the manufacturer would really like to see. But at the meeting we just heard about, Ed Marcuse talked about a whole series of types of recommendations that could be made around vaccines. And so it just seems to me that, not necessarily doing the work in this room at this moment, but thinking about not only what would be an appropriate level of risk, which would be a useful discussion to have, but what kind of recommendation to make, based on certain levels of risk, would be also something that it is important for this Committee to begin thinking about. And those are hard questions, complex questions, but ones that are going to be unavoidable.

DR. MODLIN: Good point. Sam?

DR. KATZ: In Dennis' perspective, I'd like to point out an historical aspect, which may be a little bit apples and oranges, but we used oral polio vaccine for a long time with an appreciation that maybe one in 750,000 individuals, either a recipient or a contact, would develop vaccine-associated paralysis, and there was an evolution. Now, there was another vaccine

which we now use.

Measles vaccine we have continued to use, though we know about one in 75,000 children may get thrombocytopenia with that vaccine, and it's one which we haven't changed. We have a different product than the original one, but we still continue with that and it has not surfaced at least as an issue that's destroyed public confidence.

We had whole cell pertussis vaccine for a good number of years and eventually we were able to switch to another product which is acellular pertussis vaccine. So this isn't totally a novel situation. It's one in which we've managed to survive and managed to continue with successful immunization programs, but making changes. And the question is, you know, how much information do we need, either to go back or to make a change?

DR. MODLIN: Walt?

DR. ORENSTEIN: I think this is one of the most controversial recommendations the ACIP has made, certainly in recent years. And I'm talking about the original recommendation for universal vaccination,

with discussions about the cost of the vaccine, whether the benefits exceeded the risk, even before there was any known effect on intussusception. I think, in my opinion, what has happened is the intussusception tipped the balance, because I think this, in my opinion, made it through by the skin of its teeth. In fact, the original vote was very, very close. And I'm not sure there's any new information that has -- would lead us to change that assessment. I mean, we're talking about -- I remember with health care providers at the list price of I think $37 a dose or something on that order, there was substantial concern. And so I think this was perhaps different than some of the other recommendations that were made where there was very strong strength of conviction in those recommendations.

DR. MODLIN: Good point. Bob Chen?

DR. CHEN: Yeah, just following up on Sam's comments, I think we are in a tricky situation in that most of our classical pre-licensure trials are really better designed in many ways for efficacy outcomes than they are for safety. And I think within reason, we can

detect events somewhere between one in 1,000, one in 5,000. And historically, we've had to wait till post-marketing to get rare events than that. And as Sam noted, events in kind of the one to 100,000 range ultimately, one way or the other, be it Guillain-Barre Syndrome after swine flu, be it acute encephalopathy after whole cell pertussis vaccine, is enough to force us to change our policy. And so the tricky thing is that bridge. How do we get between that one in 5,000 level of confidence in the pre-licensure trials to that ultimately one in 100,000, which does take time, but in which our technology for surveillance is improving. So it may turn out that, whereas, before it would take us five, ten years before we get at that, we may be able to get at that a little bit sooner after post-marketing. And so that kind of -- that gap of kind of -- we license it saying it's safe and effective. But then fairly soon after that, once we use it in the population, our ability to detect it is better. So I think that is our dilemma and our challenge.

DR. MODLIN: Jon?

DR. ABRAMSON: I think everything we do in medicine is

risk versus benefit. I mean, that's what we do. So from my standpoint, this has to be a disease-by-disease discussion. You cannot make a generalization about what a particular incidence of a risk is and say you would accept it or not.

But I want to get back to rotavirus and the subsequent vaccines that are coming on the market. And my concern about them is the following. It is my understanding, not being a biostatistician, that if you study 60,000 children, that you can tell whether a risk is one in 10,000 or not, but you cannot tell if it is one in 50,000 or one in 100,000. And therefore we have already made in other words, the Academy, let's put it that way, has made the decision that we will not accept a risk of intussusception of one in 10,000, which is I think approximately what we think it is. Therefore, I don't know that these vaccines that are coming down the pike in trials are going to be able to tell us what we're going to need to know to feel comfortable to make a universal recommendation. That is my concern.

It's not that I don't think rotavirus vaccine could be a good vaccine. I think it could be a good vaccine if

it was safe enough.

DR. MODLIN: Further comments or discussion? Dixie?

DR. SNIDER: Well, this is obvious, but I think it needs to be stated for the record, and that is, one of the consequences of this -- which was clearly not intended by the ACIP -- was the impact of -- then of rotavirus vaccine availability -- of this particular vaccine availability in other settings outside the United States. And one of the other problems that we have to confront and figure out how to deal with is the issue of risk versus benefit in different populations. And unfortunately, in the consideration of the use of this vaccine in the United States, we were not able, despite considerable effort, to identify particular risk populations, although we do know that there is some apparent gradient with socioeconomic status with regard to the more severe outcomes, if not the incidence of disease. And we didn't have enough specific information about risk groups in the U.S. to be able to do risk-benefit analyses in subsets of the population and make some decisions about whether there could be a targeting of the vaccine, even after we

became aware of intussusception. And certainly, we don't have much information about many developing countries, except that we know that there seems to be probably a lot more of it, certainly a lot more severe outcomes as a result of this infection. And I think many of us believe that this product, were it available in many developing countries' situations, may be doing tremendous amount of benefit and relative -- and relatively little harm. And yet, because of actions in the United States, it has not been available, and maybe because of cost it wouldn't have been available anyway, I don't know. But that's another part of the equation that it seems to me that it's important to think about for the future, how do we make these kinds of decisions for the U.S. but in the context of knowing that we're in a global situation in terms of how the ACIP recommendations are viewed, despite our disclaimers in those statements in that regard.

DR. MODLIN: Thanks, Dixie. Roger?

DR. GLASS: Well, to just follow up on the discussions before license -- before the recommendation, I think the anxiety about the recommendation was really over

the issue of cost and not over the issue of benefit. And in the first nine months that the vaccine was introduced, the uptake was actually good in the private sector, even before it -- in the first nine months. So cost, which we were concerned about in the recommendation, was less of an issue once it was introduced.

On the other hand, the reason to introduce the vaccine was discussed for a long period at this meeting, and it was based on the benefit. And given the risks that were decided at this meeting of one in 11,000, we're now in the process of looking at further data on what the benefits would be. We would estimate that somewhere on the order of 150 hospitalizations for rotavirus would have been prevented for the one intussusception event that occurred, and hundreds, up to 1,000, outpatient visits or doctor visits for lesser severe disease would have been prevented. So we're dealing with a tremendous disease burden issue compared to the intussusception.

Furthermore, if you think that the intussusceptions that are the terrible ones, if you will, are the ones

that require surgery, those risks change again. So in the terms of risk/benefit, I think we still have to look at the benefits. And the anxiety in the early period about cost, which we were concerned about, did not play out as an issue once the vaccine was introduced.

TECHNICAL WRITER: Could I have your name, please?

DR. GLASS: Roger Glass, NCID.

DR. MODLIN: Walt?

DR. ORENSTEIN: I'd like to say that I agree with Roger. The biggest issue was cost. I don't think that issue had gone away. I think that was a very serious issue, to the point we had even negotiated a federal contract for it at the time. We didn't consider what a $400 million oral rehydration program would be, $100 for every baby born in the country for some sort of oral rehydration. That would need to be considered as we consider other rotavirus vaccines because that's as -- clearly, we all prefer primary to secondary prevention, but I think we would need to justify that primary prevention, I think. So I think cost was a continuing issue and would have been an issue

had we continued on with the program. I think what was not an issue at the time was feeling that there were any significant risk factors for serious disease, and I think that's what changed it. So I guess in my opinion the one -- I agree completely that you could prevent something like over 150 rotavirus hospitalizations for every one intussusception that was caused. But I think there is a value put on those, and it's not simply just the hospitalization value.

DR. MODLIN: Other points, Paul?

DR. OFFIT: I just want to follow up on I think an interesting comment that Jon Abramson made. It's -- I remember Maurice Hillerman once said to me that, you know, he never really breathes a sigh of relief until the first two to three million doses are out there. And I think Jon's point is that, you know, you can do a study of 60 or 80 or 100,000 children and that'll tell you that the risk of the next rotavirus actually, the next whatever vaccine is not, you know, one in 10,000 or one in 15,000. But the only way you're going to know whether or not it's, you know, a risk of 100,000 or one in 500,000 is obviously -- it can only

be done post-licensure. So if one then is not going to have a universal recommendation say for vaccines which, you know, would be of universal benefit, and you're going to have a more guarded recommendation, I mean, is it -- would that work? In other words, could you then get your two or three or four million children immunized over a reasonable period of time that would enable you then to make the universal recommendation? Is that the paradigm that we're talking about?

DR. MODLIN: It sounds like that probably you had no choice. That probably is about the only way in which it could work.

Karen, do you have any comments about that?

DR. MIDTHUN: No. I mean, I agree with what Paul has said. You know, we -- there was a meeting last November which many of you probably participated in and also where we had a safety workshop, and I think that was one -- one way of proceeding that people discussed.

DR. MODLIN: Sam?

DR. KATZ: In answer to Dixie's comments, I think they're very important. And in Georges Peter's summary, it states that the current figure is 452,000

deaths a year from rotavirus gastroenteritis in the world. We talked previously about higher figures. Oral rehydration may have reduced it somewhat, but that's a very large number. As a pediatrician, you can't help but be exercised by that.

The other point I would make to Dixie is that what we've done in this country has always been a source of concern. How is this going to affect the rest of the world? But again, I'd give you three -- three historical ones. This comes from being older than you, Dixie.

One is, we stopped smallpox vaccination in this country in 1971, and there was great concern that this was going to destroy the smallpox eradication program. But smallpox elimination continued for another six to nine years. It was 1977 that the last case occurred, in 1980 that the World Health Assembly said, okay, no more smallpox vaccine. So the fact that we stopped six years earlier in this country didn't deter what went on elsewhere.

The same thing happened when we switched to an activated polio. Everyone said you're going to destroy the oral

polio program, the global program. They'll read in Somalia that we're using inactivated vaccine and they won't accept oral vaccine in sub-Saharan Africa or Asia where polio continues. Steve Coche I don't think is here, but I don't think that's been the problem. There are other problems that have arisen, but not because we made a change.

And similarly, we changed to acellular pertussis vaccine and most of the world is still using whole cell DTP and they haven't stopped using it.

So I think the fact that we do something -- maybe we have a glorified image of what the United States' policy does to the rest of the world. I think you can have differences between what we do and what's done elsewhere.

DR. MODLIN: Yes, Dr. Reilly?

DR. REILLY: Kevin Reilly. I'd like to try to clarify a couple of comments related to the international. While I agree with Dr. Katz's comments on existing vaccines and the evolution of the newer vaccines for existing diseases, the situation we were faced with, RotaShield was, at the time of the recommendation --

U.S. approval was the only approval and the ACIP recommendation was the only recommendation in place at that time.

We would have been prepared to -- We're clearly very aware that this is a significant -- a much bigger disease in underdeveloped countries than in developed countries. We would have been prepared to continue with that program if we thought there was a reasonable chance that countries would -- you know, underdeveloped countries would accept the vaccine, even in the face of ACIP recommendation to discontinue use.

Now, our own internal caucusing of departments of health and ministers of health in underdeveloped countries clearly indicated that even with WHO recommendations to try to use the vaccine, the departments of health were not prepared to accept the vaccine that had been turned down by a major country licensing or recommendation board. So the ACIP recommendation for RotaShield specifically was very, very important and the non-use of it in the U.S., and we didn't get as far in Europe, but the likely non-use

of it in Europe would have been a major detriment to its use in underdeveloped countries. So one was a usage issue.

The price of the vaccine was brought up. Clearly also we're aware that underdeveloped countries have special needs in terms of the acquisition of vaccines. We would have sold the price issue in some way or another for underdeveloped countries, and there is a patent and a history of that in the vaccine industry.

DR. MODLIN: Thanks, Dr. Reilly. Any follow-up comments for Dr. Reilly? Yes, David Salisbury?

DR. SALISBURY: David Salisbury. I'm not sure I'm going to add very much clarity to the debate, but I think that we're going round and round about the difficulties of understanding numbers and understanding feelings. And whilst we can put numbers onto some of the studies that we do, we still get stuck with what we feel about them. And we feel that one in 10,000 is a bad number, but we don't know what we feel about one in 20,000. What if it turns out that the true risk of the RotaShield is one in 20,000? How would we feel about that? Why, incidentally, are our feelings any more right than

anybody else's feelings? And while we've heard so much about different statisticians' views of the feelings, we've -- and the numbers, and we've heard so much about our organizations' views, I haven't heard anything about an informed public debate on what the benefits and risks might be. And is that because it hasn't happened or is it because I simply don't know about it? And if it's the latter, then I apologize wholeheartedly.

But there is another dimension here, and that is the user dimension, as to what is acceptable. Is it acceptable for this number of children to be dying and to be admitted to hospital, against this particular adverse event? And why do we rate this adverse event so high compared with other adverse events? I think we have to explore our own feelings a bit more clearly. What is so terrible about intussusception, other than the fact that, as mostly pediatricians and physicians, we don't have control over it? What is so terrible about it that we have taken this action, compared with other adverse events? Now, the risk of ITP after measles-containing vaccine -- after MMR is not what Sam

said. It's actually one in 23,000. That's not that different.

Most parents, if asked if they want a child walking around with no platelets, or even better -- or even worse, sitting in the back of their car with no platelets, might reasonably feel uncomfortable about that. But we haven't -- we haven't responded to that number and that risk.

So, clearly, there's something special here. And I do think we need to have some better understanding of how we interpret numbers, how we interpret feelings, and how the public interprets those influences that we put on them because we're going to have to face this over and over and over, and I suspect we will have the same problem with every live virus vaccine that turns up, forever and a day.

DR. MODLIN: Okay. We're going to need to --

DR. SALISBURY: The final --

DR. MODLIN: I'm sorry.

DR. SALISBURY: The final thing I'd just say is I disagree with Sam again, because the stories do carry. And whilst it might be nice to think that they are seen

in the context of the environment in which a problem happens, the world is not like that. I can assure you that what the IOM does on a Monday is in our newspapers on a Tuesday. And the fact that it has no relevance in terms of the exposure to mercury doesn't stop the journalists saying that's what's happened in the United States. So it's -- it's not a clean categorization.

DR. MODLIN: Jon?

DR. ABRAMSON: I think it's important that we respond that the Academy respond and try to give you some reasoning for it.

Number one, we were told by the company at the time that unless we had a universal recommendation, they would not make the vaccine. So it was a universal -- it wasn't give-the-parents-an-option-kind of issue.

Number two in the equation is that these -- some of these kids had needed to go to surgery and it appeared to be a higher amount than normally for intussusception. Some of it probably relates to that we're not used to detecting it in one- and two-month-olds or -- sorry, not one-month-olds, but two and three months old.

Two, it's probably harder to detect in the two-month-old.

Three is there's a shortage of pediatric radiologists, tremendous shortage of pediatric radiologists in this country.

So there's a number of very definite reasons why we were concerned about that one in 10,000 number. And though I have a lot of empathy for that the equation varies tremendously country to country, our primary responsibility, at least from the American Academy of Pediatrics, is to make a recommendation for U.S. children, and that is our primary responsibility. So for those reasons -- or some of -- those are some of the reasons why we felt we had to make -- stop the universal recommendation.

DR. MODLIN: Jon, if I read Trudy's paper correctly, the rate of surgery in the, quote, "vaccine-associated cases" was not higher than in the cases that were not vaccine-associated.

DR. ABRAMSON: Well, the initial --

DR. MODLIN: Is that right?

DR. ABRAMSON: When we made the decision, the initial

DR. MODLIN: I just wanted to --

DR. ABRAMSON: Yeah, yeah.

DR. MODLIN: -- make that point. We're going to bring this to closure pretty quick. Walt, we'll give you the last comment.

DR. ORENSTEIN: It's actually about 50 percent surgery, if I remember correctly, in all the cases, which is not obviously insignificant.

I think there are several things. One is, our policies are made in public and that's one of the reasons we have open public meetings here. Second, we insert values all the time, you know, in our immunization recommendations. You use whole cell pertussis vaccine. If we were to use your recommendations, I think we would have shifted to the Lederle whole cell vaccine and never used acellular pertussis vaccines. We made a judgment on IPV many years ago -- or a number of years ago, not many years ago -- to implement IPV because of concerns that we could maintain high immunity levels and not run the risk of having any of these adverse events.

I think that on this recommendation specifically there was concern, even before the adverse event, about whether the cost was worth the benefit. And so I think that changes, even though the cost/benefit ratio doesn't in terms of the risk/benefit evaluation, with the detection of this risk.

DR. MODLIN: Thanks a lot. We need to bring this to some closure, at least for today. Let me ask the voting members of the Committee if there are any members of the Committee who would be -- who would be willing to reconsider this at a future meeting. We're not -- this is not a commitment to issue a new recommendation or to change our recommendation, it's just a commitment to reconsider the RotaShield statement or the RotaShield recommendation. Are there any that would be willing to? Myron, did you -- what?

DR. LEVIN: What I was going to say was that there are only three members of the -- speaking for the ACIP now, not for the working group. There are only three members that I could think of who were actually at the meeting, and it may be that -- for some of us who weren't there, that we should have the time to digest what we've

been told by Georges, some of the information that Sam said we might want to collect, and also what I've heard today, which were some very important comments. I think in all fairness, speaking for myself now, I would like to have an opportunity to digest all that and then at a -- probably in February, answer your question.

DR. MODLIN: Okay.

DR. SMITH: I agree with that comment. You know, I haven't been involved and I would, at the minimum, like to read Georges' 15-page summary and also have a chance to talk to other people.

DR. MODLIN: Okay. Lucy is nodding agreement with --

DR. TOMPKINS: Same.

DR. MODLIN: -- Natalie and Myron. I would feel the same. Dr. DeSeda?

DR. DESEDA: I was going to say that I think that we do need some information, particularly related to other strains and different vaccines. Even though we may not have the numbers, that would be useful. And I think that it's possible to reconsider, but not at this date.

DR. MODLIN: Dennis?

DR. BROOKS: I was there at the meeting when we made the decision and I really don't want to reconsider it.

DR. MODLIN: You don't. Okay. Rich?

DR. CLOVER: I think I agree with the majority of the opinion that's been mentioned. This is a risk/benefit issue, and one of the things I'm struggling with the data on is, if we understand the risk, is one in 10,000, 11,000. Further discussion of the benefit of the vaccine in prevention of hospitalizations, et cetera, in that context, may be useful information before I would ever consider reconsidering the recommendation.

DR. MODLIN: All right. Bonnie?

DR. WORD: I'd have to agree with the majority of people.

DR. MODLIN: Paul?

DR. OFFIT: I guess just personally I think that I would feel uncomfortable on a vote for the vaccine because of my conflict with Merck.

DR. MODLIN: Okay. Peggy?

DR. RENNELS: If we're going to revisit it, I think there are other data that we need to hear. Intussusception isn't the only side effect.

DR. MODLIN: All right. Dixie, I don't think we need a formal vote on this. I think we have a consensus, and so that we will thank Myron and the working group for a terrific job that they've done so far and plan to revisit this, probably at the February meeting. Myron?

DR. LEVIN: And so just to say that our task then will be to accumulate some of the information that Sam said we might; to poll the ACIP and see if there's additional information such as Rick mentioned; and see if we can do that in a timely fashion and then be ready to respond in February.

DR. MODLIN: Terrific. Any other -- Is there any other information that any other members of the Committee or anyone else, for that matter, would like to focus on when we come back in February or later? If not, we will break until 10:30. Thank you.

(RECESS FROM 10:03 A.M. TO 10:32 A.M.)

DR. MODLIN: Could I ask everybody to take their seats, please. Could you please be seated so that we can begin.

The rest of the morning's session will be devoted to

influenza, and there are going to be a number of important informational items, data, issues that we need to be focusing on because, in all likelihood, there will be some very important decisions that the Committee is going to need to make soon, probably as early as the February meeting.

Dr. Keiji Fukuda is going to lead the discussion. And while Keiji is coming to the microphone I'd like to note that an error in this morning's announcements. I understand that the Harmonized Schedule working group will not be meeting tomorrow at 7:00 a.m. However, the Yellow Fever working group will be meeting at noon tomorrow and at a time and -- noon, but at a location to be announced later. Right, Rich? Okay. Keiji?

DR. FUKUDA: Thanks, John. Actually, Bonnie is going to head off this session. We have a --

DR. MODLIN: Sure.

DR. FUKUDA: -- several speakers to go on.

DR. WORD: Okay. I think as John has indicated, you can see we have the rest of the morning. The working group actually has been very busy since we last met you we were last here. We were actually all here

together September 10th and 11th in Atlanta for our last working group meeting. And at that time we looked at four additional topics that were related to the potential of expanding influenza vaccine into children. We looked at some additional safety and effectiveness data as related to inactivated influenza, as well as looking at some more practical things like the economic issues related to expanding the use of this vaccine into children, as well as what are some of the implementation and feasibility issues. And then finally, we got down to looking at some options with that.

So this morning what we would like to do is have a series of presentations come up this morning and we have -- The group actually was broken down into four working groups again, and we had some invited guests. So, essentially, what we're going to do is have some presentations related to that to give you a summary of all of our findings.

Before we begin that, we're going to start with Tim Uyeki, who's going to just give a brief overview again of the burden of influenza disease in children.

That's going to be followed by Kathy Neuzil, who's going to give us an update -- their summary on safety and efficacy. Kristin Nichol and Carolyn Bridges, this will be interesting because hopefully Kristin will be able to telephone in. She's on speaker phone. We'll be utilizing her slides here and you'll hear her voice via speaker phone. If not, Carolyn Bridges will be doing all the discussion if it doesn't work.

That will be followed up by Natalie Smith, who will be presenting the feasibility implementation study -- or summary. Ben Schwartz is going to come up and give us a little bit about program funding, and Keiji Fukuda will finally summarize it and tell -- let you know what some of the options that we came up with and some -- you know, to determine when and if we're going to bring it to this Committee.

So without further ado, I bring Tim Uyeki to get things going.

DR. UYEKI: Okay. This is a huge topic and I'm going to go through it fairly quickly with a brief summary. Basically, what I'd like to present is a sort of a summary of the available data out there, and I'm going

to briefly talk about morbidity in terms of attack rates during epidemics of influenza, some of the hospitalization data, the little data that's out there about outpatient visits, some of the common complications and a rare complication that the Committee might be interested in hearing more about.

In terms of morbidity attack rates, there have been a number of longitudinal studies looking at families over quite a few years, looking at the percent of children with clinical illness during influenza epidemics. These have been done in Tecumseh, Michigan; Cleveland, Ohio; Houston, Texas; and Seattle. And I'll present data from two of these studies.

Using culture -- primarily viral culture, but some serology, Paul Glezen and colleagues -- this is data estimated attack rates for respiratory illness associated with an epidemic of influenza H3N2, Harris County, Houston, Texas, 1976. If you look at it by age group, in terms of the percent of the population in that age group ill, you can see that more than a third of young children less than one year and less -- and one

to four years were -- in fact, had clinical influenza. And contrast this with the overall attack rate estimated in the population of 18 percent and less for adults.

If you look at data from the Seattle Virus Watch, 1966 through 1969, primarily serologically detected influenza infections, again, look at young -- young children less -- age zero to one or two to five, in terms of the rates of influenza A infections per hundred person years, substantially higher in young children than older children and in adults.

I don't think the numbers are important to fixate on because annual influenza epidemics vary in severity from year to year, but it's more the trend that young children are primarily impacted more than other groups.

When you look at what kind of complications children are hospitalized for influenza, generally these are descriptive case series where children who are hospitalized are then cultured for a number of different respiratory viral pathogens or in some cases just looking for influenza. And some of the more

common conditions that are found in hospitalized kids due to influenza, both influenza A and B, are pneumonia, bronchitis, croup, bronchiolitis, fever without a source -- that would be fever with no respiratory symptoms, just simply high fever presenting like a sepsis-like syndrome -- and febrile convulsions. There was a recent paper in Pediatrics this month from Hong Kong looking at febrile seizures during the winter and during the influenza season there you will find up to 30 to 40 percent of their children hospitalized for febrile convulsions are in that period that's due to attributable to influenza A.

But in terms of looking at hospitalization rates, we really have -- I think the Committee is probably familiar with two of the more recent studies that were published in the New England Journal last year, one by Hector Izurieta and one by Kathy Neuzil, and these use indirect methods to try to come up with excess rates of hospitalizations. And generally the idea in Izurieta's paper was he looked at two large HMO populations from 1992 to 1997, northern California Kaiser and Group Health Cooperative of Puget

Sound -- looked at hospitalization rates for defined acute respiratory conditions and tried to use local virologic surveillance data to define periods when influenza was circulating and adjusted for when RSV was circulating.

In terms of excess rates, this was rates for these acute respiratory conditions during the influenza period and subtracting out the summer baseline rates. And the point is more to look at the relative rates in the various age groups, and you'll see in the northern California Kaiser for children age zero to one, the rate is substantially higher, whether you're looking at the rate during the influenza period or you're looking at the excess rates, substantially higher in children zero to one, next higher in children two to four.

The same trend is seen in the healthy children in Group Health Cooperative where the rates are substantially high -- highest in children zero to one and then decrease as you -- as you get older, and keep -- these are healthy children.

When you look at high-risk children during the influenza periods, children with chronic underlying

conditions, the rates in general are much higher than in healthy children. Again, there's a trend that very young children have much higher hospitalization rates, and this is true for both northern California Kaiser as well as Group Health Cooperative.

Kathy Neuzil and colleagues looked at 15 years -- I'm sorry, 19 years of data from the Tennessee Medicaid populations of healthy children less than 15 years old, and they did a similar kind of analysis, looking at hospitalization rates for acute cardiopulmonary conditions. They also defined periods when influenza and RSV were circulating, and they looked at excess rates. Some of these age groups are stratified smaller than Izurieta's, but basically you can see in young children, particularly less than six months old, again the highest excess hospitalization rates and then as you get older it decreases. But basically children less than one year have very high hospitalization rates.

If you look at an analysis they did looking at only high-risk children, these are chronically ill children, same population, same -- similar type of

analysis. Again, children less than one year have very high excess hospitalization rates. And still children less than three have pretty high rates. And it's important to realize it's difficult to compare all the different rates, but these rates are essentially two to four times higher than for healthy children. In terms of outpatient data, there's really not a lot of outpatient data out there but, again, Kathy Neuzil and colleagues looked at a cohort of healthy children in the Tennessee Medicaid database, and I'll just sort of present not their data, but sort of a summary from the paper. They concluded that influenza appeared to account for up to 35 percent of excess outpatient visits in the winter in children younger than three years. And in terms of total outpatient visits -- again, this is healthy children -- the rates were highest for infants less than six months old, next highest for infants six months to one year old -- to less than one month -- and then one to less than three years. And actually this is almost a quote from one of Kathy Neuzil's papers that's in press in the Journal on Infectious Diseases. It's fairly impressive. This

is a 25-year perspective study of children that are followed for culture-confirmed influenza and almost ten percent of children had a symptomatic health care visit that was associated with culture-positive influenza each year. So a substantial number of -- percentage of health care visits associated with influenza.

I'm not going to present an overview of all the types of conditions or common complications of influenza, but I'll just discuss some data of one fairly common one, which is acute otitis media. And if you'll look at the data that's out there, there's a six-year study in Finland looking at both hospitalized and outpatients. In this study, acute otitis media was diagnosed in 35 percent of patients that had influenza A. In a similar study of children age two months to seven years, 42 percent with influenza had acute otitis media.

You can look at the -- in some clinical trials of vaccine and look at the unvaccinated arm to look at the burden of acute otitis media with influenza. In one trial in Finnish day care children less than three years old,

two-thirds of the unvaccinated group who were influenza-positive had acute otitis media. And similarly, you can look at the unvaccinated arm of a live attenuated vaccine clinical trial of children age 15 to 71 months old. Of the children who were unvaccinated who were influenza culture-positive, 21 percent had acute otitis media in the first year. In the second year, 12 percent had acute otitis media. It's a fairly common occurrence.

And I just wanted to summarize -- bring to the attention of the Committee some rare neurological complications that people may have heard about, specifically acute encephalitis and acute necrotizing encephalopathy. In general, acute encephalitis tends to be associated with influenza pandemics, although there have been sporadic case reports from England, Jamaica, Hong Kong, Canada, Japan, the United States, and other countries during annual influenza epidemics. But in general, this is uncommonly reported with both influenza A and B.

However, in Japan, this is a different situation. There have been, since 1994, a substantial increase in

cases of acute encephalitis and encephalopathy that have been associated -- that are associated with influenza A, and these cases are all in young children. And sort of the clinical characteristics, clinical course, there's a sudden onset of high fever and a rapid onset of neurological symptoms, often within a day and a half of the onset of the fever. Seizures are very common. There's a rapid progression to coma in a large percentage of the cases. This is not associated with aspirin use and it's not a Reye's syndrome-like picture.

On neuro-imaging often there's bilateral thalamic necrosis, brain stem involvement, and there can also be cerebellar involvement. There is a fairly high percentage of neurological sequelae -- paralysis, decreased functioning -- and there is a high case fatality ratio, and death occurs commonly -- or often shortly after onset. And studies that have been done in Japan, more descriptive studies but -- or limited surveillance studies have estimated that there are between 100 and 200 fatal cases of acute encephalitis or encephalopathy in Japan per year.

And I'll just present some data from one paper that was in Lancet last year. It's a cross-sectional survey that was done to look at influenza-associated encephalopathy from January to the end of March of 1999 in all medical facilities, conducted by the Japanese Ministry of Health. And most of these cases had confirmed influenza, but not all. Some were clinically diagnosed with illnesses compatible with influenza during the influenza season. There were 217 cases reported. Eighty-three percent were in children less than five years. Girls were equally infected as -- are affected as boys. There were 58 deaths in this case series, and on average, death occurred within 1.1 days of the onset of the illness. There were 56 with neurological sequelae. And neurological complications, particularly seizures, often occurred within 1.5 days of onset of illness. And only three patients in this survey in this -- was reported had used aspirin.

So one of the things I'd just like to point out is that the impact of influenza may really be underestimated. Influenza may be infrequently diagnosed if patients

are presenting with atypical symptoms. If you look at case reports or case series in the literature of hospitalized patients or, you know, outpatients, there are -- it's hard to quantify this, but certainly there are children, particularly young infants, who may present with non-respiratory symptoms, particularly just with gastrointestinal symptoms -- nausea, diarrhea, vomiting or just diarrhea -- and physicians may never suspect this is influenza. Fever without a source, sepsis-like syndrome. So these -- these -- In young children, presentations may be not your typical upper respiratory illnesses.

In addition, influenza is rarely confirmed by testing. It's usually clinically diagnosed.

So, in summary, from the available data, it appears that attack rates in young children are quite high, and higher than certainly older children and in adults. Hospitalization rates are highest in young children. In general, there's really a real lack of good outpatient and mortality data. I did not present mortality data. There's really not good mortality

data in young children -- or in children due to influenza that's published.

And then finally, rare complications such as acute encephalitis and encephalopathy are not seen in the United States, but are a growing problem in Japan, and it's not understood why this is being observed in Japan and not in the United States or elsewhere.

That's all I had.

DR. MODLIN: I suspect we probably ought to -- given the number of speakers, should continue on. We'll certainly try to make ample time for discussion later on. Is that fair, Bonnie? Thanks.

DR. NEUZIL: Good morning. I'm Kathy Neuzil and I'll be summarizing the working group's perspective on the trivalent inactivated influenza vaccine in children, with a focus on safety and effectiveness or efficacy. This is a challenging topic. We know that influenza vaccine has been licensed for the last 50 years. So we've tried to condense our study a little bit, and I'll tell you how we did that.

We did a Medline search for trivalent inactivated influenza vaccine studies in children. We obtained

additional studies by looking a references in Medline articles. We excluded any studies of whole virus vaccine or foreign TIV that were not comparable to U.S. vaccines. And we also excluded any study made prior to 1981, because prior to 1981 the vaccine had a reduced antigen content compared to the current vaccine.

And in the next ten minutes I will try to summarize what we thought were the key studies, and I'm really focusing here on randomized, controlled trials. There are a number of smaller immunogenicity and safety studies that won't be included in this talk but are available in the minutes from our working group. And really, we can divide these into three categories: trials on children in day care; randomized controlled studies that were done comparing the trivalent vaccine to the live attenuated -- and I'll be focusing on the trivalent; and then there are two unpublished studies that I want to tell you about briefly.

If we first look at the studies of children younger than the age of five, these are predominantly studies that were done in day care populations and with an end point of acute otitis media, and the first was done by

Heikkinen and others and this included 187 children aged one to three years who received the trivalent inactivated vaccine versus 187 children who remained unvaccinated, actually did not have placebo. There were no safety data reported as part of this study. Overall efficacy for proven -- culture-proven influenza was 83 percent in these young children, and likewise there was an 83 percent reduction in acute otitis media associated with influenza.

Similarly, Clements published a study in 1995 that looked at 185 day care attendees and the age here was six to 30 months. And actually the day cares were randomized, not the children, to receive either the inactivated influenza vaccine or placebo. Again, we really don't have reports of safety data in this paper. The outcome again was acute otitis media, and this paper showed that influenza vaccine was protective against acute otitis media during the influenza season, not before the influenza season and not after the influenza season.

The third published study in day care children was published in 2000 by Hurwitz and others, and this looked

at day care attendees who were 24 to 60 months of age, who again received either the inactivated vaccine or actually hepatitis A vaccine. You can see that this was a smaller study compared to the other two studies that I have shown you. We're told that adverse reactions were assessed by the parents and that both vaccines were well tolerated, although there are not safety details given in this paper.

Vaccine efficacy overall was based on seroconversion. It was 45 percent, you can see, with a confidence interval of five to 66 percent. However, there were no significant differences in the effectiveness measures -- respiratory illness, otitis, physician visits, antibiotic use. In a companion paper, however, there was a reduction in the number of respiratory illnesses in the contacts, in the family members of the children, but not -- this study actually did not have the power to detect a difference in the children.

The second set of studies that we looked at were randomized controlled trials of the inactivated and cold-adapted influenza vaccine in children. There

are four published randomized controlled efficacy trials. But as you'll see, these actually represent two studies. There was a large family study at Baylor which was a three-year study which was published in three separate papers, and then a large five-year study that was conducted at Vanderbilt. So I'll review those two studies.

Again, these studies used comparable vaccine to what we're using now, same antigen component, split-virus vaccines. The cold-adapted vaccine as actually changed since this time. It was bivalent at that time. The concentration in some of the studies was slightly different. So, again, I will just focus on the inactivated vaccine for this portion of the talk.

The first study was by Gruber and others in 1990, and again, this was the Baylor family study in which families were actually randomized to receive either placebo, inactivated vaccine, and cold-adapted, and there were 189 healthy children who were members of those families, between the ages of three and 18 years. And the year of this study -- It was reported in 1990. The year of the study was 1985, and the circulating

strain that year was a B strain, which was a drift strain from the inactivated vaccine.

The families were contacted by telephone to assess safety data, and you can see here that there were no serious adverse effects. The only adverse effects reported were local tenderness at the site that did not limit function, and it occurred in about 20 percent of children who received the inactivated vaccine and about 19 percent of children who received placebo.

Now, for all of these studies that were done in Houston, they assessed these children by calling the parents weekly and would actually make home visits if there was a clinical illness, obtain blood specimens from these patients and obtain nasal wash or throat culture specimens from these patients. So these were very rigorously followed children.

If we look at laboratory-confirmed infection, I've broken it down by age groups: age three to younger than six, six to younger than ten, and then ten to 18 years of age. You see again what Tim showed us, which is if we first look in the placebo group, either as defined by laboratory-confirmed infection or clinical

illness, influenza is a common disease in children. If we define it by laboratory parameters, 30 to 55 percent of children have an influenza illness, and here we see that 30 to 40 percent of those children were symptomatic with that illness.

We also see, if we compare the placebo groups to the group that received the inactivated vaccine, that the inactivated vaccine was efficacious and appears to be more efficacious as the children increase in age. The overall efficacy here was significant. It was 62 percent for infection and approximately 76 percent for clinical illness.

Year two of this study was reported by Dr. Clover and others in 1991. Again, same study design the following year. The circulating strain that year was an H1N1 drift strain and we have no additional safety data than from the Gruber paper.

If we look here -- and I've just shown you laboratory-confirmed clinical illness -- we see that this particular year approximately 20 to 25 percent of children had an influenza illness, and the age groups were reported differently in this paper, but there were

actually no illnesses in the ten- to 19-year group, so highly efficacious and not statistically significant in this younger group.

Now, Piedra reported the third year of this study and we're told during this year that local and systemic reactions following vaccination were more mild and did not differ between the groups. We're told that the protection rate against symptomatic H3N2 infection was 76 percent overall, did not have the power to compare within the age group, but did show that same pattern of improvement with age. And interestingly, they followed these children to a fourth year without giving them an additional dose of vaccine and reported that the protection from the prior year's vaccination did not extend into year four.

Now, the second large efficacy trial was done by Cathy Edwards at Vanderbilt, and it included over 5,000 healthy subjects who were randomized to receive either the inactivated vaccine, the live vaccine, or placebo over a five-year period of time. Dr. Edwards originally reported this data cumulatively in adults and children in 1994 and we actually together

re-analyzed the pediatric portion of this data and reported it this year. And the pediatric portion included 791 healthy children between one and 16 years of age who participated in years two through five. Year one was a pilot year, included very small numbers of children. So this reanalysis included 277 children who received 635 doses of the trivalent vaccine. During the two years of this study there was an H3N2 circulation. One of those strains was a drift strain from that which was included in the vaccine, and two of the years there was H1N1 circulation.

The safety assessment and the report of safety was quite detailed and included fever, local reaction, systemic reactions that you see listed there -- sore throat, coryza, lethargy, et cetera. What I will show you -- The assessment for local reaction was done by diary cards for the five days following vaccination, and I will show you the results that were significant and similar to what we see in adults.

The most common side effect in children was sore arm and redness and induration associated with the trivalent vaccine. And you can see that this appeared

to increase with age in that the children in the 11- to 15-year-old age group had more induration than the younger children.

If we turn to efficacy, there was efficacy based on seroconversion and efficacy based on illness, and I divided these into the H1 and H3N2 years and you can see again that vaccines were highly efficacious in preventing seroconversion and appeared to be more efficacious with increasing age. And our age groups were one to five, six to ten, and eleven to 15.

If we look at culture-positive illness, there's an important distinction between the trials that were done at Baylor. Patients presented to clinic, which means ill patients selected themselves to come to clinic, and that's quite different than going to somebody's house. This was quite a large study, 5,000 people. So you can see that overall culture-positive rates were much lower, about four to seven percent, than were seen in the Baylor studies where they went to their homes. Because of this, this study did not have the power to break up culture-positive influenza illness by age group, but we can look at all the children

together and the estimates are that the vaccine was approximately 92 percent efficacious for H1N1 disease and approximately 77 percent efficacious for H3N2 disease. So, again, quite similar to numbers that we hear in young and middle-aged healthy adults.

Just one slide on studies in high-risk populations. Again, there were thousands of healthy and high-risk children who were vaccinated and who we have information on prior to 1981. But since 1981, we have reports on studies conducted in a limited number of children with a limited number of conditions. Safety profiles appear comparable. Immunogenicity studies appear comparable, but not enough numbers to comment on efficacy.

Now, at the last working group meeting there were two presentations of unpublished data that I think are important to mention briefly, remembering that they are unpublished data. And David Greenberg conducted a study at the University of Pittsburgh evaluating the inactivated vaccine in children age six to 24 months with an end point of acute otitis media. I think this study is important and it will be important to look at

these published results because he included healthy infants six to 24 months of age, gave 525 doses of the trivalent vaccine, and half of these doses were in the six to 12-month age group. So this will be the largest reported series we have -- when it is reported -- on this age group.

Limited safety data at present. There was no SAE that was definitely related to vaccine or placebo. There was a 66 percent reduction in culture-positive flu in year one, no reduction in year two in which illness rates were quite low, and interestingly and different from what you heard at the beginning of my summary, no difference in acute otitis media episodes.

And finally, Eric France and others in the VSD are working on population-based studies to try to get an idea of less common side effects with influenza vaccine in children. And they're looking at the group health and the various Kaiser Permanente populations. They started with the 1997 to 1999 data. They know that they have 148,000 influenza vaccines given during this time in this population. On initial analysis, they've compared the time period after vaccination to various

control periods in these same children, and right now are looking at a variety of different outcomes, actually over 1,000 outcomes for inpatient, outpatient, and emergency department visits. And on preliminary screen there have been no obvious associations, no surprises with influenza vaccine. So, really, in summary, these inactivated vaccines are well tolerated in all age groups. There's insufficient power in the published studies to assess uncommon adverse effects. The studies do support the protective efficacy of TIV against all three strains against -- of influenza virus, including among young children and including drift years. And the Committee thought that it was important to have continued safety monitoring, including these studies that look at rare events and studies that look at co-administration of influenza vaccine with other vaccines in early childhood. Thank you.

DR. NICHOL: Good morning. I'm Kristin Nichol here in Minneapolis this morning and I'm pleased to work with colleagues from the CDC to present to you the summary of the economics subgroup work for the September 10 and

11 meeting for the influenza working group. Next
slide, please.
In this slide, I would like to acknowledge the economics
subgroup participants, including not only members of
the ACIP, but also staff from the CDC and consultants
-- Tracy Lieu and Lisa Prosser from the Harvard
Children's Health System, as well as Ken Zangwill from
Harvard UCLA Medical Center. Next slide, please.
In the next few minutes I would like to briefly touch
on some issues relating to definitions for various
terms used in economic analyses, frame some of our
deliberations in the context of cost effectiveness and
other kinds of preventive services, as well as what we
know about cost effectiveness of some other
immunizations, particularly childhood immunizations.
Then describe the methods that our group used, as well
as very briefly describing the results of five
published studies that address the economics of
influenza, vaccination in children, mention some
studies that are still in progress, and finally
summarize some of the unresolved issues that the group
identified. Next slide, please.

First, a few comments about definitions and types of economic analysis, and it's important to understand that there are differences between different types of studies, because sometimes one may otherwise then be in a position of trying to compare apples to oranges.

Cost effectiveness analysis, or CEA, is a type of economic analysis that presents the results in terms of cost per health care outcome. For example, dollars per life saved.

A cost utility analysis, or CUA, presents the results of the analysis somewhat differently, typically in terms of cost per unit of quality-adjusted health outcome such as dollars per quality-adjusted life year or QALY. Now, the QALY or quality-adjusted life year incorporates the impact of the intervention both on the quantity and quality of life, and the importance of this distinction versus the outcomes included in cost effectiveness analysis will become apparent in the next slide.

And finally, the third type of economic analysis is the cost benefit analysis, or CBA, in which all outcomes are assigned a dollar value and the results are

typically presented as net costs or savings.

In the next slide we have summarized for you the types of monetary costs typically included in each of these three types of analyses, and it is important to note here that each type of analysis may include different types of monetary costs, such that the results often cannot be directly compared and it is very important to understand which costs have been or have not been included in the particular study or analysis. And please note that under costs averted or prevented with the intervention, the most significant difference in monetary costs that may or may not be included have to do with the so-called indirect costs that generally refer to productivity, losses that are prevented or productivity gained -- experienced because of the intervention, with cost benefit analysis typically always including that particular kind of cost; cost effectiveness analyses sometimes including them, sometimes not including them; and with cost utility analysis, generally those costs not being included as a monetary cost but actually implicitly being incorporated into the denominator or the quality

adjusted life year. Next slide, please.

Finally, there are a few caveats to keep in mind when considering economic analysis studies. Very importantly is the notion that cost effective interventions do not need to be held to a standard of cost savings in order to be worthwhile. Surely if an intervention is cost saving, it is generally considered dominant and frequently thought worthy of adoption. However, most interventions available in the health care system today are not cost saving, but are nevertheless thought to be cost effective, and cost effective interventions may be considered for adoption even if they are not cost saving. Certainly, it depends on what is considered to be a cost effective threshold or a value that society or the payer is willing to pay for that outcome. And it also depends on the importance of the disease, both incidence as well as severity of morbidity or mortality associated with the disease, as well as other factors such as feasibility or logistics, availability of the intervention in the case of vaccines and so on.

So, finally, these three types of studies are not

necessarily identical or equivalent, although we hope usually they provide similar kinds of conclusions, but they are different metrics. Next slide, please.

Now, some comments on the context and, in particular, how the pediatric studies looking at the economics of influenza vaccination might fit into a broader perspective. In this slide we have reproduced for you a figure from a recent review of economic studies, in particular, of clinical preventive services that were published from 1976 to 1997, and the study is part of a larger, ongoing effort exhaustively to catalog economic analyses for all kinds of health care services in this country.

With regard to preventive services and the summary of the studies that were available through 1997, on the horizontal axis are various categories for the outcomes, their findings in the studies, ranging from cost saving on the left all the way to interventions that cost more than $100,000 per quality adjusted life year to interventions that actually increase costs and result in poor health care outcomes, the last category being clearly a category where those interventions

would not be considered worthwhile.

The median cost for quality adjusted life years for all the clinical preventive services studies was $14,000 per quality adjusted life year, with more than half of them having a cost less than $50,000 per quality adjusted life year. For immunizations in this study of those papers that addressed the economics of immunization across the age spectrum, the median cost was about $1,500 dollars per quality adjusted life year. Next slide.

This is a final slide providing some context as we moved into our review of the studies addressing influenza vaccination in children, and this slide summarizes some of the economic analyses that have previously been published addressing other childhood immunizations and shown are results of studies for MMR, DTaP, hepatitis B, varicella, pneumococcal conjugate vaccine, and then a study that compared IPV versus the OPV strategies for polio immunization.

As you can see, as summarized in the right-hand column, many of the childhood immunizations, particularly those adopted earlier, are thought to be cost saving,

both from the societal as well as the health care payer perspective, including MMR, DTaP, and hepatitis B. In addition, varicella was found to be cost saving when it was studied.

On the other hand, pneumococcal conjugate vaccine was not found to be cost saving, but was found to generate costs of approximately $80,000 per year of life saved and this was thought to be a reasonable cost for the outcome achieved. And finally, when the recommendation was made to move from oral polio vaccine to IPV strategy for immunization, the incremental costs of the change are shown here as $3 million per vaccine-associated paralytic poliomyelitis case prevented.

So this is some information providing perspective in how to interpret economic studies.

With regard to our charge to review studies for pediatric influenza vaccinations, the methods we used included a literature search and an in-depth, structured review of the five published studies. For that structured review we used CDC's checklist for evaluating economic studies. We assigned a main

reviewer and had extensive group discussions. We also briefly reviewed works in progress that had not yet been published. Next slide, please.

The five published studies that we reviewed are those listed here and I will now briefly describe the results of each of these studies. Next slide.

The first study is -- that I will summarize is the study by Martin Meltzer and colleagues from the CDC that assessed the economic impact of pandemic influenza in the United States. And shown here are the results of this study, applying a set of assumptions that would be compatible with a typical epidemic scenario, so that even though the paper is addressing pandemic influenza, the results that we reviewed actually would apply to interpandemic influenza, period. And in that study, it was found that influenza vaccination of children going up to age 18 or 19 would likely not be cost saving unless the cost of vaccination, both direct and indirect cost, including parental work-loss time, were less than about $20 per child vaccinated. It was also noted in that study that economically it might be more efficient or it would be more efficient to immunize

high-risk children as opposed to children in the general population because of the greater economic return on immunizing high-risk versus healthy children.

In the next slide we present the results of an Office of Technology Assessment report published in 1981 that assessed the cost effectiveness of influenza vaccination across all age ranges. We have shown just the results for younger age groups in this slide, and in this study -- it was actually a cost utility analysis. So the results are presented as cost per quality adjusted life year saved for all people in the age groups listed and the results have been adjusted to 1998 dollars.

As can be seen, the cost per QALY ranged from $724 for people 15 to 24 years to $1,032 in 1998 values for children less than three years of age. In that report, the authors noted that it was most cost effective again among high-risk persons than among the general population, but the authors also note in that report that even the highest cost, which was for the children less than three years of age, quote, "this is a very

low price to pay for a year of healthy life," end quote. Next slide.

The next study is a study that addressed the cost effectiveness of influenza vaccination based on the results of the clinical trial assessing the internasal influenza vaccine for the prevention of influenza in healthy children, and I apologize for the typo in that slide.

Presented as break-even cost per person vaccinated, meaning once licensed and available on the open market, if the live attenuated vaccine costs more both for the vaccine and administration than the break-even cost, then vaccination will generate net cost to society. However, if the cost of vaccine and administration are less than the break-even cost, then vaccination would be cost saving. As you can see, the break-even cost varied, depending on the type of vaccination setting that was being described, from a group-based program that would be expected to be highly efficient such as at a school site or at some other public walk-in clinic versus individual-based program where the parent would take time off from work to bring the child into the

health care provider for immunization. Next slide, please.

In this slide, I summarize the final two studies, the cost effectiveness of influenza vaccination in children six months to five years and five years to 17 years, conducted by the same group. And they found net costs or savings ranging from, for the younger children, $1.28 of savings in a restricted setting -- that is a setting requiring a visit to a physician's office -- to savings of $21.28 in a more flexible or highly efficient setting with somewhat similar findings for the older children. Next slide.

To summarize these studies, first of all, it's important to note that the studies differed substantially in the analytic methods and outcomes that they -- the analytic methods they used and the outcomes and costs that they included, and they differed in quality, as well. However, they generally do suggest that influenza vaccination of healthy young children may be cost saving if vaccination cost -- that is for vaccine and its administration -- are less than about $20 to $25, and this was the common theme that

we saw in reviewing these studies. At higher vaccination costs, however, cost effectiveness will clearly depend on the agreed-upon threshold for defining what is cost effective and worthwhile. In thinking back to the context slides, the cost effectiveness ratios that these studies present are comparable to some of the recent childhood vaccination vaccine recommendations made by ACIP, but the older childhood vaccinations are more clearly cost saving.

Next slide.

It is also worth noting that a substantial portion of the benefits due to vaccination in all these studies are due to the indirect costs prevented, largely due to parental work loss avoided. With healthier children, the parents miss less work. This is also the case for several other immunizations, including -- for varicella, for pneumococcal conjugate and was also the case in the analysis for rotavirus vaccine.

The illness burden with influenza is notably less than for healthy children versus high-risk children and again the overall benefits from vaccinating healthy children may be less than for vaccinating high-risk

children. Next slide, please.

There are several pending studies that will provide additional useful information. The CDC and Harvard are collaborating on a study to assess the economic implications of various strategies to reduce influenza morbidity in children and I understand that this study is just underway.

In addition, Martin Meltzer and others from the CDC are working on two economic analyses of, one, economics of routinely vaccinating healthy children less than five, based on the studies that have already been reviewed today, the Neuzil and Izurieta studies published in the New England Journal in 2000. Likewise, another study assessing the household-based costs and benefits of vaccinating day care children against influenza is also being completed by Martin Meltzer and others from the CDC. This study is based on the Horwitz study published in JAMA last year, also looking at the effectiveness of influenza vaccination of day care children in reducing influenza-related morbidity among household contacts.

And finally, there is a stochastic model of community

influenza and prevention that incorporates herd immunity into the model that is being conducted by Policy Analysis Incorporation in collaboration with Wyeth Lederle vaccine which will be looking at the clinical and economic benefits of vaccinating healthy children.

Well, finally then, there are outstanding issues and some knowledge gaps identified by our group, including, of course, understanding what the ACIP will consider to be an appropriate threshold for defining cost effective. In addition, the group noted that certain aspects of understanding the epidemiology of influenza, complication rates, health care use, impact on productivity for children and families is less than complete, particularly in some circumstances having an understanding over time and regional variations.

We've already heard a review of vaccine efficacy and side effects in children. The group was also very interested in understanding more about the incremental costs and benefits of immunizing all children versus high-risk, the implications of age-based versus risk-based, recommendations for achieving higher

rates in all groups versus the economic benefits of just high-risk versus all, the implication of vaccination versus testing and treatment strategies which will be addressed by the CDC/Harvard study, again, the costs and benefits of vaccination by setting and compliance level and the implications of herd immunity, and finally, how all of this might be considered in the context of feasibility and vaccine supply. Thank you.

DR. MODLIN: Kristin, this is John Modlin. Can you hear the Committee discussion -- Dr. Nichol?

DR. NICHOL: Yes.

DR. MODLIN: Okay. You can hear us so that you can participate, terrific. I assume that you would be staying on the line here for at least the rest of the discussion, hopefully. Bonnie?

DR. WORD: Actually, Natalie Smith is next.

DR. MODLIN: Okay, Natalie?

DR. SMITH: Let me apologize ahead of time. I seem to be having technical difficulties with my own voice. It's fading in and out, so I'll do my best. I want to thank the implementation work group for all their work in discussing these issues, and let me start

off with a summary of some of the implementation challenges that we discussed. Obviously, a big one is if we routinely recommend a vaccine, either -- we discussed the TIV and the live attenuated vaccine -- we will be adding one or two doses to the routine schedule, depending on the age of vaccination of a child. It's obviously a seasonal vaccine, which we don't have a lot of experience with in children in trying to administer vaccines over a couple-month time frame.

As far as I understand it, the licensure of application will say something and maybe the company or FDA could comment, but as of now there's no concurrent administration with other vaccines. So I think there's ongoing work that's going on this area, but that's another significant issue if you've got to -- if you can't give other vaccines the same day.

And of course, we need to continue to make sure that high-risk children are immunized. I think we're doing a not-so-great job in immunizing kids, for instance, with asthma already. So we wanted -- we would want to continue to have a focus on the kids that are actually

at highest risk. Next overhead.

Delivery issues, and as we know, as someone -- we run a fairly large public sector program in California with adult flu vaccine and there are ongoing discussions between the world of private providers and traditional mass flu clinics, either administered by the public health sector or by a private group such -- I think you all know grocery store chains, pharmacies, that sort of thing.

As far as the live attenuated vaccine, again, as I understand it, the licensure of application will say that it's for healthy children only and is likely not to be given to, for instance, children with asthma, and that's a whole other issue of how do we screen out youngest children and whether they have reactive airway disease or not, how do we make that distinction about which vaccine they might need, in the case that we have both vaccines.

And also again, with the licensure for the live attenuated, it looks like -- the application, again, states 12 months of age and older. So if we -- we would continue to need to give the trivalent to six to

12-month-olds and providers may, in fact, need to stock both vaccines, and that's a whole other issue. And storage and handling, including culturing issues.

Now, regarding manufacturing, the ability to -- the realistic ability to increase production and also on-time distribution. I don't need to tell you about all the struggles we've gone through in the last year about getting our vaccine on time and into people on time.

Reimbursement, I was going to talk about this more, but I understand Ben Schwartz is going to discuss this in more detail. As far as reimbursement, a lot of providers are obviously paid on capitated plans, for instance. So there needs to be adequate lead time to establish reimbursement rates in both the public and private sectors.

And the impact on the VFC and the 317 program, as you all know, the funds are already somewhat limited. And again, Ben can address this, but at least the last couple of new vaccines, there hasn't been a line item for states to implement the new vaccines, the operational part of it. We may get money for the

vaccines, but not for doing all the public education and outreach and delivery that needs to go along with actually getting these vaccines into kids' arms.

As far as communication, risk communication, education, a lot of people don't understand influenza epidemiology in children and, obviously, we need to make the case if we do recommend this for routine flu vaccination of children. It may often be perceived as a quite mild disease by both providers and the public. Effectiveness, it won't prevent all flu and it won't -- it's sort of similar to the rotavirus situation in that it didn't prevent all diarrhea. In this case, it won't prevent all the things that parents think are flu, like the croup, stomach flu, and all of that. So we'll have to -- education campaign would need to work on this issue.

And then adjusting perceptions of safety regarding both the trivalents and live attenuated virus, there are obviously different messages that may need to go out, depending on which vaccine is used. For instance, I know from talking to hundreds of reporters myself about the traditional killed vaccine, they're

always asking me can you get flu from the flu vaccine, and our spiel is usually that it's killed -- it's a killed vaccine, therefore it's impossible to get flu from this vaccine. So obviously, the issues would have -- and the messages would have to be tailored depending on which vaccine you're talking about.

As far as epidemiology, I think that needs to be improved and, obviously, we'll be doing efficacy and safety monitoring, but we'll also need to monitor immunization coverage levels and how we're doing in implementing this vaccine and how we're doing in implementing this vaccine in sub-populations, including those at highest risk of developing severe complications if they did get influenza.

And then the need to improve flu surveillance, I know Dixie -- I know there's a lot of money being talked about going into increase public health surveillance for bioterrorism, but I would, you know, also make the strong plea that we need some dollars to improve our flu surveillance nationwide, including at the local and state level. Next slide.

And then finally, Geoff Evans can comment on this more

in detail, but my understanding with the Vaccine Injury Compensation Program, if you routinely give a universal recommendation for children, that compensation program would need to cover possible adverse or adverse events in both children and adults. So that's a whole other issue that Geoff can comment on. Next slide.

We did have some nice data presented by Dr. Peter Szilagyi from the University of Rochester and I did not prepare a handout on this. They're still undergoing data analysis so it's still somewhat preliminary, but you can see his colleagues there. They've done a number of studies, including focus groups, with primary care providers. They've done two surveys of providers, including both pediatricians and family physicians; a time and motion study where they actually assess how long it takes to give shots and talk to the parents; and then a database study including insurance data from Rochester.

And let me just talk about his preliminary conclusions. Most -- he felt overall -- this is all the studies -- that most of the docs felt that universal flu

vaccination is feasible. The key barriers and issues are cost, vaccine safety, how to do reminder recall, and the impact on all the other vaccinations. Feasibility more difficult if it's only an injected flu vaccine if six to 12-month-olds are added, and as already alluded to, flu vaccine not licensed for administration with other vaccines.

And then they're looking at significant additional practice time costs for clerical and nursing time in the additional visits.

And then finally, their group felt that current practices for flu vaccination are inefficient and consumes substantial time and effort and they would recommend that vaccination-only hours be added. And universal flu vaccination will result in substantial additional visits unless all current visits are used as opportunities for vaccination.

We concluded our session of the subgroup by having very nice presentations by Eric France, giving the managed care perspective; Jon Abramson from the Academy of Pediatrics; and Rick Zimmerman from the Academy of Family Physicians. And they're all three here at the

table, so I'm not going to try to summarize their comments. They all did talk about the importance of looking at burden of the disease and evidence-based medicine, and they all emphasized how important it is that if we do recommend this we need to have a very solid education campaign directed to the providers and the public. And as I understand it, the Academy of Pediatrics committee will be meeting shortly to talk about this and Jon can elaborate on that. And as of September 11th, the Academy of Family Physicians had not yet discussed it in detail. So I think I'll stop there.

DR. MODLIN: Great, thanks, Natalie. Ben?

DR. SCHWARTZ: As Natalie pointed out, I'm going to be discussing the economic issues as they relate to the vaccination program.

When we talk about cost and economics, one of the areas to discuss clearly is the cost benefit or cost effectiveness of vaccination. But another area that's important to discuss is the economic implications on the vaccination program.

If you recall back when we made the recommendations for

pneumococcal conjugate vaccine, there were substantial discussions about the impact that this might have on the vaccination program and, subsequently, the NIP has updated the committee on the impacts of those costs and the two-tiered system that has been developed in some states where VFC-eligible children receive vaccinations, but those who are covered under the 317 Grant Program may not receive vaccinations. So that one of the things we wanted to consider in looking at making recommendations for influenza vaccination in children is the impact financially on the vaccination program.

In doing this, we got the information from Dean Mason's group in the immunizations services division and did several calculations which I'll share with you on this and the subsequent overhead.

There were several inputs and assumptions that were made in coming up with these economic figures. First we assumed that vaccination might be recommended universally for children between the ages of six and 35 months. We assumed the children would receive two doses in the first year and, subsequently, would only

require a single dose for vaccination. The influenza vaccine costs that were input are those in the current public sector program, which is about $4.25 per dose, and there are two manufacturers with slightly different costs, and this is an average.

We took data from influenza specifically that suggests -- or for the entire pediatric program, I'm sorry, which suggests that 45 percent of vaccine purchase is covered under the VFC program, about 11 percent under the 317 Grant Program, and states provide funding for an additional six percent of vaccine purchase.

We looked at several different vaccine coverage scenarios, looking both at what the impacts might be as the program was initiated and the first couple of years of the program, and then also looking at what the cost might be in a steady state after several years.

And finally, the costs that I'm going to present are only vaccine costs and do not include cost for vaccine administration under the VFC program which varies state to state and may be on a range of between $4 to $6 and greater than $10 to $15, and there are no infrastructure costs included for the state health

departments where additional administration of vaccine in public settings may require hiring additional personnel and additional infrastructure costs.

The scenarios that I'd like to present are something that I call the first program year, where we estimate that the vaccination coverage might be about 20 percent, and that the vaccine that would be used is the inactivated vaccine. And the 20 percent estimate for coverage in the first year may be a little bit optimistic if we compare what was achieved for rotavirus vaccine and for varicella vaccine. Neither of them reached the 20 percent level in a single year.

The second program year we also assumed that the coverage would be 20 percent, but that fewer children would need two doses because they would have gotten those two doses in that first program year and would be getting vaccinated for the second time and therefore only require a single dose.

As a steady state scenario, we assumed 80 percent coverage with inactivated vaccine; and in an alternative scenario, still 80 percent coverage with

half of that being the live attenuated vaccine and the other half being inactivated vaccine. And arbitrarily, I assumed that the live attenuated vaccine would cost $15 per dose. This is not based on any knowledge from the manufacturer, nor is it a suggestion to the manufacturer of what costs might be acceptable.

Currently, influenza vaccine coverage among young children is relatively low. We estimate that about ten percent of the U.S. population falls into one of the high-risk groups, and that the vaccine coverage level in that population may be about ten percent, yielding one percent overall coverage in the U.S. population. The total costs of this given the model may be about $390,000 for about 90,000 vaccine doses. Shown in the table below are the costs that would accrue to the VFC program, the 317 Grant Program, the state funding from the various scenarios, and also the total number of vaccine doses that would be used in each of those scenarios.

With a 20 percent vaccine coverage rate in the first program year where all of the children six to 35 months

of age would require two vaccine doses, the overall cost would be about $10 million, the bulk of that being borne under the VFC program, 317 costs of about $1.7 million, and a little over two and a half million doses of vaccine would be required.

In the second year, because many children would have received two doses in the first year and therefore only require a single dose, costs and vaccine utilization would both likely decrease, although that may be offset by increasing coverage that would occur.

Under a steady state scenario, using only the inactivated vaccine, VFC costs would total about $25 million, $4.9 million to the 317 program, $2.4 million to states and about seven million doses of vaccine used altogether. And if we assume that that would represent a mix of the live attenuated and the current inactivated vaccine, the cost would be about double of that, although the total number of doses would remain the same.

I think the bottom line here is that under any of the various scenarios, even either shortly after implementation or even in a steady state situation, the

costs are much more reasonable than we've encountered with other recently-recommended vaccines. And it's likely that there would be sufficient time, as the program was ramped up over several years, to increase funding, to increase infrastructure in order to support this program.

DR. MODLIN: Bonnie?

DR. WORD: Actually, I won't get up because we do have two more presentations. Prior to the presentation of options, one of the things that I forgot to mention was Dr. Karen Midthun was kind enough to give us a summary of the VRBPAC meeting, because the outcome of that meeting clearly had a direct impact on the options working group committee. So Dr. Midthun.

DR. MIDTHUN: Hello. I was just going to give a very brief overview of the biologic license application as it was presented to the Vaccines Advisory Committee this past July.

At the July Advisory Committee, we presented safety and efficacy data in support of the biologic license application for the live attenuated virus vaccine developed by Aviron and the indication sought by Aviron

in their submission of their BLA was prevention of influenza in persons one to 64 years of age and travelers to areas where influenza is circulating. Major questions presented to the Vaccines Advisory Committee for their consideration were: Are the data adequate to support the efficacy in persons one to 17 years of age? The committee was almost evenly split with regard to whether they thought this was the case or not. And of note, the majority who voted no indicated that they would have voted yes if lowest age for the indication were raised either to 15, 18, or 24 months of age.

Another question considered was: Are the data adequate to support efficacy in adults 18 to 64 years of age? Thirteen members of the Advisory Committee voted yes, two voted no.

The next question was: Are the data adequate to support safety in persons one to 64 years of age? During this discussion, Aviron clarified that they were seeking an indication in healthy persons, they were not seeking an indication for high-risk populations at this time. And with this additional

information, the majority of the committee voted no, that the data were not adequate, but they also indicated that this was based on the fact that additional safety data analyses were still outstanding and they looked forward to these additional analyses and information. With regard to time lines, as Aviron has publicly acknowledged, the FDA completed its review of the biologics license application and issued a complete response letter at the end of August. A typical time line for biologic license applications is as follows. Upon receipt of the sponsor's reply to our complete response letter, FDA has up to six months in which to complete the review of that new material. Upon completion of the review, FDA will take an action, and this can either be, for example, issuing an approval letter or issuing another complete response letter if there are still additional items that need to be worked out.

Thank you. Are there any questions?

DR. WORD: I guess the last presentation that we have is the options that the Committee finally --

DR. MODLIN: And Keiji is going to present those?

DR. WORD: Keiji is going to present those, yeah.

DR. FUKUDA: As you can tell, there's been a lot of discussion and a lot of data presented, and in a sense, the working group has been working on this since about sometime in 1997 when the working group was formulated. And so the basic question is whether -- the basic question is: Should ACIP recommend routine influenza vaccination of children? That's the question that we've been wrestling with.

And both Rick Zimmerman and Jon Abramson sort of framed it very nicely that there's a couple of bottom line issues.

Basically, the first issue is whether influenza is a serious health risk for children. The second issue is whether influenza vaccine is effective in children. The third issue is are there any important influenza vaccine safety concerns related to children. And then the fourth issue revolves around a series of different considerations but, basically, can a recommendation be practically implemented. In other words, would it be acceptable both to parents and physicians, can it be feasibly carried out, is it an economically sound move,

and are there programmatic concerns.

Some of the time line considerations for the Committee to think about are this. Currently we're in the October, 2001 meeting and you've been hearing summary presentations and there will be some discussions. The next ACIP meeting is in February of 2002. This is when we typically have our extended influenza session and this is when the Committee takes a vote on the vaccine recommendations for the coming season. And then based on what Dr. Midthun has told us and what happened at the VRBPAC meeting, it's clear that the fall and winter of 2002 is the earliest possible time when we would have a licensed live attenuated influenza vaccine available. It could be later than that.

So I think at this time there are two main issues for the Committee to think about. The first one is when should -- when does ACIP want to vote whether to recommend routine influenza vaccination of children, and really the options -- and I'll go through this in a little bit more detail -- are to do this at the next coming meeting, in February, or to do it at a later time. And I think the second sort of implicit idea in when

you take a vote is when you would want to see those recommendations take effect.

And then when you take the formal vote, the real issue that you're going to be grappling with is what should be the upper age range for routine influenza vaccination of healthy children. And the realistic options that you're going to be looking on are going to be six months to two years, six months to three years, or six months to another older age limit.

So let me just go through some of the considerations in the timing of the vote. One option is to take a vote in February of 2002, with the idea of having the recommendations implemented for the fall of 2002. The pros is that if this were done, this would begin to provide protection as early as possible to children. The second pro is that since a live attenuated vaccine would not be licensed at that time, you would be able to deliberate the issues related to children separate from the issues related to live attenuated vaccine. In other words, focus on whether you want to recommend vaccination of healthy children.

A third pro would be that the recommendations could be

published in the annual ACIP influenza prevention and control document. This is the document which basically summarizes the epidemiology of influenza and the vaccine recommendations.

And then the fourth benefit is that it would provide some moderate lead time for implementing educational efforts. I'm not really sure whether it would allow the companies to try to ramp up their vaccine production, and if this is possible, it would probably be a very limited ramping up.

Now, in contrast, there's some cons. The Committee -- You've been hearing presentations over the last year or two, but the Committee may feel that it is still not adequately prepared to vote on the issue.

Probably another, perhaps more important concern, is that the pediatric community out there may not be sufficiently prepared to accept a new vaccine recommendation.

As has been pointed out, the availability of vaccine for the coming season is never certain, and it won't be certain for the next year.

And then, finally, the February session is already

usually fairly long and complicated. Tacking this on would make it a longer and more complicated session. So the next timing option would be to take a vote in June or October of 2002. This would provide you with a little bit more time to deliberate the issues. It would allow a dedicated session to be held, focusing simply on pediatric influenza vaccine issues, and at that time a licensed live attenuated vaccine may possibly be available. And if so, that would provide another option for vaccinating children. And probably the publicity of that licensure would help to focus attention on children.

There are some cons to taking a vote later in June or October. One is that you would definitely have reduced time for educating the public and developing the educational materials. There would basically be no lead time to try to ramp up vaccine production. The recommendations would have to be published separately in a supplemental document. This creates a fair amount of work preparing the document, but also it would take the recommendations out of the main document and they're generally less-read when it's done that way.

And then, finally, if a live attenuated vaccine has been licensed, then ACIP will probably be trying to grapple with both the pediatric issues in live attenuated influenza vaccine issues and this will prove -- may prove confusing both for the Committee, and then for the public if additional recommendations go out simultaneously.

You could take a vote later, with the idea of not implementing anything for 2002, but implementing something in 2003 or later. If you do that, more relevant information might be available, particularly some of the economic studies, some of the feasibility studies and so on. This would provide you with some more time to deliberate issues. It would definitely provide more time to educate the pediatric community as to why this recommendation would be coming out. And then, depending on the timing of the vote, it might provide more lead time for manufacturers to prepare more influenza vaccine.

The cons for taking a later vote is that the longer that you go without grappling with this issue, more high-risk children -- or more children at high risk for

complications will go unvaccinated. And then depending on the timing, again, you'll be facing the potential confusion of dealing with both pediatric and live attenuated vaccine issues at the same time. Now, that's simply the timing issue. I think the -- when you finally take the vote, again -- really, I think these are the main issues that it's going to boil down to.

The first option is going to be whether you want to recommend vaccination -- influenza vaccination of children who are six months to two years of age. The major pros for this -- and when we come to that point, we'll list more detailed pros and cons, but I think the major pros would be that this would be a fairly conservative recommendation, supported by the recent hospitalization data in children. Since it would be a small age range, it gives you the option of expanding upwards. And in terms of feasibility issues, it would have the least impact on pediatric practices.

I think the major con for this is that because it is a conservative recommendation, again, it might leave many high-risk children unvaccinated.

If you consider moving the age limit up to three years, I think the major pro is that this would provide protection for more healthy children who would be at risk for influenza-related hospitalizations. The cons, the major cons would be that the risk of flu-related hospitalizations in that group, based on the available data, is both smaller and a little bit less clear. As it tails down, it's not really clear where we sort of move out of the clearly at high risk category. And then as we increase the age limit upwards, it does increase the logistical and feasibility issues. And here I'm particularly thinking about pediatrician offices.

And then there is the possibility of recommending flu vaccine for kids six months to some older age group, might be four, might be five, might be older. And again, here I think that the major pros would be that this kind of move might increase vaccination of children with chronic medical conditions. This would be in keeping with the line of thinking for recommending vaccine for people 50 to 64 years of age. And if, in fact, there is some herd immunity that can be attained,

then there is possible dampening of community epidemics, again depending on how many children are vaccinated and how high the coverage rates are.

The cons against going up to a higher age limit is that the higher risk of flu-related hospitalizations has not been shown. And in fact, the available studies would suggest that those older kids are not at higher risk for serious complications such as hospitalization. And again, the higher you go up in terms of age limits, it just increases the feasibility issues, again, particularly for pediatricians.

So, in summary, I think the two main things -- and probably this first thing is the main thing that you want to just give us some sense of is when you're going to want to take a vote. And again, the options are going to be to take it at the next meeting in February or to do it later in the summer if you want these recommendations implemented for the fall of 2002.

And then when we have that discussion and we take that vote, the likely main options are going to be to do nothing or to recommend vaccinating children six

months to two years, three years, or some older age. I'll stop there.

DR. MODLIN: Keiji, thank you. Is that it, Bonnie? A lot of information. Unfortunately, we don't have nearly enough time on the agenda to have the discussion that we had hoped to, and we actually did have to shorten the discussion time because of other pressing issues on the agenda, but we do have about 20 minutes. So let's open it up. And if we can, begin to focus on the issues that Keiji has raised, but I think we also have an opportunity to ask some questions of each of the presenters. We'll start with Lucy.

DR. TOMPKINS: Tompkins. Just one quick question for Dixie and John, in view of what Keiji had said about probably the need for a dedicated session on this, what are -- what's on the table right now for February of 2002?

DR. MODLIN: We take this at sort of a meeting-to-meeting and month-by-month basis. We had thought we were going to have a light agenda this time, and it obviously didn't work out that way. So it's -- it's unpredictable, Lucy. We certainly will try to

provide as much time on the agenda as we hope will be needed, but it's not always possible.

DR. TOMPKINS: But possibly it may not be feasible, right?

DR. MODLIN: I wish we could be --

DR. TOMPKINS: For the kind of discussion that we probably should have.

DR. MODLIN: Right. Peggy?

DR. RENNELS: Peggy Rennels. When will the feasibility study data be available to us?

DR. FUKUDA: Ben, I don't know. You're probably the closest person to that. You might want to address when you think Peter Szilagyi and -- will finish with the analysis.

DR. SCHWARTZ: The analysis of the feasibility study is just about finalized. There are manuscripts on different portions of that study, and we can probably get the information out to the Committee within the next month or so.

DR. MODLIN: Jon, this is something that obviously you would want to coordinate with the Academy and with the AFP. Do you guys want to chime in?

DR. ABRAMSON: Yeah, we've set -- We're meeting this weekend in San Francisco at the Academy meeting, and we've set aside two hours. So it's a major chunk of time we've set aside to try to come to just the issues that Keiji brought up. I think all of us feel that these children, whether you use a cutoff of two or three, that they are high-risk and, therefore, we need to deal with that issue, and how, when, are all the issues that Keiji has brought up. But I think we will try to come to a decision at the meeting this weekend, and then we will certainly share that decision with the ACIP.

DR. MODLIN: Terrific. Rick or Dr. Mahoney?

DR. ZIMMERMAN: I think there -- the four questions that we'll be looking at, is it important? And I think clearly this is an important issue in terms of the burden of disease. The second question is the vaccine -- are the vaccines effective? I think that's also pretty well met. For the youngest children, I think there is limited safety data and I think there are a number of implementation issue. So our -- the implementation, we would like to see a little bit more,

particularly published, safety data, even for the trivalent.

My personal opinion or suggestion is that we consider something along the lines of the polio, and this is not one of Keiji's options. It's yet -- I guess option C. My suggestion would be to consider it, again, like polio. Our move is towards vaccination of pre-school age children and that be a goal that I think would be brought up at the February meeting. But the exact -- when does the recommendation fall to routinely recommend, I'm not sure that there will be the sufficient -- all the issues from implementation to safety to availability, et cetera, answered, certainly in February and maybe not for the fall of 2002.

And so my suggestion is to consider a potential step-wise approach where we begin to consider increased vaccination, perhaps in 2002, with a goal over several -- over perhaps a three-year time period, of moving to routine vaccination. Again, point the direction, as we did with polio, and take it in steps based on availability and working out the feasibility and publication of safety data.

DR. MODLIN: Okay. I would point out, as Keiji has already told us, we've been considering this since 1997, so I just want to point that out.

Paul, and then Dr. Neuzil. Yes?

DR. OFFIT: I guess this is a question for Kathy Neuzil and maybe Karen Midthun. Are there data -- it sounds like the answer is no, but are there data on the relative capacity of inactivated or live attenuated virus to protect the young child, i.e., the less than two-year-old. And if not, when are those data anticipated?

DR. MIDTHUN: I think that -- is this on? I think that, you know, Kathy Neuzil did a nice job of evaluating or sort of going over, you know, the data that are there. I mean, all of the trivalent influenza vaccines that are licensed in the U.S. -- not all of them, but both Wyeth and Aventis Pasteur's vaccines are licensed to six months of age, and so they have the indication for use for prevention of influenza. Evans' vaccine is licensed now at the age of four years, but I think that some of the points that were brought up are well-taken. I think these

vaccines were licensed with that broad indication but, nonetheless, have been targeted toward, you know, high-risk individuals and I think the point that if one is to use them routinely that one would want additional data. For example, looking at concurrent administration with other vaccines is, you know, one that -- you know, that's not the kind of data that's currently available.

DR. OFFIT: My question is relative. I mean, is there you could make the -- at least the immunological case that a lot of attenuated vaccine is a prime to a young child, it would be better than a parental vaccine. That's sort of priming the mucosal immune system. So I'm just trying to -- are there data --

DR. MIDTHUN: No.

DR. OFFIT: -- that compares the two in any sort of head to head way, and would -- are those data anticipated? Because if we've come to making a decision, it would be interesting to know whether or not, for the young child, one vaccine is better than another.

DR. MIDTHUN: Do you want to -- I'm not -- Right now we obviously don't have those data in hand, you know,

where those kinds of things can be compared. I think perhaps in the literature there are some studies where people have looked at using the inactivated or the trivalent in studies concurrently and I just -- I just can't remember right now whether Cathy Edwards or someone else may have done some of those studies.

DR. MODLIN: Kathy?

DR. NEUZIL: We reviewed those originally for the working group as part of the safety and efficacy working group. We didn't present it today because of time and because of what happened this summer with the licensure. The issues, though, are there any studies or are there any ongoing studies that compare the current live attenuated vaccine for which they're seeking license to an activated. That answer is no. There are these prior studies, including Edwards, Glover, Gruber, with an earlier version of the cold-adapted vaccine which is not necessarily comparable to the current version, which compared these. And immunogenicity does look better in those studies in the younger groups with the live attenuated and in the older groups with the inactivated. But

that's with the caveat that these vaccines have changed, and they're small numbers. So the answer to your question is no.

DR. MODLIN: Sam?

DR. KATZ: I'd just like to put in a plea for the child. In 1985 we had DTP, OPV, and MMR. In 2002 we have now added, and I have to write them down to remember them - these are injectables -- inactivated polio, hepatitis B, hemophilus influenza B, varicella-zoster, pneumococcal conjugate. I would propose that to consider another injectable vaccine would be inappropriate and that we should hold until you have a live attenuated vaccine. (A), the advantages of mucosal vaccine, but (B), the pincushion effect is one which parents, nurses, physicians, and infants are very, very concerned about.

DR. MODLIN: Bonnie?

DR. WORD: Just a comment to add to what Dr. Katz said. I can appreciate what you're saying about the injections. However, even the vaccine that was reviewed, they only were going for indication down to one year of age, so there's still going to be a certain

group of children who will need to receive the injectable. And looking at -- go through the vote, most of them -- most people would not have approved -- well, they -- if they said they would have approved it if -- for safety if they had not gone for an indication in younger children. So I'm not sure. I'm not sure what the company is going to do, if they're going to pursue that same indication and do different studies so we still may be waiting.

I think one of the things, too, that the working group wanted to just try to separate out the need for influenza and not tie it in necessarily with the availability of the live attenuated.

DR. MODLIN: Sam, does the fact that we're not talking about two-month-old infants or six-month-old infants make any difference in your opinion?

DR. KATZ: Well, I think that Karen pointed out that the application was for one year and above. And sitting on VRBPAC, I don't think I'm giving away confidential information. There were a number of questions asked. One was: What if you give it at the same time as MMR, do you have data on that? What if

you give it when you give varicella-zoster, do you have data? None of those data were available, but they did say that studies are underway so that I would hope that by the time vaccine was licensed, you would have some studies as to how this would be effective and whether there was any interference, any augmentation of reactivity, anything of that sort. But they did not present any data under a year of age.

DR. MODLIN: Myron?

DR. LEVIN: Yeah, could I ask Kathy a question? You presented data on the inactivated vaccine entirely, and you also said that the older children responded better than younger children. I couldn't tease out from what you presented whether or not we know that six- to 12-months-old kids, for example, respond adequately as children a little older than that age, because most of it's group data -- up to two, up to five, whatever, one to three. And the numbers --

DR. NEUZIL: That's --

DR. LEVIN: -- were small. So it may be hard.

DR. NEUZIL: -- right. That's a good question. If you look at the data that -- the Clover data and the

Gruber data started at age three. The Edwards data started at age one. And that's why I think this Greenberg data that is unpublished will be very important because that had 250 doses to six to 12 months old, which are data that we don't have post-1981.

DR. MODLIN: Good point.

DR. NEUZIL: Could I --

DR. MODLIN: Jon?

DR. NEUZIL: Oh -- Could I make a comment?

DR. MODLIN: Sure.

DR. NEUZIL: I keep using my turn answering questions. I would just like to make the same plea that I think Rick Zimmerman made, which I think there is a lot of area between a no-recommendation and a universal recommendation. And I think we should put options on the table that consider more lenient recommendations, in that I think there are perception issues. We talk about rotaviruses. There are barriers to a parent who wants to have a child immunized. You know, as a parent of a very young child, I meet barriers when I take my one-year-old and somebody says we don't give vaccine to children this age; or as an internist, when I ask

the children who are contacts of my high-risk patients to get vaccine. So I think there are other options and other ways that we can encourage more choice in this matter than currently exists.

DR. MODLIN: Georges?

DR. PETER: I think one of the other elements that also should be considered is the possible impact of a universal immunization of young children upon the community occurrence of influenza. The experience in Japan has been published in the New England Journal of Medicine. The experience from Tecumseh, Michigan, years ago suggested that it would. And I believe that the studies of progress in Texas under Paul Glezen that is examining this issue with the live attenuated influenza vaccine, because indeed if that were to demonstrate benefit in term -- then indeed that would be a very strong argument that I think -- for a universal recommendation. So I would hope that those issues could be examined at our -- next time you consider this, in further detail.

DR. MODLIN: Jon?

DR. ABRAMSON: Yeah, I'm going to give a personal, so

I'm not at the moment talking for the Academy, because I don't know what we're going to do. But let me again -- I think we lose sight of the fact that the ACIP has recommended for 50- to 64-year-olds a vaccine, with a risk group at that age that is not as high a risk for hospitalization as the young children are. These children are high-risk. Now, how long are we going to allow that to occur when we recommend the vaccine for high-risk children? That's number one.

The second point I'll make is, out in the community, what is happening? Thirty percent attack rates. So children are coming in and being vaccinated all the time around the time when they may get flu. They may get vaccinated, a day later get flu. They may have been vaccinated two days after having flu. So those kinds of things are going on all the time in the community.

DR. MODLIN: Yes, Gary?

DR. OVERTURF: One other implication, the reason why I would like to see a staged introduction of a recommendation is because, particularly in an era when we don't know what -- whether we can ramp up supply, if you make a recommendation for routine immunization,

it also leads to other things, like mandates for use for attendance at day care centers. And if you don't have adequate supplies of vaccine, you may have children then who are excluded from day care centers because they can't get vaccine. So that puts another burden on the implementation. It's another community phenomenon.

But I think -- I think Jon is right. I think we have more than enough data to define this as high risk. We have more than enough data to suggest that these children need protection.

DR. MODLIN: Speaking of the data and high risk, Kathy, could I ask you, in your studies -- or maybe if anyone knows if Hector Izurieta's studies -- my recollection was is that there was not a -- that deaths were not a major part of the outcome, it was just hospitalization in the pediatric age group, unlike the over-65 age group where we had similar morbidity in terms of hospitalization. Is that right, mortality was not a major issue?

DR. NEUZIL: That's correct. We actually looked at mortality. But even with very many children, I can't

remember -- the overall number was two million child years and I cannot remember the exact number that were high-risk. But we didn't have the power to detect excess mortality.

DR. MODLIN: And I guess the other -- Kristin Nichol, are you still on the line?

DR. NICHOL: I am.

DR. MODLIN: Great. One other question I had was whether any of the economic analyses that you have reviewed actually took into account the possible effect of reduction of disease in the family -- in the family setting, similar to Georges' question earlier. In other words, if you immunized six-month-old or one-month-old children -- or one-year-old children, everybody has recognized there's potential for reduction of disease in the family and in the community and the degree to which that potential reduction may occur. Was that taken into account in any of the economic analyses that you reviewed?

DR. NICHOL: That was somewhat taken into account in three of the studies, the Luce study, and the Cohen, and White studies where they looked primarily at

parents becoming ill and secondary illness and work loss. I would say -- and others from our group are also present with you -- it was probably imperfectly modeled in the studies, but three of the studies did include some of the secondary illness parameters.

DR. MODLIN: Thank you. Let me get a sense of the voting members of the Committee now, what -- how you would like to proceed. Maybe we could go around the room the other way. Myron?

DR. LEVIN: Well, clearly, we have to do it at a subsequent meeting. I guess one of the issues in my mind is the question I asked Kathy, which is how much data do we really have that would set the lower bound of it? And my sense is that we can't decide in February. It would have to be later.

DR. MODLIN: Okay. Jaime?

DR. DESEDA: My concern is mostly adding another shot to -- you know, an already busy schedule, but I think that -- at least for me -- it would be too early to make a decision.

DR. MODLIN: Okay. Lucy?

DR. TOMPKINS: Agree it should be a staged

discussion and certainly can't make a recommendation in February.

DR. MODLIN: Okay. Natalie?

DR. SMITH: Yeah, I feel the same thing, and I'm concerned about what kind of lead time the manufacturers need, as well, to ramp up production.

DR. MODLIN: Dennis?

DR. BROOKS: I agree it should be a staged discussion and I must admit I'm for the mode of transport of the live attenuated than inactivated.

DR. MODLIN: Rick?

DR. CLOVER: I agree, a staged discussion, and I'm not ready for consideration of a universal recommendation in February.

DR. MODLIN: Okay. Bonnie? I should have called on you first.

DR. WORD: I guess I've heard this a lot, so I probably am ready for a discussion because I've heard a lot of the information. However, you know, I think if you don't do it in February, I think, as you said, then you have to -- I think if you going to set it, then we're doing it in June, but I think you have to finally just

you have to set a deadline.

DR. MODLIN: Paul?

DR. OFFIT: Yeah. My sense is I don't think we should plan to wait for licensure of the live attenuated influenza vaccine to make this decision because there's no anticipating licensure from the FDA, as we all know.

The second thing is, I think -- so I would be in favor of having this discussion in February about the use of the -- you know, the trivalent inactivated vaccine, and if we think there aren't enough data, then I just think we need to sort of go through that in detail and have that discussion. But I would hope that we could try and have that discussion in February.

DR. MODLIN: Would you want -- assuming that we have the discussion, would you be prepared to take a vote on the recommendation? I mean --

DR. OFFIT: Assuming the data are adequate to answer our questions, yeah.

DR. MODLIN: Okay. Peggy?

DR. RENNELS: I pretty much agree with Paul. For me, the implementation issues are very important and

we haven't heard the results of the feasibility studies. So I think we need to continue the discussion in February, and whether or not I would be ready to vote depends on what we hear.

DR. MODLIN: Okay. So we've got a split -- I don't sense a strong consensus of whether or not we should take this up in February. I suppose that probably -- Keiji, would you like a specific decision now? It sounds to me like it's clearly what you would prefer.

DR. FUKUDA: I think if we have an idea when you want to take it up, we can prepare for it a little bit better. I mean, I think that, depending on what the time frame is, we'll go about trying to pull things together a little bit differently.

DR. MODLIN: It doesn't sound to me like we have a consensus that the Committee is -- wants to take any hold action on this. Do --

DR. SMITH: I guess, to clarify it, I would certainly like to discuss it in February. I think that's important because I think we are going to get more data, especially the feasibility study.

DR. MODLIN: Okay. If there are more data, would you

be prepared to make a decision in February? Natalie?

DR. SMITH: Yeah, if there's adequate data.

DR. MODLIN: Myron?

DR. LEVIN: The word that you heard, about -- from a number of people, was staged. And I think it implies that if the information were adequate, many people would -- would make -- would be willing to make a decision. I would. But I'm doubting that we will have it all in, myself.

DR. SNIDER: I was going to say, John, I think that what I heard was a lot of interest in discussing this topic in February. What wasn't clear was what kind of decisions people would be willing to entertain, whether that would be a recommendation to expand usage of -- and encourage usage in certain populations to get started, so to speak, on attacking this problem, versus making a much -- something much closer to a universal recommendation.

DR. MODLIN: Well, it sounds to me like we do need to put it on the February agenda. We will -- We will pose the questions to the Committee, depending on our assessment -- or the working group's assessment of the

nature of the data that are available at the time. And I think we'll just have to leave it fluid like that. Is that reasonable, Bonnie?

DR. WORD: Yes.

DR. MODLIN: Okay. Keiji?

DR. FUKUDA: Yeah. John --

DR. MODLIN: Can you live with that?

DR. FUKUDA: That would be fine. Just -- Can I make just two points?

DR. MODLIN: Sure.

DR. FUKUDA: One -- Well, actually, one is just information for the flu working group. They were not able to set us up for the lunchroom so they've given us something called the board room, but go and get your lunch before we meet and have our lunchtime meeting. So we'll be meeting in the board room.

DR. MODLIN: Okay. We have one more item on the agenda before lunch, and that's a update on the current influenza vaccine supply. Pardon? Mr. O'Mara?

DR. FUKUDA: Actually, John, can I -- one other --

DR. MODLIN: Sure.

DR. FUKUDA: -- issue while Dennis is setting up.

Georges brought up the issue of herd immunity. The reason why that hasn't been brought up is that the data on those studies is vaccinating kids who are much older. So we would be talking about whether we want to be vaccinating kids who are in school and high school and so on, and this really brings the discussion up to 18-year-olds and so on. That's a whole different argument, and so we've largely focused on high-risk kids, you know, for complications. And so if you want to open that up, we can bring that into the mix, but it really -- there probably is much less data and it is a completely different discussion.

DR. MODLIN: Thank you. Thanks very much. Mr. O'Mara, we have -- we're entering our lunch hour, so I just remind you of that. We do appreciate your coming.

MR. O'MARA: Good afternoon. I'm going to provide you with a very brief update on influenza vaccine production and distribution in the United States this year, using data that are provided by the three influenza vaccine manufacturers that are participating in the U.S. market this year -- Aventis

Pasteur, Wyeth Lederle, and Evans vaccines.

I showed you these first two slides at the last meeting. Just to put things in perspective, this represents cumulative influenza vaccine doses distributed by month. The gold line is net distribution in 1999, the light blue line in 2000, and the dark blue line is the projected number of doses that the companies believe would be distributed this year. And these data were as of June 15th. Note that at that time the companies were anticipating producing up to almost 84 million doses and that about 53.5 million of those doses were anticipated to be distributed by the end of October. Here are the same data on a cumulative percentage basis. Note that about 64 percent of the total projected supply for this year was anticipated to be out on the street by the end of October. But we did caution at that time that these numbers could and probably would change, and indeed they have.

Here are the same two slides with updated numbers from October the 1st, and as you can see, the numbers of doses projected to be produced has declined somewhat by about four million doses. And the numbers that we

anticipated would be distributed by the end of October have also declined, down to 44.6 million doses, approximately. And on a percentage basis, that means only about 56 percent of the total projected vaccine supply this year will be distributed by the end of October.

In June we suggested that we were going to see a delay in distribution of vaccine, less severe and less lengthy, we believed, than we experienced last year. But now you can see that that delay is even more enhanced, according to these data.

And here are comparisons of the most recent projections, in the dark blue bars, against actual distribution for the first two months of the season. And as you can see, the distribution so far is slightly ahead of the most recent projections. But that gives us little cause for comfort at this point.

And on a percentage basis, then, approximately 28 percent of the projected influenza vaccine supply for 2001 was distributed by the end of September.

So with that, let me stop and see if there are any questions.

DR. MODLIN: Any questions for Mr. O'Mara?

(NO RESPONSE)

DR. MODLIN: Thank you very much. We sure do appreciate this update.

Karen, just one last thing, do you want to say anything about the Evans thimerosal vaccine?

DR. MIDTHUN: Yeah, I'd like to mention two things. We, at the end of September, approved a supplement to Evans' license application for their influenza virus vaccine. It is --

DR. MODLIN: That's Kristin signing off.

DR. MIDTHUN: It's a supplement that licenses a new formulation of their vaccine, which is a thimerosal-reduced formulation. It contains less than one microgram of mercury per dose of vaccine and, you know, compared with the 25 micrograms of mercury in the earlier formulation of their vaccine, and this vaccine is licensed down to four years of age. And Evans has indicated that they anticipate making roughly half a million doses of this thimerosal-reduced formulation available this year to the U.S. market.

The other thing I wanted to mention was that yesterday we approved Wyeth's supplement to their influenza vaccine. So we've been able to release a number of trivalent influenza bulks from Wyeth, and perhaps Dr. Reilly would like to mention something about that from Wyeth?

DR. MODLIN: Dr. Reilly?

DR. REILLY: We thank you for the releases, first of all. Wyeth expects to start shipping their influenza vaccine late -- in late October at this stage, and with large shipments in November and the early part of December. So we are on track at this stage for the quantity that we've estimated for the fall season.

DR. MODLIN: Dr. Reilly, thank you. We'll reconvene at 1:30.

(LUNCH RECESS FROM 12:41 P.M. TO 1:42 P.M.)

DR. MODLIN: Could I ask everybody to take their seat so we can get started, please? Could I please ask people to take their seats? We have a quorum of the Committee so we will go ahead and get started.

The next item on our agenda will be what I hope will be a final review of the hepatitis B statement that has

been in gestation for a period of time, and I'm hoping that we can complete work on that. All of the members of the -- voting members of the Committee and others should have received a copy of the latest draft. Hal, I don't know what it is that you specifically wish to go over. Are there are specific items that you want to cover?

DR. MARGOLIS: I want to go over their recommendations -

DR. MODLIN: Okay.

DR. MARGOLIS: -- since that's -- that's the most --

DR. MODLIN: Okay.

DR. MARGOLIS: And there's one --

DR. MODLIN: I know it's cold in here, but Gloria and the others are doing everything we can to fix the situation quickly.

DR. MARGOLIS: What I thought I'd do is actually go through the recommendations. Now, sitting at everybody's place, at least on the Committee and for the liaisons, are a -- an evidence table, which I promised of some sorts we would put some of -- something out there and then have time for discussion. I'd like

to leave that for the -- for the end, if that's all right with the Chair.

I think the -- And the discussion began the last time and I know there's -- this will probably generate the most discussion in terms of the issue of the birth dose of hepatitis B vaccine, and there is change in wording here to reflect a stronger recommendation. And I guess that -- I'll just leave it at that and let the Committee start, or if there are any -- if there's any discussion with it. I think this was -- These are the -- This is exactly what's in your -- you know, in the last handout, so it was -- It is recommended that the first dose of vaccine be administered soon after birth and before the infant is discharged from the hospital, but no later than two months of age. And then explanatory information about that, in fact, you can use combination vaccine with a monovalent birth dose of hepatitis B vaccine.

DR. MODLIN: Myron? There's nobody back there.

DR. LEVIN: I'll speak up. It just struck -- I agree with what you've written. It just struck me that if your intent or our intent is to encourage people to

vaccinate at birth that might -- this case might be made a little stronger than it is in the previous text. It gives a reason or two for it, but it doesn't really spell it out as strongly as I think you could. I mean, I know you don't want to re-write it again, but that's the way it struck me, that if -- we should make the case stronger for it up front, and then you make the recommendation here.

DR. MARGOLIS: All right.

DR. MODLIN: Rick?

DR. ZIMMERMAN: I guess my concern is that this is -- With the coming -- With one combination vaccine on the market and another coming, this essentially is going to establish a four-dose system. And I don't know what experience we have -- There's obviously then a cost associated, but it's going to make a four-dose system fairly routine, and that certainly is not, I guess, what we had planned in the past.

DR. SMITH: Yeah, I agree. I have the same concerns. I certainly understand from a population-based approach that we should -- about recommending the birth dose, but especially as -- if we get another combination

vaccine, there are a fair number of providers that at least we -- I've talked to in California that feel strongly that they want to wait and use the combination vaccines and not give that birth dose. So I think there you're letting them -- You know, they still have that option to do that if they feel strongly. But -- And it is an issue if they're going to -- there's going to be a lot of four-dose -- you know, that fourth dose being given.

DR. MODLIN: Jon.

DR. ABRAMSON: Yeah, again, we'll be discussing this this weekend, but I basically am in agreement with you that the arguments for doing it outweigh the arguments for not. You laid them out in the pros for doing it versus the cons, and the arguments from the pros are disease prevention, potential lives saved. The arguments for the cons are convenience. Plus, I don't think you made a good enough case about the data that are out there that implicate -- that strongly suggest that you will -- you get better vaccination rates, not only for this vaccine, but additional vaccines, if you why, I don't know, but there are data out there that

make that case. So for all those reasons, my own personal opinion is that this is a reasonable thing to do and we'll be discussing it. So I cannot give AAP approval yet, but we'll be making a recommendation to the Board.

DR. MODLIN: Hal, to me it seems like just another -- it's sort of another incremental push. We are still permitting vaccine to be given at two months of age, but it is yet another step in that direction by actually using the word "recommended" for the first time. Is that fair?

DR. MARGOLIS: Correct. I mean, last time, in 1991, we had two options and we held them equal, one being at starting at birth, the other starting at one to two months of age, so we've, you know, moved to a recommendation for the birth dose. And yeah, I actually hadn't gone back and retooled some of the background information. It had gotten pretty strong, but -- and there were comments, and that part just, you know -- we can -- we can deal with. But yes, this is a significant incremental change in the recommendation.

DR. MODLIN: Okay. Jane Siegel, you just walked in, I understand. I didn't mean to surprise you, but do you have anything to say about this? We're talking specifically about the shift in language to specifically recommend the birth dose here.

DR. SIEGEL: I think I've always been in support of a strong recommendation for the birth dose.

DR. MODLIN: Yes, Dr. Mahoney?

DR. MAHONEY: Mahoney. Some members of the American Academy of Family Physicians have noted some concerns about this that I'd like to share, and perhaps even raised in the past. One is the fact that in many cases there are -- there is often a delay and sometimes a complete disconnect between what gets done in the hospital during the newborn period and what reaches the office. In that case, many people will err on the side of caution and end up giving three doses in their office when, in fact, someone may have given a dose in the hospital before they left. Again, it speaks to the issues of, you know, most effective utilization of vaccine supply and cost.

The second issue really is another one of practicality.

That is, some hospitals don't like to pay for this during the newborn period, and I don't know what position this will put them in if this endorsed, but that does exist in some health care markets across the country.

DR. MODLIN: This is rebuttal to your first point. Isn't that really more of a communications issue than a public policy issue over immunization?

DR. MAHONEY: Well, it could be, but it does reflect the reality of diversity of practice settings in which we find ourselves.

DR. MODLIN: And if we had a firm expectation that the birth dose of vaccine would always be given, it might even turn -- serve to be less of a communications issue and actually promote -- well.

DR. MAHONEY: I agree.

DR. MODLIN: Other comments regarding this? I -- Hal Deb, did you have your finger up -- hand up?

MS. WEXLER: I wasn't going to be the last. I hope this is going a little bit longer, but I have a statement to make if -- I guess first of all, I just wanted to say that -- on the recommendation it says "and no later

than two months of age." I really think -- and you know, all of you received my letter -- we surveyed -- the Immunization -- I'm Deborah Wexler, Immunization Action Coalition. My organization surveyed all 50 states by e-mail in the past two weeks about how they feel about the birth dose. We surveyed all the hepatitis coordinators. Fifty states responded. Forty-eight states said they would help -- it would help greatly -- it would help their state if the ACIP supported a recommendation for the birth dose, and you all have a copy of this at your table. The two states that said it wouldn't help their states were states that support the birth dose, but they didn't think it would help change some doctors' minds. So that was two states. One state said the AAP recommendation would help change their state's mind. That would help even more than the ACIP. And the other said they feel like they have 95 percent of their births -- babies getting vaccinated in the hospital already and there are some just recalcitrant docs who couldn't be convinced no matter what they felt.

I guess I'm concerned and I just wanted to bring out

all the errors that are occurring. Someone was concerned that the errors of -- that the vaccine dose information doesn't get sent to the clinic. My greater concern is that the errors are occurring because the obstetrician's office or the family doc's office -- information isn't getting correctly into the infant's record in the hospital. Those errors are occurring, transcription errors. An infant died in Michigan because, while the baby tested -- the mother tested positive in the doctor's office, it was recorded as negative on her prenatal record and the baby didn't get vaccinated and died of hepatitis at age three months. So even more serious errors that involve infections and lost lives will continue to occur without some kind of, you know, strong recommendation for a birth dose.

And documented in here are states' examples of all the errors that are -- that they know of that are being made, which include mis-transcription, not testing the mother at all, mis-ordering -- the wrong test being ordered, antibody instead of surface antigen. So this is an issue that's just fraught with medical errors

being made, and I think the stopgap here is to give the birth dose, to give it within 12 hours of birth, ideally. Unless of course, you are willing to put your signature on a piece of paper and says I'm fine with giving this at two months of age. I confirm that this mother is surface antigen negative and -- But really, I do believe that this is going to save lives. It's going to prevent disease and should only be given at two months of age if someone is willing to say for sure that they trust or they believe that this test result was done properly, the right test was ordered and that there is no mistake. But ideally, the real prevention is giving the birth dose.

DR. MODLIN: Thanks, Deb. Let me ask the voting members of the Committee if there's anyone that has any major problem with this shift? Jaime?

DR. DESEDA: It's a point for clarification, really. And it has to do with page 60 but it's actually page 37, line nine through 13, where it specifically says that if anybody finishes the hepatitis B series before six months then you have to give another three-dose series instead of a general dose.

DR. MODLIN: Okay. That's a different issue than we're talking about right now, which is really strengthening the recommendation for the birth dose. Maybe we could -- Maybe we could come back to that in just a second, if that's okay, and raise it again. Let me again ask members of the Committee if they have a problem with the shift here, which is really a major shift in many ways. Lucy?

DR. TOMPKINS: I think Ms. Wexler's point is very well-taken, that this is a systems problem and that if we don't -- I personally would leave off the "no later than two months of age," simply because we really believe that all children need to be immunized right away, regardless of the mother's status.

DR. MODLIN: How do others feel about Dr. Tompkins' suggestion? Jon, how do you feel about it?

DR. ABRAMSON: Well, how I feel about it -- How I feel about it and how I think that the Academy's going to feel about it are two different things, so I think that we will not have any problem getting this by. I'm less certain about whether we'll have a problem getting that, because then it denotes all sorts of other issues

that get thrown up. You're taking choice away, forcing a -- forcing a pediatrician to do something. I honestly think this is easier language to get past the -- passed. I understand what you're saying, though, Lucy.

DR. MODLIN: People are going to raise the issue of whether or not we've done our proper fiduciary responsibility in doing an economic analysis, based on the likelihood that we will have combination vaccines in the not-too-distant future and what the effects may be on the costs. Is that -- okay.

Other comments?

DR. LEVIN: How about if you just strengthen the sentence by making two different sentences? Your first sentence would be: It is recommended the first dose be given before discharge from the hospital, period. If this cannot be done or if this is not possible or not chosen, whatever language you want to use, then the first dose should be given no later than two months. At least you then come out with a -- you know, a strong bullet statement.

DR. MODLIN: Jane?

DR. SIEGEL: I think by stating it that way, it really takes the oomph out of recommending the birth dose because as soon as you have alternative ways to do it, the message is that this is really not -- not so necessary. So I feel like we need at this time --

DR. MODLIN: I feel like Myron was trying to do the opposite, but it may all come down to the wording here. I'm hesitant to spend a lot of time, but do you have a suggestion, Myron?

DR. LEVIN: No, I was just going to respond to Jane. I was feeling just the opposite, that connecting them by a comma takes the oomph away and that having a sentence as a stand-alone that that's recommended gives it a little more force. But you obviously don't feel that way.

DR. MODLIN: Paul?

DR. OFFIT: It's -- I mean -- I think what Deborah said is exactly right. I'm just trying to understand the way this plays out, though, in the heartland. If you say it is recommended that the first dose be administered at birth and before discharge, that's the

recommendation. I mean, does that really take away the choice of giving it at two months? Because by saying -- Essentially, we think it's the best medicine. We set the bar there. And then we hope that people ultimately come up to that bar. It is -- That is the recommendation. Does that put physicians that are practicing in a box? I mean, is that the sense that I'm getting from -- I guess from Natalie and from Jon? I mean, does it really take away the choice?

DR. SMITH: Yeah, I mean, I just -- it's all anecdotal to me. I know that there are many physicians that feel like they very carefully screen their patients and they want to use combination vaccines and they want to make sure they still have options. But that's -- I am personally comfortable with this language.

DR. MODLIN: Georges?

DR. PETER: John, I would second Natalie's point of view. I think historically the Committee has always provided a range. Indeed, as long as you state that the preference is, indeed, to give it at birth, you've made your point. But I've had a number of physicians who have said they don't want to give it in the hospital

because there's a markup cost of the vaccine. It's cheaper to give it in their practice and they -- and some of these people are correct, they have very good compliance. So I would not take away choice. I would -- In fact, I think this language is very clear.

DR. MODLIN: Let me ask again the voting members, is there anyone who can't live with this language? In other words, who feel strongly we shouldn't change the recommendation in this way.

(No response)

DR. MODLIN: Hal, if that's the case, why don't we go on.

DR. MARGOLIS: All right. The other point here had to do with pre-term infants. And again, I know the -- actually Tom Saari on the CID has been working with us on this, and I think this is close to the language. And I know again that's going to be discussed this coming weekend. So again -- But it really captures the issue that there are now a number of new studies and extant data that show that vaccination of pre-term infants of any gestational age and weight born to a surface antigen negative mother should be delayed until one month of

age. And this really kind of brings together -- As you recall before, we had different weights and the very low birth weight and the very pre-term, so this again -- surface antigen negative and then information -- and it is redundant. There are redundancies in terms of the post-exposure issues. They're both here and they're in the post-exposure section, and I think we feel pretty strongly that that's probably the best way, in terms of -- you know, for practitioners. But -- Jon, I don't know if you have any newer --

DR. ABRAMSON: Well, I have a little concern about the definition of "premature." Because if you're -- You're now talking about a 36-week -- by definition, a premature could include a 36-week. I think you're counteracting what you're trying to do in the first -- that's different than a 1000-gram baby. So I need more -- I need more detail on that.

DR. MARGOLIS: Well, and -- again, I'm -- Tom and I have had these discussions. The data actually goes that spread and, in fact, we had that before, up through 36 weeks, by the definition of pre-term. So there -- there --

DR. MODLIN: Neil Halsey, aren't most of the data here broken down, whatever studies have been done have compared infants less than 2000 grams with those greater than 2000 grams? You would know.

DR. HALSEY: I'm sure that Hal knows that those are what the original data were. There are some conflicting data. I know Hal knows those and can summarize them, but the original data were 2000 grams. The Academy statement that was made several years ago made that cut point, but there are more recent data.

DR. MARGOLIS: I mean, there are both groups, and what is evident is that -- there were some data also that is that, you know, 2,000 to 2,500, there may be some poor immunogenicity. So, again, this is -- You know, I know you're going to -- The committee -- your committee is going to struggle with it a little bit more to get those definitions. I think we can deal with that in the background, and if it -- We would like to see the two statements the same. So if the Committee is willing to let us work together as it evolves from the COID standpoint, which we've done on all the other statements, I agree with you that the 36-week is, yeah,

a little bit end-running where we were in the first part of this. But -- And again, I'm going to leave it to you to -- your group to decide whether we, you know, put a gestational age piece in there. The first draft I know of yours says any gestational age.

DR. MODLIN: I think it certainly would be the desire of the Committee to have it reflect the data as accurately as possible in order to provide maximum guidance. Otherwise, questions will just continue to come up. It may very well be that we can choose that. Jon?

DR. ABRAMSON: Yeah, Tom is trying -- Tom Saari is trying to write a whole statement on vaccines and prematures, so not just hepatitis B. And we have -- We will get to a little bit of it this time, but I don't think we'll get through the whole document. I doubt that very much. But I know there are studies and I don't think that -- I think they're more weight-based

DR. MARGOLIS: Yes.

DR. ABRAMSON: -- than age-based. And so I'm not sure we shouldn't be putting a weight in there.

DR. MODLIN: Hal, why don't we put a place-holder there with a -- sort of an indicator that we -- I think we would like to see perhaps some weight-based data, if they are robust data and --

DR. MARGOLIS: Right.

DR. MODLIN: -- make a judgment on that basis. Would that be okay?

DR. MARGOLIS: Yes. And the major change was, in fact, the -- actually under 1800 gram that it really looks like that group has a, you know, better response than was -- was initially appreciated, if one goes out to the one-month -- now again, all of this -- as Off has pointed out here, and we've been very consistent in that in terms of infants born to surface-antigen positive mothers, and with that -- it's HBIG in vaccine and don't count the first dose of vaccine again because of this issue of probably not having a good thriving response, especially in the very low birth weight. So again, we'll work with Tom and again, he and I have been back and forth on this and we left it at this -- and actually didn't revise it at this point.

The other -- I think most of the other changes which

are in there were wording changes, again suggestion and again, now that everybody is here, I want to thank everybody for all the comments and you clearly picked out the areas where there needed to be changes, emphasis, re-writing. I would say most of the others are all re-writing and really aren't changes in direction, unless people would like to, you know, bring up discussion.

There is one new addition -- and I guess I have to -- didn't do a very good job here -- is -- and that's the issue of children coming from other countries where hepatitis B immunization is in place. It's this piece down here, in terms of immigrants. And again, we are working with Bill Atkinson to have consistent wording and I think this is -- at least this is the last versions, the consistent wording. So we know that now there are about 120 countries where hepatitis B immunization is in place and the issue becomes, you know, written documentation and we have tried not to get into a kind of a testing situation. And so it says: Children, including adolescents, who immigrated from countries with infant, childhood or adolescent

hepatitis B immunization programs should be -- oops, something jumped as well -- somewhere I lost a page, sorry. One of my -- here I thought I was helping you and actually I'm confusing you. I actually lost -- somewhere, it looks like a sentence dropped out of this. Well, I'll have to fix that. Actually, the --

Well, but the big issue is, is an infant with a third dose at greater than equal to six months of age, so there are many countries where the third dose actually is administered before six months of age. That's to give you the background here. I -- we're going to have to fill in some words. I don't know where that got lost. Clearly older children and adolescents with a three-dose schedule is fully acceptable. And then children who received their last dose at less than six months of age should receive an additional dose at six months of age. And again, as I say, this has to do with a number of countries who give vaccine on, you know, 0-1-4 schedules, you know, 0-2-4 schedules and those types of schedules.

And then lastly, children in whom a complete hepatitis

B vaccine series cannot be documented should receive the complete series.

DR. MODLIN: Any questions or comments regarding this portion? I assume this is consistent with the general recommendations that we just finished.

DR. GALL: John, could I ask Hal a question? Hal, I -- in this document, I don't see --

DR. MODLIN: I'm sorry, Stan?

DR. GALL: -- about immunization during pregnancy. You have a couple of other places like drug abusers and other things, and is that basically intended to be silent so it's perfectly okay or not okay? I think there should be some statement.

DR. MARGOLIS: It's in the background, and in fact, I think we had strengthened it in the background. But you're right, it's not in any of the recommendations and one of the areas I guess it could be put in is actually this next section, and that has to do with vaccination of persons in groups at increased risk of infection. And I guess what we could do -- we did put a section in here about integration of immunization into other prevention activities that are going on for

these -- you know, many people at risk. I guess if -- and I think that's a very good point, is to put that type of recommendation there. It's all in the background, but it's never been brought forward to the recommendation piece.

DR. SNIDER: Hal, this is Dixie --

DR. GALL: I think it would be very helpful if --

DR. MODLIN: Why don't we let Stan finish, Dixie --

DR. SNIDER: Oh, I'm sorry.

DR. MODLIN: -- and then we'll --

DR. GALL: I think it'd be very helpful if there would be some statement because this is not an uncommon question that I get calls from physicians about when when pregnant women are in these very special situations.

DR. SNIDER: Well, I agree with Stan. I was just going to point out that there is a section in the general recommendations that deals with this --

DR. MARGOLIS: Right.

DR. SNIDER: -- so there may be another place where you can use some of that language.

DR. MARGOLIS: Yes. And I would say this is probably

the best place to put it then, because it does pertain to all of these risk groups.

DR. MODLIN: Dr. France?

DR. FRANCE: Thanks, Eric France. On page 62, Hal, you were just discussing how if one receives that third hepatitis B shots under age six months, then you should repeat another dose, a fourth dose after age six months. And yet maybe that conflicts with, as Dr. Deseda was mentioning, on page 37 where it suggests, in line 11, that if you're sort of off the series, you need to repeat the three-dose series. Or at least that's sort of how it reads there. When this occurs, it says on page 37, line 12, they should receive the three-dose vaccine series with an age-appropriate formulation and schedule.

DR. MARGOLIS: Yeah, that's an inconsistency that we've missed and we'll -- we'll fix that.

DR. FRANCE: I guess then, along those lines is, would the general recs be that they repeat the whole three-dose series or if -- if you're from another country and you've completed the three-dose series before age six months, should they repeat all three

doses or is a fourth dose acceptable? I'm still not clear in my mind which is the right approach.

DR. MARGOLIS: The data would support that they need the third dose. The first two doses are adequate in terms of priming. It really becomes an issue of -- at least in terms of long-term protection and immune memory, so -- so you've put that --

DR. MODLIN: How does it become an issue with the interval between the second and the third dose, which is important?

DR. MARGOLIS: Yes.

DR. MODLIN: And this is the reason why we --

DR. MARGOLIS: Yes, and what happens is -- in that setting.

DR. MODLIN: Bill Schaffner?

DR. SCHAFFNER: Once again, compliments to the chef. I do have four small points for your consideration, if I may. Let me give you page references. On page 65 we have a recommendation to immunize inmates in correctional facilities. Excellent. Now, the background for that is on page 19, and if you'll have a look at that quickly, you'll see that the entire

rationale for that recommendation is intra-institutional hepatitis B. And on the basis of at least a brief conversation in Tennessee and what I've heard from some other places, at least some prison administrations are taking that very literally and they don't understand that one of I believe the Committee's major goals here is to immunize these folks before they get back out on the street, because this is a high-risk group. And so I'm suggesting that this background paragraph be expanded just a bit to include that broader public health objective.

DR. MARGOLIS: Good point. We basically said that this was primarily due to non-prison acquisition, but that, in fact, more recently that has occurred. You realize there's going to be a whole document on prevention of viral hepatitis -- I think I described it the last time -- in the correction setting, and we'll go into this in exquisite detail, but we will strengthen that.

DR. MODLIN: You had three more, Bill, or two more.

DR. SCHAFFNER: Thank you. I direct your attention to page 63, and here -- bravo. As we had spoken about

at the end of that first last -- at the end of that first paragraph, last sentence: Vaccination should be initiated in high-risk adults and adolescents, even though completion of the vaccine series may not be assured at the time the series is begun. Hoorah, that's great.

Previous page, number four, right at the bottom. Now, this is in the context of vaccination of adolescents. There is an emphasis on a slightly different sylLAble. The schedule chosen for vaccination should take into account the feasibility of delivering a complete immunization series to this age group. I think maybe just a little subtle wordsmithing can make those compatible, and I think the emphasis once again should be on immunize 'em, and we'll worry about dose two and three down the road.

Page 63 again, item number one, last sentence: All clients in STD clinics should be considered candidates for vaccination. I would urge that you suggest -- urge that you consider the following: All clients in STD clinics should be immunized, period.

And then lastly, perhaps the most touchy, on page 26

-- touchy, sensitive. The first large paragraph, last long sentence describes the state of school immunization requirements in the country today, and importantly says that 24 states require hepatitis B vaccination for entry to middle school or seventh grade, et cetera, et cetera.

When I read this I was reminded of what we say in our varicella statement: And the Committee urges other states to do this, also.

DR. MODLIN: That's a good point. I assume that none of the voting members have any issues with Dr. Schaffner's suggestions? Thanks, Bill.

DR. MARGOLIS: Probably the -- Two comments, one in terms of the STD clinic and the word "consideration", the reality is, and I think we now have a lot of experience, is that not 100 percent of people who come into STD clinics, in fact, are there for STD treatment or are at risk. And I think now -- Yes, it's -- you know, it's a wiggle word, but it's the fact that it reflects now that we're much farther along. Just to let the Committee know, 25 percent of STD clinics in this country are routinely vaccinating. Recent

survey conducted in -- and that's different than four years ago where it was about ten percent, so there's been a dramatic change. And in fact, as we now look at who's in an STD clinic, not everyone should be vaccinated.

DR. SCHAFFNER: Sure they should.

DR. MARGOLIS: Well, there are people who are immune. There are people who -- well-documented, and so in the background it discusses that. If the Committee feels we should take the word out, I will take it out.

DR. MODLIN: Tom, did you have a comment specifically about this?

DR. VERNON: I wanted to buttress the first suggestion that Bill Schaffner dealt with and that is the immunization in correctional facilities. While Hal and his team, I believe Glaxo Smith-Kline and certainly we, have been talking with corrections officials over the last several months about how a better job can be done in that high risk population, it is repeatedly stated that we really don't have a hepatitis B transmission problem in the institution itself. And the recommendation to us by Dr. Les Wright, who is now

the medical director and deputy commissioner in the New York state correction system and a former health officer in two states, says we corrections officials need to understand that we have a responsibility to contribute to the public's health, and that is to immunize this population while we -- while we have them in place. And so on page 65, indeed, on line 16 I would certainly want something to the effect that corrections officials can make a substantial contribution to the elimination of hepatitis B by vaccinating inmates who will be returning to their communities and may reassume high-risk behaviors, something to that effect.

DR. MODLIN: Rich Clover I guess may be representing the adult folks on the Committee -- or Lucy, how do you feel about the wording with respect to STD clients and patients who are STD clinic attendees in terms of the nature of the recommendation here? It's a matter of emphasis, obviously.

DR. CLOVER: Sure, I think the people presenting to STD clinics should be screened and vaccinated, if indicated. I mean, if they've had the vaccine,

clearly they don't need it again. And if they're serologically immune for whatever reason, they don't need to be vaccinated again.

DR. MODLIN: Does not screening, though, represent an issue if it's sort of a loss of an opportunity to immunize in this population?

DR. CLOVER: Yes.

DR. MODLIN: Lucy, how do you feel about that?

DR. TOMPKINS: Somewhere in between Rich and Bill. I mean, ordinarily, I would just completely agree with Bill because you can see I don't want anybody to have any choices about anything. But I mean, why single out -- you know, yes, generally people who attend STD clinics are in high-risk groups, but on the other hand, we're not mandating that everyone in the United States be immunized for hepatitis B. And so it is a little discriminatory to say they should all be immunized without some due consideration about whether they actually need it or not.

DR. CLOVER: Yeah, John --

DR. MODLIN: Would the Committee be comfortable -- Yes, Rich?

DR. CLOVER: I guess I need to follow up -- When I said screen, I'm not talking about serologically screening them. I'm talking about just asking the appropriate historical questions, and then if they're in need for vaccination, then vaccinate them.

DR. MODLIN: Dixie?

DR. SNIDER: I'd just like to ask how -- because I hope he's had an opportunity to discuss it, but you know, we have the CDC Advisory Committee here making a recommendation that's quite appropriate about immunization, but it affects another program within CDC that, unfortunately, is not represented here. Dr. Mastro's -- is not at this meeting, and so I just wondered what feedback he's had from the STD program with regard to the feasibility of doing routine immunization? I'm not talking about just cost, because I think that's one issue, but the other has to do with the appropriateness of it and the feasibility of doing it.

DR. MARGOLIS: All the demonstration projects have been carried out with the Division of STD Prevention, and in fact, they agree with the recommendation that

considered evaluated -- people need to be -- all the clients coming into STD clinics should be, you know, considered for hepatitis B immunization. The reality has now moved to some of the things that Rick has pointed out, and so -- and it's interesting that again in a five-year period, personnel and the ability to do this was actually seen as a barrier back in '97 and now it's not seen as a barrier, that, in fact, integration of immunization into these clinic settings is very doable. So yeah, I think we can wordsmith this to make it, you know, to point out that everybody should be considered as a candidate and there are -- and again, a lot of that's in the background, and what I'm hearing is you want better direction in the recommendations and we'll work that out.

DR. MODLIN: I assume the Committee is comfortable with letting these guys work it out? Everyone's nodding. Fair enough.

Hal, other major issues?

DR. MARGOLIS: Well, I'd like to ask the Committee because Bill made a very strong recommendation that we recommend school entry laws for hepatitis B. That is

a change in direction, and I turn that back to you in terms of discussion.

DR. MODLIN: I don't think you're going to get much push-back from that recommendation, I suspect. It's certainly consistent with all the other recommendations that the committee has made, and I -- is there anyone who would disagree with adding that extra phrase?

(No response)

DR. MARGOLIS: Okay, the other -- Actually, let me ask the Committee because really, in terms of the recommendations, these -- all the rest are things we have gone over before. What I wanted to put up there was this trial evidence table which I put on your chair and now which I have shuffled and actually am not -- I've got -- I've got -- I was trying to find the overhead is what I'm trying to find. I have a hard copy, but maybe I'm not going to be able to do it. What I -- what well, somewhere I -- what I used is -- I think, as everybody recognizes, there is no standardized set of grading in terms of strength of the information, the and then ultimately a recommendation. I -- You

know, and everybody seems to choose one that might work best for them, so I used the one that Jane had suggested in terms of -- Well, for some reason I can't find the overheads, but you've got it all in front of you. What I did was I took all the elements from the recommendations and, using a grading system that's been used by HICPAC, the Hospital Infections Control Advisory Committee, went through and, you know, used basically a strength of recommendation categorization. And basically they all fall -- at least we think, but I think, looking at the data objectively and using not these raw placebo-controlled clinical trials or efficacy trials that show the outcome but that, in fact, controlled trials were used for -- for looking at immunogenicity, and that has been accepted as a surrogate for protection or efficacy, you know, since the original trials were done with these vaccines. And what you really see is that for all of the -- I apologize, I don't know where I shuffled this, but as I say, again, you have in front of you -- If you look at recommendations for infants -- both infants born to a surface antigen positive mother, surface

antigen negative mothers, infants born where maternal status is unknown, and then I went through vaccination of older children -- there are really only a few where -- actually there has not been a study done, even in a particular risk group. It only gets to some of the post-exposure settings such as recommendations for -- if you go down into that last page of post-exposure, for instance, victims of sexual assault or household contacts of a case of acute hepatitis B over an infant infant household contact of a case of acute hepatitis B where there really aren't clinical trials to, you know, make that recommendation and they're extrapolated from best evidence and best theoretical extension of other available data, really all coming from post-exposure prevention of perinatal HPB infection.

The Committee felt very strongly that we should have an evidence table, and I guess I ask you in terms of how we put such a table together or how we work this back in the recommendations. There were only a few in the Committee who, in their comments back to me, discussed the evidence issues. Some wanted it in all

of the recommendations, that we actually grade all of those previous recommendations versus having a table, and I'm asking for some guidance.

DR. MODLIN: Well, let me start again with maybe Bill and Jane, who have been more involved with this than anyone. How do you feel about -- in other words, having a -- looking at a separate table explaining the -- explaining the evidence table, the strength of evidence guidelines, and then have separate designations in parentheses after each recommendation or simply just one table.

DR. SIEGEL: Well, drawing from the experience of the HICPAC guidelines for infection control, we do put an evidence rating for every recommendation, and that's to help the user, in that all Category 1 recommendations, everybody do it; Category 2 recommendations, the evidence isn't as strong so it's up to -- there's choice involved.

DR. MODLIN: I think what Hal is asking is do we include these actually in -- it's in the text. In other words, do we include it after the recommendation for the birth dose at strength of recommendation IA, or do we simply

have a separate table, as he has prepared for us in the handout here? Does anybody -- I don't have -- I don't care one way or the other, but I wonder if other people have --

DR. SIEGEL: I would just say that it's helpful to have it with the recommendation.

DR. MODLIN: With the recommendation. Okay.

DR. SNIDER: And just -- John? Dixie. Just for the record, our policies and procedures just say that you have to have it, it doesn't say which way you do it.

DR. MODLIN: Gary?

DR. OVERTURF: We, in our statements, put the table in at the end, and we -- at the end of each recommendation, we put in a statement. We put in the category that it's in, so I think that's helpful because people can immediately refer back then to the table.

DR. MODLIN: Bonnie?

DR. WORD: I was going to say, I actually just like the way it is in the table, because sometimes as I'm reading recommendations, I find it -- like I'm -- when I'm going through it I'm like okay, IA, IIA. This way I can just go to the back, flip it and look at it in the back.

DR. MODLIN: Hal, it sounds like the consensus is to include it actually with the recommendation in the text.

DR. MARGOLIS: Okay. I guess one of the other things which, again, this Committee hasn't, you know, picked their -- their standard, and the pneumococcal recommendations are different than these. Again, are there strong directions in terms of which we should go on the --

DR. MODLIN: Rich?

DR. CLOVER: There was a point that Jane was trying to make and I was just talking about. I feel like it needs to be -- we need to pick which rating system we like and be consistent across our documents. And you know, I don't have a preference, but I would encourage us to be consistent.

DR. MODLIN: Jane?

DR. SIEGEL: I would just say my main argument for this particular system is that it's very simple and is -- because there are a lot of other systems that maybe give more information, but they're more complicated. It's a very simple system and everyone can relate to it.

DR. MODLIN: Well, we have began using another system with recent statements, there's no question about that, and I think Rich's argument for consistency is a good one. And I don't want to get bogged down in comparing one system with the other because I think the value of both are probably quite similar, but -- Rick? Rick Zimmerman?

DR. ZIMMERMAN: Just one way or the other, and it could be by mentioning either the efficacy or the immunogenicity, wouldn't necessarily have to do both, but it would be nice in the table to know which ones are studies really based on efficacy, you know -- I guess some of the IA's could be either efficacy or bridging immunogenicity type data or outcome data. And I think the efficacy's -- should be somehow pointed out because they're different.

DR. MODLIN: Okay. Hal, are there any other major points?

DR. MARGOLIS: Well, the last issue -- and there is one last issue, and this was raised in terms of what I guess now is -- it was the old Table II, now Table III, and this has to do with schedules. In the background, I

guess just as the opener, the issue in these had both schedules for infants born to surface antigen negative mothers. This is kind of the broad picture of these issues. Went on with surface antigen positive and then untested mothers and then children, adolescents and adults. And all the data that goes around the various schedules are in the background. Some of these are not FDA-approved schedules. They're not in the package insert. These are schedules that have been used -- and on the previous statement they're ones that have been discussed here in various votes and, you know, kind of interim movement and I think I -- because this was raised as an issue, is -- you know, does the Committee, you know, want to go with these schedules, which include some that are not in the package insert. And Karen Midthun is one who raised this, and others who've -- you know, from the FDA have raised this.

DR. MODLIN: Karen, yes?

DR. MIDTHUN: I think that -- I know that there are recommendations, for example, for the recommended schedule in the package insert, and the recommended schedule is zero, one and six months, and then for the

adolescent two-dose schedule for Merck it's zero and four to six months, for example. I am aware that there are published studies looking at different schedules. I couldn't get a sense, looking at this document -- you know, because the references aren't in there yet -- you know, what the strength of those data are. And I guess I would ask consideration be given to -- to indicate that the recommended schedule is this, but you know, if -- there are other data that support these other schedules and that, you know, if that's how it's practical for you to give the vaccine, you know, go ahead and give it. But I think there is a distinction between what has been approved schedule in the package insert versus, you know, data perhaps for other schedules that have not yet been approved.

DR. MODLIN: And Hal, the appropriate place to make that distinction would be both in the text in the background and in the table. Is that what I'm hearing?

DR. MARGOLIS: Well, in the past we haven't done it in the table. We've used the broad ranges, and in the background, it's there. And you're right, we don't have all the string of how many hundred references this

thing's turning out to be. I just didn't want to put all that in at this point. But every one for which there's a schedule here, those data are in -- are, you know, in the background. So I guess the question is, you know, is it --

DR. MODLIN: It certainly --

DR. MARGOLIS: -- should this be reworked in terms of the data versus it being under the user table and the data staying in the background?

DR. MODLIN: Karen, it's -- I guess for me it's a little hard to respond personally without actually seeing the seeing the actual text.

DR. MIDTHUN: I agree.

DR. MODLIN: How do others feel about this, the issue that Dr. Midthun and Dr. Margolis raise? There is an FDA-approved schedule and that we currently do recommend in the text schedules that differ somewhat from the approved schedule, for which I think almost all of us would agree there are sufficient data to support that recommendation, at least in my view it would. But how do others feel? Peggy?

DR. RENNELS: I think there should be in the

recommendation -- it'll point out what the FDA-approved schedule is and that, based on other data, you know, we feel there should be a range. But that can go in the text. I don't think it needs to go in the table.

DR. MODLIN: Other comments? Myron?

DR. LEVIN: Just two generic comments. One has to do with the tables in general, and I think a lot of people use documents like this by quickly going to the tables. And what struck me is that you had a richness of detail in the text that isn't always in the table. In fact, there's some disagreement -- and I'll go over it with you later off-line -- but I think the tables ought to be -- stand alone as much as possible, and I didn't feel that they were. That's one generic comment.

And the other is, I would put something in the beginning, in your preamble, about the success to date you've had in getting so many people vaccinated and how the incidence of hepatitis B has actually fallen, which I think it has. And I think there should be something positive said up front about how well we're doing as you try to get people to do better.

DR. MODLIN: Jane?

DR. SIEGEL: Just one other comment. In the recommendations, the discussion on page 46 has a good discussion about how to manage non-responders, but I don't think it comes through in the recommendations, so I think the recommendations --

DR. MARGOLIS: You're correct.

DR. SIEGEL: -- have to have a statement about management of non-responders.

DR. MODLIN: Hal, is there anything else?

DR. MARGOLIS: That's all I have.

DR. MODLIN: Okay. Let me ask the Committee. We've made a number of changes and suggestions here. Do the voting members of the Committee feel comfortable voting on the document with suggested changes, or would you rather see one more draft? The major change, of course, is the strength of recommendation for the newborn dose, and most of the others are less -- less consequential, probably. Ready to vote? I see a lot of nodding.

Okay. I actually have to -- Well, first of all, we need a motion, and first of all, I need to ask who is

conflicted with Merck or SKB -- Dr. Rennels, Dr. Offit, Dr. Clover and Dr. Levin, so we are not going to have a quorum -- or a -- unless you pick someone.

DR. SNIDER: So the ex-officio members are permitted to vote on this particular issue.

DR. MODLIN: I need a motion from the floor. Lucy?

DR. TOMPKINS: I move that we accept the recommendation.

DR. MODLIN: That we adopt the hepatitis B statement as presented?

DR. TOMPKINS: Yes.

DR. MODLIN: Do I hear a second?

DR. SMITH: Second.

DR. MODLIN: Second, okay. Given those that have stated conflicts, those in favor of the motion? Dr. Ward, Dr. Clover, Dr. Brooks, Dr. Smith, Dr. Tompkins, Dr. DeSeda, too, and Dr. Modlin, Mr. Graydon.

UNIDENTIFIED SPEAKER: Dr. Clover's not -- for the record --

DR. CLOVER: I did not vote.

DR. MODLIN: Oh, I thought I --

DR. CLOVER: I was not voting.

DR. MODLIN: Excuse me, Dr. Clover did not vote. Let's start over again. Those in favor -- Dr. Word, Dr. Brooks, Dr. Smith, Dr. Tompkins, Dr. DeSeda, Dr. Modlin, Dr. Heilman, Mr. Graydon. Those opposed? Those abstaining? Those abstaining are Dr. Rennels, Dr. Offit, Dr. Clover, Dr. Levin, Dr. Midthun and Dr. Evans and Dr. Groom.

UNIDENTIFIED SPEAKER: And Dr. Diniega.

DR. MODLIN: And Dr. Diniega, I'm sorry. The motion passes. Hal, thank you.

We, I think, clearly would like to see the final product as -- once it's available. I don't know how many people -- I think most everybody in the room recognizes that this is a bit of a milestone, so I'm happy that we've gotten there.

The next item on the agenda -- next two items -- next item on the agenda is another hepatitis vaccine issue and that's the inclusion of Twinrix in the VFC program for adolescents that are 18 years of age only. Is that right, Melinda?

DR. WHARTON: That's right.

DR. MODLIN: Okay.

DR. WHARTON: There are revised resolutions for inclusion of Twinrix, the GSK licensed hepatitis A/hepatitis B combination vaccine, for the Vaccines for Children Program. This vaccine is labeled for use in persons 18 years of age and older, and for this reason, the use of this vaccine in VFC is limited to children in their last year of eligibility at age 18. I'll start with the hepatitis A statement. The purpose of the resolution is to revise the previous resolution to incorporate the use of a three-dose combination hepatitis A/hepatitis B vaccine for use in persons aged 18 years, and so there is a notice made under eligibility that it is limited to that age group. The Twinrix schedule is added to the hepatitis A vaccine schedule. Minimum intervals are added to the dosage interval table. Under contraindications and precautions, Twinrix is added -- Twinrix is added for use in persons under 18 years of age because of the labeling. And there is as notice at the end of the statement that vaccines approved by ACIP for inclusion in the VFC program are not available for use in the program until ACIP recommendations have been published

and after CDC has established a contract for purchase of the vaccine.

So are there any -- is there any discussion related to this revised hepatitis A vaccine resolution for VFC?

DR. MODLIN: Melinda, in the interest of time, why don't we do them both?

DR. WHARTON: Fine.

DR. MODLIN: Then we can open it up.

DR. WHARTON: The hepatitis B resolution is not surprisingly similar. The resolution is intended to revise the previous resolution to incorporate the use of a combined hepatitis A and hepatitis B vaccine for use in persons aged 18 years. The age distinction is added to the eligible groups. The -- Let's see, the Twinrix schedule is added to a catch-up -- a schedule using Twinrix is added to the catch-up vaccination schedule. There is an addition to the dosage interval table with minimum intervals, and there is a contraindication added of use of the vaccine among persons 18 years of age and older.

I should add that there is a omission from the contraindications and precautions table which was

inadvertently omitted when we put this together. We are not used to thinking about two vaccines when running a statement for one vaccine, and in the previous resolution I went over, pregnancy is listed as a precaution for use of hepatitis A vaccine. And because this is a combined product, that precaution for the hepatitis A component should be listed in the hepatitis B resolution, and that will be added. So consider that an inadvertent omission to the contraindications and precautions table.

So those are the changes that are proposed in the hepatitis A and hepatitis B resolutions. Does anyone have any questions?

DR. MODLIN: I think most of us had an opportunity to review this in advance of the meeting. Are there any comments, questions, changes, suggestions? Hearing none, may I have a motion that the VFC resolutions -- Can we vote on both of them at the same time?

DR. WHARTON: Don't look at me.

DR. MODLIN: Dixie, I --

DR. SNIDER: Yes.

DR. MODLIN: Great. I would like to entertain a

motion that we accept the VFC resolutions for hepatitis A and hepatitis B vaccines as amended. We have the same issues regarding eligibility to vote as we did at the last vote. Come on, Dennis.

DR. BROOKS: I'm trying to figure out the best way to say it. I guess I entertain the motion to accept the hepatitis A and hepatitis B resolutions as stated.

DR. TOMPKINS: I second.

DR. MODLIN: Okay. The motion has been made and seconded. Those in favor? Same conflicts as we had with the last vote is the way I -- conflicts with Merck and with Smith-Kline. All those in favor, Dr. Word, Dr. Brooks, Dr. Smith, Dr. Tompkins, Dr. DeSeda, Dr. Modlin, Mr. Graydon, Dr. Heilman. Those opposed, none. Those abstaining, Dr. Rennels, Dr. Offit, Dr. Clover, Dr. Levin, Dr. Groom, Dr. Diniega, Dr. Midthun and Dr. Evans voted for the resolution, so the resolution passes.

Melinda, thank you --

DR. WHARTON: Thank you.

DR. MODLIN: -- very much. Those will be the quickest two votes we've ever taken since I've been on the

Committee.

The next item on the agenda will be a review, our annual October review of the harmonized childhood immunization schedule. We need to call it childhood immunization schedule now that we have an adult schedule that we'll be talking about later. And Natalie, will you or Margaret be leading the --

DR. SMITH: Well, Margaret's not here. Actually, I'll ask Melinda to go back up in a moment, but --

DR. MODLIN: Terrific.

DR. SMITH: -- just as -- by way of introduction, we reviewed the childhood schedule, as you all know, back in June. And really there are just some very general, minor changes with this version you have in front of you. And then Melinda's also going to be discussing again the possibility of putting a schedule on the flip side of the document for those children who start late or fall behind in their shots.

DR. MODLIN: Just as a reminder, this is an exercise that we've always waited until October to step through in the past and it's led to some problems. So this year we've done things a little bit differently and actually

started this process back in February, and I think it's made a major difference.

DR. WHARTON: I apologize for the fact that you didn't get this material in advance. We've actually -- Margaret Cortese, who's the person who's done a really wonderful job on this in the childhood preventable diseases branch, is out on an outbreak investigation, and I kind of dropped the ball in trying to cover for her, so I apologize for that. However, I think that the issues that we have to talk today about are, as Natalie said, are very narrow in that we really tried to take the guidance we got from you all in June and incorporate it into the document which I believe you should all now have. And the issues for discussion are, at least as I understand it, quite limited.

I'd like to point out just a few changes that have been made since the last time you saw it.

John, can I borrow a pencil, just to point with?

First, this purple bar, the -- which previously had been the adolescent assessment, in recognition that perhaps properly speaking, 11 and 12-year-olds are not adolescents, has now been changed to the

pre-adolescent assessment, and the last column has been -- all the inclusive ages left in the period of which we would normally consider children 13 to 18. There has been an explanation added to what the green bars mean, which was one of the additions -- one of the enhancements to this schedule, which I should say at the outset, we have plagiarized from the State of Minnesota where Diane Petersen and others have used it with great success for a number of years. The green bar is now listed as indicating age groups that warrant special effort for immunization if these vaccines had not been given previously. So that is the language that's been incorporated, explaining the meaning of the green bars, which we have called catch-up bars. Perhaps in recognition of the votes you just took adopting the hepatitis B statement, some change in the hepatitis B wording is needed. Under the footnote, we state that for infants born to hepatitis B surface antigen negative mothers that they should receive the first dose of hepatitis B vaccine at birth or by age two months. Would it be the Committee's wish that we should say at birth here? That's the -- yes, okay.

So we can change that.

There is another change which is something that came up at CDC after the previous meeting that I wanted to highlight because this isn't an issue that had been discussed previously. There have been -- A number of questions have come up about appropriate use of the licensed DTaP/Hib combination vaccine, which is licensed for completion of the series for children -- for the fourth dose of the series for children who began the series with one of the licensed DTaP products. And there's been many questions that have come up about can this vaccine be used in a mixed sequence. And because of the previous guidance from the ACIP that both DTaP and Hib vaccines can be used in a mixed sequence, language has been added. DTaP/Hib combination products should not be used for primary immunization of -- in infants at ages two, four or six months, but can be used as a booster beginning at age 12 months following any Hib vaccine. Now, obviously, in the future perhaps we'll have a combination product that would be licensed for that indication, but we don't at the moment, so that's the source of that language.

Does anybody have any issues with that? It's in the footnote. We can take it out if it's a problem, but -- yeah, Karen?

DR. MIDTHUN: I guess I'd just like to address what -- well, first, can we go back to the hepatitis B? I thought I heard discussion earlier from a number of people saying that although the recommendation was for an immunization at birth, they didn't want to make it difficult for certain people who might elect not to vaccinate until two months to do that, and I guess my question is if you eliminate the by age two months, how does that relate to the comments that were made earlier on that issue?

DR. MODLIN: I agree, I think we probably should reconsider that specifically, in light of the fact that the AAFP and the AAP probably have not had an opportunity to weigh in on this.

DR. WHARTON: Well, and we do have a bar that goes all the way through that age interval. So perhaps actually that it should be administered at birth wouldn't be completely consistent with the graphic, either.

John, are we going to have further discussion about that or should we just plan on leaving the hepatitis B language the way it is in the footnote?

DR. MODLIN: I think it's something that probably can be settled one way or the other before the schedule is actually published. If I understand, the Red Book Committee is meeting this weekend so that -- which this issue will be discussed, and then I think it's going to be a matter of negotiating I think with our -- amongst the three --

DR. WHARTON: Okay, so we will -- we will wait a final decision on that language from -- yeah.

DR. MODLIN: Yes, Georges?

DR. PETER: Do we want to have the -- given the discussion that just took place, to have the wording of hepatitis B underneath birth, but still retain the bar going from zero to two, to emphasize that the recommendation is for --

DR. WHARTON: The issue of the position of the title.

DR. PETER: Yes.

DR. MODLIN: To make it left-justified. Yes. Back again.

DR. WHARTON: Okay. Well, I did have that on my list, I just hadn't gotten to it yet.

DR. MODLIN: It's the same issue as the footnote, and why don't we agree that this is something that probably can be negotiated reasonably. I don't think the ACIP is going to -- I'm speaking for the Committee -- is likely to get hung up on that issue today.

DR. WHARTON: Okay.

DR. MIDTHUN: Can I make one more --

DR. WHARTON: Okay, yes?

DR. MIDTHUN: -- just one more point? On item number three where you talk about the DTaP/Hib --

DR. WHARTON: Yes.

DR. MIDTHUN: -- it can be given at 12 months of age, the label for that combination product says it should be given at 15 months of age. I think it has to do with the data for DTaP having been -- you know, you give that at 15 months --

DR. WHARTON: Right.

DR. MIDTHUN: -- or more and I guess I would ask the question, would you be willing to have some language in there that's sort of reflective of what you have up

in two where you say the fourth dose of DTaP may be administered at age 12 if you don't -- In other words -

DR. WHARTON: Yeah. The issue -- if this was a statement, I would be perfectly willing to add whatever qualifiers one would like. The issue has to do with space. And I wonder if -- My personal preference would be, if this language is problematic, to delete it. But we can go back and look at it and see.

DR. MIDTHUN: Yeah, I mean, technically, you know, it would be consistent with the label if you said but can be used as a booster dose beginning at 15 months of age. I mean, that would be the other thing to consider.

DR. WHARTON: Okay. Are there other comments from the Committee about this sentence and whether or not we should leave it in there?

DR. MODLIN: Karen, why don't you go over that one more time?

DR. MIDTHUN: The DTaP/Hib product is approved for a fourth dose at 15 months of age, and so that last sentence right now says that it should not be used for primary immunization of infants at two, four and six

months, but can be used as a booster beginning at 15 months of age following any Hib vaccine. I mean, that would be consistent with the label.

DR. MODLIN: Beginning at 15, rather than 12 months.

DR. WHARTON: I see nods.

DR. MODLIN: I think that's a reasonable change.

DR. WHARTON: Okay.

DR. MODLIN: How do others feel? Okay.

DR. WHARTON: Thank you, Karen. Another change that's been made has to do with -- There was a lot of back and forth in the working group about a real desire to be able to present some current and updated information regarding contraindications to vaccination, and there was talk about what might be on a page two, what might be on a page three of the schedule. And I'm not sure we are going to get page two done this year, much less page three, but what we ended up doing was adding some language to what I've called the box at the bottom, which says for additional information about the vaccines listed above and contraindications to immunization, referring people to the NIP website where those updated tables are

placed. Does that seem to the Committee to be a appropriate way to handle this issue, where we provide some information in the most efficient way?

DR. MODLIN: I think it's fine. I think the last time we discussed this issue there was concern that the other partner organization should be listed, their websites, in a similar way in terms of where similar information can be obtained. Is that right, Jon?

DR. ABRAMSON: Yes, and I also think that we need to have a place where people know that if there's a shortage, they can go to a website. I don't think we can get -- we have inundated with calls about shortages, just like we do, and it would be very useful -- not necessarily to list each one as a shortage, but to note, for instance, in the front page where it says for additional information about the vaccines listed above and contraindications for immunizations, just adding the words for additional information about -- also about shortages.

DR. MODLIN: How about the words vaccine supply?

DR. ABRAMSON: Yeah, that's fine, or whatever your wording, but to make it clear that they can go and get

information because we're getting called all the time about shortages, when we don't really know as much information as the CDC does about it.

DR. WHARTON: That's a good point. We'll see if we can -- I mean, I would hope that the -- for additional information about the vaccines listed above would cover that, but perhaps we could think of a way to do that. That's a good point.

Okay. Another decision which was made in coming up with this figure for presentation today, we had had some discussion about adding a green bar -- that is, special efforts need to be made to administer the vaccine -- to the Td dose listed here. But in light of the ongoing shortage of adult formulation Td, we didn't do that, but if the supply issues are resolved this year would propose presenting that next year. As an example, where due to supply issues, we could actually indicate a need to catch up people who may have missed a dose because of supply issues, and we might leave it on for a couple of years and then take it off.

And then the final issue related to this schedule that I had on my list had to do with placement in the bar,

and we will wait resolution of that by the other organizations in terms of how they come down. Those are all the issues that we had intended to highlight for the recommended childhood immunization schedule. And again, I think I was remiss at the beginning in not giving credit to the people who really did the work on this. It wasn't me. It was Margaret Cortese, Trudy Murphy, Diane Petersen for the original format, and Ron News [phonetic] for the graphics, who has done a great job.

DR. MODLIN: Let's open this up for discussion.

DR. SMITH: Melinda, did you want to discuss the flip side of the schedule?

DR. WHARTON: Well, I am, but I was going to try to finish this up first, so yeah, John, I actually have another topic that I need to address while I'm up here.

DR. MODLIN: Oh, okay. Well, let's see if we can focus on this and just address the questions. Committee members, Dr. Neuzil?

DR. NEUZIL: Melinda, if you could help me here with visual aid, but if you look at that schedule, the column on the right at the bottom has a few lines left where

you've used up the room on the column on the left, and I have a suggestion. You say on the adult schedule, which we'll present in about an hour, under influenza vaccine, you say influenza vaccine is recommended annually for children age older than six months with certain risk factors. On the adult footnote we actually list those risk factors, which I think you have room to do. And the reason I suggest that is because influenza vaccine in high-risk children has the poorest coverage rates --

DR. WHARTON: Sure.

DR. NEUZIL: -- of any vaccine in pediatrics, and perhaps you should say children with asthma, and use up the rest of those lines --

DR. WHARTON: Well --

DR. NEUZIL: -- to make it easy.

DR. WHARTON: -- that's an excellent suggestion if we've got the space to do it. I think my assumption was that we didn't, but perhaps I'm thinking of a very expansive list and perhaps there is a shorter list that wouldn't take up so much room. We will try to do that. I guess I want some reaction from other people before

I say we're going to do it. What do you-all think?

DR. MODLIN: Well, certainly our philosophy has been to be as terse as possible with the footnotes and to refer to other information wherever we can. However, I do think it, you know, on the other hand, it is an excellent suggestion and it may -- where we -- particularly these days that there are many immunization providers that are not as familiar with the risk factors for young children as they should be, and so I think it's appropriate.

DR. NEUZIL: I would only recommend it if you still have that white space --

DR. WHARTON: Right.

DR. NEUZIL: -- at the end of today. Right, use it up.

DR. WHARTON: And I understand and we will -- if we can come up with a way to convey useful information in a couple of lines, we'd be very happy to do that.

DR. MODLIN: Other comments or questions about this side of the schedule? Dr. Wexler?

DR. WEXLER: Deborah Wexler. I have one comment on the bar on the hepatitis B dose one. Since people

often don't look at the footnotes and we have a bar across the top that defines the orange bar as range of recommended ages, I would suggest to ACIP and AAP that we consider putting just hepatitis B number one in column one for birth, and then put a green catch-up vaccination bar through one to two months, so people know they can catch the kids up, but the recommendation is for birth. It's a thought.

DR. MODLIN: Dr. Overturf?

DR. OVERTURF: I thought we had resolved this earlier, but I think -- I think the way it is, I would rather see us emphasize the birth dose down in the footnote, but leave the bar the way it is because that's still the recommendation. I think it -- I'd feel a little bit uncomfortable. I don't really look at those as catch-up doses, and I still think that binds the physician a little bit too much.

DR. MODLIN: Well, in fact, it is now the ACIP recommendation that we give the birth dose. On the other hand, this is the Harmonized Schedule and we have to recognize that there are two other organizations that have not gone that far yet. And in the interest

of harmonization, which is what this is all about, I think I'd vote for leaving it the way it is at the moment.

DR. WHARTON: It might be something to consider.

DR. OVERTURF: We'll bring it up next week when we review this as an option, but --

DR. SNIDER: Just for the record, I think the way we resolved it was that we would negotiate it with AAP and AAFP as to how to express it in the schedule. We didn't really say how it would be done.

DR. MODLIN: Okay. Fair enough. Dr. Vernon?

DR. VERNON: Tom Vernon from the Merck vaccine division. Melinda, for each of the vaccines that has a recommendation of series, two or more doses, it's clear from the chart, except for hepatitis A. Does there need to be something in the footnote which indicates that it is a two-dose vaccine?

DR. WHARTON: Maybe so. We'll look into that.

DR. MODLIN: I think that's a good point.

DR. WHARTON: Yeah.

DR. MODLIN: Dr. France?

DR. FRANCE: Eric France. I made this play last year

and I'll try again this year. Maybe I'll try again next year, too. Of all these vaccines that we give, hepatitis B is the only one where there's a recommendation we do serology for those special cases of kids who were born to hep B positive moms. I think at KP it's not very often that we actually have the completion of that serology done. I was just talking with Hal and he says that, from his estimate, it's only about 30 percent of the kids who actually get serology completed, and so I believe that a lot of back office people look at this and if they were seeing, under infants born to hep B positive moms, a statement saying serology should be done at nine to 15 months of age to confirm conversion, we would probably improve the number of those tests that are actually being done. So I would suggest that statement be added to that section.

DR. MODLIN: How do others feel about Dr. France's suggestion? Again, we're taking up some of that valuable white space that Dr. Neuzil was -- had her --

DR. NEUZIL: Well, there wasn't any left in that column.

DR. MODLIN: Larry?

DR. PICKERING: Yeah, Larry Pickering. Just to thump the dead horse one more time about the bar for hepatitis B, one is, one of the major questions we get from private pediatricians is do I really need to give the birth dose in the hospital? Can I give it at two months of age? We at the -- people of the Academy have really issued statements supporting the birth dose, but I think that series of questions, combined with an article that will becoming out in Pediatrics by Amanda Cooper on a national survey of AAP members showing that when the combined vaccine comes out, the majority of pediatricians who give the birth dose will move away from it. And I think one of the things we perhaps need to do is put our emphasis on the many states who don't do new pregnant woman screening to get the screening ensured in all women who deliver infants.

The second issue is, Melinda, aren't all the influenza viruses now split viruses and so you can eliminate --

DR. WHARTON: I believe that's correct.

DR. PICKERING: -- can eliminate those words from number nine, give you a little more space.

DR. MODLIN: Rick Zimmerman?

DR. ZIMMERMAN: One way to save a little white space under hepatitis B, there's the fourth underlying thing, all children and adolescents who have not been previously immunized against hepatitis B may begin the series at any visit. That statement is now redundant with the green bar and so there would be a sentence saved that could be potentially used for other purposes.

DR. MODLIN: Gary, did you have a comment about that?

DR. OVERTURF: I was just saying that we were looking for white space.

DR. MODLIN: Okay. All right, other comments or suggestions? Okay.

Shall we go to the flip side?

DR. WHARTON: Sure. Now, on the flip side, although we had good intentions for this meeting, due to great difficulty in getting conference calls arranged in the last few weeks, we are not as far along as we had hoped to be. But I at least want to show you what it is we have done to date and get some guidance from the Committee about what direction you would like us to go with this.

The origins of the planned page two was from the

Minnesota schedule, which again, is a format that's been used very successfully by the Minnesota Department of Health, which on the second page or the back side of the routine childhood schedule includes a schedule for children who start late or who are behind, so what we have referred to as a catch-up schedule, which does get kind of confusing if you're talking about green catch-up bars on the other schedule. So Margaret and -- with Ron's help with the graphics, had put together a draft page two, which I should warn you is put here primarily for formatting, and I think that we are not prepared to say we're sure we have all the words right. But that this is modeled after the Minnesota schedule, which lists the vaccines, minimum interval between doses and then for Hib vaccine and pneumococcal conjugate vaccine, the detail that is needed to parse out the recommendations, which, of course, vary by what age the child is at the time he or she presents for immunization. And then there is a separate table for catch-up of -- catch-up schedule for children who are older. And then the footnotes are limited in this version.

There's a second version which Margaret and Ron mocked up which is based on a table that is in the book NIP publishes on the epidemiology and control of vaccine-preventable diseases, or the Pink Book, that has tables that have fewer words in them, but footnotes that have many more words. And the fact of the matter is, the recommendations are complex, and to convey them in a way that is useful is going to require a fair amount of text somewhere and we have to make a decision philosophically about where we want it. Do we want it in the table or in footnotes? And two different groups of people with two different -- have taken two different approaches to this, and we at CDC felt like we couldn't really go forward on -- with a good table for -- a good proposed page two without some guidance on which of these approaches the Committee prefers. And again, I would present this to you at this point as a sort of philosophical or aesthetic question rather than a technical question, which approach do you like? And then once we know that, if you want us to continue to work on developing this, we'll do that, although I think the time is quite short to get this finished up for

January publication.

DR. MODLIN: This is largely a matter -- almost exclusively a matter of formatting, how it looks and what its effect is going to be. Comments from voting members? Dennis?

DR. BROOKS: I just want to say I showed the draft of both the first page and the second page to my staff, and they loved it. So I think the format with the footnotes in the chart there are better -- is better.

DR. WHARTON: This one (indicating)?

DR. BROOKS: Yeah.

DR. WHARTON: This is the Minnesota one.

DR. BROOKS: Yeah.

DR. MODLIN: Okay. Bonnie?

DR. WORD: I guess I'm just the opposite. I found that one difficult to -- you know, when you're looking at the table, I like the one on the second page better. I thought it was clearer -- it was easier to read.

DR. MODLIN: You've got one vote for each. Paul?

DR. OFFIT: Actually, I'm with Bonnie, I like the way it's --

DR. MODLIN: Okay.

DR. RENNELS: I like the text in the table because I don't think people read footnotes.

DR. MODLIN: So two and two. Myron?

DR. LEVIN: I agree with Peggy.

DR. MODLIN: Three and two -- two and three.

DR. SMITH: The advantage of using the format that Minnesota uses is that it's essentially been field-tested in an entire state and it seems to work.

DR. MODLIN: And that's with the text in the table itself. I just -- additionally, I happen to like it, as well, so there's a real consensus for you. I don't think you're going to have a great deal of guidance. How about you guys? Yes, Gary?

DR. OVERTURF: I have to present this next week -- I mean, this weekend to the COID and I like the one without the footnotes in the table, and, therefore, I'm going to have a tremendous influence on this whole process.

DR. MODLIN: Sounds like it.

UNIDENTIFIED SPEAKER: I'll vote you down.

DR. MODLIN: I doubt anybody's going to lose a lot of sleep over it, although it may very well be that once it -- either form, once something that -- whatever we

do, we might want to revisit again just to see how effective it's been after a year or two of being out there. Eric?

DR. FRANCE: Eric France. Just to say that we're probably the wrong group to ask. I like Natalie's point that it's really the field test. It's the office staff.

DR. MODLIN: That's right.

DR. WHARTON: And I think that's the point Natalie was trying to make, that this version, in fact, has been field-tested. Diane, do you want to add anything to this?

DR. PETERSEN: Yes, I'm Diane Petersen from the Minnesota Department of Health. We have used this format for quite a few years now, and I know it looks complicated and especially that for pneumococcal vaccine and for Hib, but it does work. Because if it doesn't work, we hear about it right away.

DR. MODLIN: There's some good guidance.

DR. WHARTON: So what should we do process-wise on this? Should we wait till we hear from AAP and AAFP for their preferences? Again, I think the chances of

getting this finalized for January production is limited.

DR. MODLIN: Maybe I can speak for the Committee and I think the Committee would be willing to go along with either --

DR. WHARTON: Okay.

DR. MODLIN: -- so long as it's something we may want to revisit after a year and see if there's --

DR. WHARTON: Okay.

DR. MODLIN: -- if there's a drumbeat for change for any reason. Is that okay?

DR. WHARTON: Rick had his hand up.

DR. MODLIN: Rick?

DR. ZIMMERMAN: Rick Zimmerman. From the AAFP viewpoint, I think it's important that we do this, whichever way we go. I think there is wisdom in using something that's field-tested, but I think we could live with either way.

DR. WHARTON: Okay.

DR. MODLIN: Okay. Other comments or questions regarding the entire -- Stan? Stan Plotkin and then Geoff.

DR. PLOTKIN: Yeah, Melinda, perhaps -- I haven't had time to study this, so perhaps this is an incorrect perception, but it appears that you're not recommending any interval between a third -- second or third and a last dose of IPV. Now, I'm not aware of data that would allow us to say that in terms of persistence of antibody that four doses of IPV given one month apart are equivalent to three doses with a six-month interval. And from an immunologic point of view, I've always felt that that six-month interval is quite important. So if my perception is correct, I would recommend some modification of what's in here.

DR. WHARTON: Okay. I believe this is completely derived from the minimum intervals table in the general recommendations, but I will check that point and --

DR. MODLIN: Stan, you're suggesting that we should have more than two months between the second and the third dose, or did I hear you wrong?

DR. PLOTKIN: Essentially, the point is that the last dose of IPV, whatever it is, should be given at least six months after the priming doses. That's the immunologic point, which allows for persistence of

antibody.

DR. MODLIN: If I read this correctly, we're giving a fourth dose at four to six years of age.

DR. WHARTON: This is on the --

DR. PLOTKIN: Well, that's -- I'm sorry.

DR. WHARTON: -- proposed page two.

DR. MODLIN: Okay.

DR. PLOTKIN: It's not page one. It's the catch-up schedule.

DR. RENNELS: But don't --

DR. MODLIN: Peggy?

DR. RENNELS: Don't the general recommendations say four months between the first and six months --

DR. MODLIN: This is IPV, between the --

DR. WHARTON: Again, I think -- we're presenting this for format and I can't vouch that everything on here is exactly as it should be. The intent was to mirror the -- you know, the minimum intervals that are in the new version of the general recommendations, but there may be some errors.

DR. MODLIN: Stan, we'll double-check with that and make certain it's consistent with the existing polio

and -- recommendations and general recs. Geoff?

DR. EVANS: Thanks. Going to the visually challenging information under reporting adverse reactions, I'm buoyed to see that it's there because I think that's new. But I also would like to see if we can get something about the compensation program to be put on this, also. We're still receiving reports where people do not know that we're in existence and, of course, we've been under a great deal of pressure from Congress, particularly to make sure that the program is being advertised, providers and the community are made aware of it. So I think this is a nice vehicle to do that. And certainly in juxtaposition to the reporting adverse reactions, it would -- it could certainly go along with that, assuming anyone could read that.

DR. WHARTON: Yeah, well, there are font issues here, clearly.

DR. EVANS: And I think that's a negative font.

DR. WHARTON: But it's possible we can squeeze some room in. I mean, it's a great point. The issue for us is just space.

DR. MODLIN: Ms. Petersen?

MS. PETERSEN: Yes, regarding the disease reporting and adverse event reporting, I'd also ask that you take off the Department of Health in Minnesota's phone number.

DR. WHARTON: I'm sorry, Diane. This really wasn't intended as a mock-up. I'm sorry. Actually, we're going to report everything to you all. We'll just let you guys take care of it.

DR. MODLIN: We need to take a vote of the ACIP that we endorse the Harmonized Schedule as presented by Dr. Wharton for the current year because otherwise if we don't do it now, we'll have to get you together on a conference call before the end of the year. Could I -- There's no conflict with the Harmonized Schedules. We would be in big trouble if there were.

Can I entertain a motion?

DR. RENNELS: I move that we adopt the Harmonized Schedule as presented.

DR. TOMPKINS: Second.

DR. MODLIN: Okay, the motion has been made that we -- by Dr. Rennels and seconded by Dr. Tompkins that we

adopt and recommend the Harmonized Schedule as presented by Dr. Wharton. Those in favor: Dr. Rennels, Dr. Offit, Dr. Word, Dr. Clover, Dr. Brooks, Dr. Levin, Dr. DeSeda, Dr. Tompkins, Dr. Smith, and Dr. Modlin. Those opposed: none. Those abstaining: none.

DR. WHARTON: Thank you.

DR. MODLIN: Thank you. Jaime, go ahead.

DR. DESEDA: Before we finish, we just approved the Twinrix. So somehow it should be included here.

DR. MODLIN: I suspect that this is something that -- We have made a point of trying to avoid too much detail with the Harmonized Schedule. We've not really approved Twinrix. All we've done is approved its addition for the VFC program at 18 years of age only, and that may be such a minute detail that it may not rise to the level of necessarily being included in the Harmonized Schedule.

DR. WHARTON: I think that -- I think the Committee's intention to cover the Twinrix situation is text that says licensed combination vaccines may be used whenever any components in the combination are

indicated in the vaccines, other components are not contraindicated. The intent was to provide flexibility in use of combination vaccines, but not have to deal with all the nuances within the schedule.

DR. MODLIN: Okay. We have a break scheduled. We are a few minutes ahead of time. So I'm going to ask everybody to return from the break at a quarter of 4:00, 3:45, please.

(RECESS FROM 3:17 P.M. TO 3:51 P.M.)

DR. MODLIN: Could I ask everyone to please be seated? The next item on the agenda is one of the first discussions that we've had before the full committee on the adult Harmonized Schedule. I've got Ben Schwartz at the top of the list here. Ben -- pardon? Ase -- yes? Okay, pardon me. Wrong Schwartz. Dr. Schwartz.

DR. SNELLER: Sneller.

DR. MODLIN: Dr. Sneller, I beg your pardon.

DR. SNELLER: That's okay. Good afternoon, everyone. Thank you again for giving me this opportunity to update you on the progress that the working group on the harmonization of the adult immunization schedule has

been involved in. I am Vishnu Sneller. I'm with the NCIP and I work with Dr. Ben Schwartz.

We made an initial presentation to this group in June. And during that presentation, I summarized the charge to the working group, which involved negotiating a Harmonized Schedule for immunizing adults with the ACIP, the AAFP, and the ACOG, and these are the partners that we were going to be negotiating with for harmonizing their recommendations.

We highlighted areas of harmonization. We highlighted the kinds of differences that we would be that we noticed in the published recommendations of these three groups and the ACIP's, and then we presented a prototype of a tabular summary that the working group had chosen to use and develop for the ACIP's consideration.

So this is a very brief progress report of the decisions that have been made to bring to this group. Between June and yesterday, the working group discussed the format and the content, the table, and the footnotes. The table in your packets is the one that the working group is comfortable with and would

like to push forward for this Committee. This is the table that is in your packet.

The primary differences have been in changes in the color scheme, and you will notice that the MMR has three different recommendations just highlighting the measles, mumps, and rubella issues under the 19 and 49 years. We did include the Lyme disease vaccine, even though it's not considered a universal vaccination because the group felt that physicians working in regions where Lyme disease is to be considered might want to have recommendations at their fingertips in order to consider vaccinations for their patients with exposure factors.

I just want to briefly go over the important things for the recommendations for this Committee that we presented in the ACIP. We are working with the previous publications, which was in 1991, which is published in the MMWR, and with various vaccines, specific recommendations since then. We are working with the ACP's Green Book, which was published in 1994 and which I believe is being updated, and we were working with the printed word of the -- ACOG's Technical

Bulletin which was published in 1991 and 1992. So you can see that we -- in this -- during this process of developing our adult immunization schedule, we are also helping our partners to update their own printed versions of the schedule of the immunizations that they recommend.

There are really -- There is only one real issue required for harmonization that still remains and which Dr. Neuzil is going to be addressing with the ACP, and this is to do with the Td booster. ACIP has recommended a decennial booster and the ACP had recommended, for persons who had completed the primary series, a single Td booster at the age 50.

And we were working on the footnotes and you will see in the footnotes for the age-based table, the footnotes included indicator conditions, the risk of exposure, the dose of the vaccine, and the interval between the doses on the bars. And for persons with the indicator conditions, which is the table that we're working on now, there are additional footnotes which indicate contraindications and special notes. For example, like there are higher doses for hepatitis B vaccination

for people on dialysis.

This is a work in progress. We are working on a companion table to the age-based recommendation which lists vaccinations recommended for people with chronic diseases and/or conditions. So we have the health status on one side and then the vaccinations as column headings and then the footnotes would indicate the contraindications and special doses, if needed. So we had been considering these, too, the age-based as well as the health conditions, as companion tables, sharing the same footnotes.

So here is what we have to do yet before January. We have to complete the table of immunizations recommended for persons with chronic diseases/conditions. We have to finalize the age-based recommendations which you have in your hand, which we hope to have some idea to do today. Dr. Neuzil will present the Harmonized Schedule to the ACP/ASIM Adult Immunization Initiative Physician Advisory Board on October 24th on the recommendations of this Committee regarding the draft schedule. And then for today, we're hoping that the Committee will consider

discussing the table, the content -- like the text on the bars, is it appropriate, is it too much, is it too little -- any additions, deletions, revisions to what you can see in the -- on the table in the tabular summary. Same thing for the footnotes, the overall appearance of the footnotes, the -- and we also wanted for you -- for comments on the overall appearance of the table and the color scheme or -- or the content, if you had any comments you could just pass it on to me. I'll incorporate that. And we would like to consider the publishing the age-based summary of the adult immunizations in the MMWR by January, 2002. Thank you.

DR. MODLIN: Thanks, Dr. Sneller. Natalie?

DR. SMITH: You mentioned American College of Physicians, but AAFP, the family physicians. I'm just curious what the story is.

DR. ZIMMERMAN: This is Rick Zimmerman. I think it's important that the American Academy of Family Physicians periodic health exam recommendations also be one of those things that's considered as we're looking at the harmonization. I also have a concern

on the colors, because as family physicians we see people across the life span. If there's one set of colors for pediatrics and a totally different set of color meanings, or at least substantially different, for adults, that creates a problem. And I would hope that we could use blue, pink, or something else so that we could have the same things mean the same things for both adults and children and not have green mean one thing for adults and another thing for children.

DR. MODLIN: So harmonization of the Harmonized Schedule. Is that right? Okay.

Before others -- Dr. Neuzil or Stan Gall, do you have any comments at this point?

DR. NEUZIL: No.

DR. MODLIN: Okay, Rich?

DR. CLOVER: Yeah, I want to -- appreciate Dr. Smeller's work in this because this is a major step forward. And in response to Rick's statement, we did use the periodic assessment table as a guideline to look at differences between the various organizations. That was part of the process.

DR. MODLIN: Thanks. Dr. Mahoney?

DR. MAHONEY: Two comments. One, this might be an opportunity for the obstetricians and gynecologists to participate in this Harmonized Schedule. I think they ought to be given the opportunity to come to the table and endorse these recommendations, much like the internists and the family physicians would be doing. My second comment has to do with just a logistical thing. Again, a lot of our members don't have access to color copies and there ought to be some consideration given to a black and white version, much like what has been done with the childhood immunization schedule. So just a suggestion that that be pursued, as well.

DR. MODLIN: ACOG is very much involved as a partner, are you not, Stan?

DR. GALL: We've been talking right along and agree with what's happening.

DR. MODLIN: Thanks. Peggy?

DR. GALL: We've, in fact, endorsed it.

DR. RENNELS: The childhood immunization schedule is entitled "recommended". Is this going to be titled "recommended adult immunization schedule"? If it is, then I would suggest you add, under Lyme, just at the

end, "may be considered," because it really isn't a frankly recommended vaccine.

DR. MODLIN: That's a good point.

DR. SNELLER: Dr. Neuzil?

DR. NEUZIL: I can comment on that. That's a good suggestion, Peggy. We debated this a lot, what to do with Lyme disease. I'd be curious to hear from people in the northeast. You know, being from a region where we simply don't use Lyme disease, I think we need to satisfy all regions of the country. The other thought would be to give Lyme disease another color with a different code. But I think you're correct, something to distinguish it is probably a good idea.

DR. MODLIN: Sounds like a good point and we need a little more thought as to just what that something ought to be. Is that --

DR. SNELLER: May I make -- May I make some comment, sir?

DR. MODLIN: Please.

DR. SNELLER: We had actually considered those wordings, and then the working group had decided not to use things like "considered," "strongly

recommended," but have a definite, you know, recommend, not recommend and so on. So they felt that the wording -- in the MMWR, the ACIP, they had said, you know, consider, discussed and so on and they --

DR. MODLIN: As far as I know --

DR. SNELLER: -- the working group --

DR. MODLIN: -- the ACIP is the only organization that has Lyme disease recommendations. Is that the case? Okay. Yes, Gary?

DR. OVERTURF: Yeah, I hazard to make a pediatric comment on this, but the meningococcal vaccine bothers me a little bit because in the June meeting, actually, it was discussed that one of the occupational risks would be to microbiologists, and that's not listed. The occupation is listed, but there's no definition of what occupation might be at risk and that one might want to consider that.

The other thing is that it's now a little inconsistent with our current Red Book recommendations on meningococcal vaccine, which is that we no longer consider splenectomy or asplenia a risk because we cannot find any data. Actually, I just was asked to

do a review for clinical infectious disease on this again and I cannot find any evidence -- never have been able to find in 25 years any evidence of a risk for asplenia in meningococcal disease. So you don't have to take my word for it, but I would ask that you might want to re-examine that, because it continues to be put up and it's perhaps -- there's very little evidence that it's a risk factor for toxemia.

DR. MODLIN: Good point. Yes, David Salisbury?

DR. SALISBURY: Thank you. Can I also add to that because we have the recommendation for meningococcal vaccine for people with asplenia and we can't find any evidence, either. So we are just as inconsistent. But there were a couple of points just -- if I could raise, Chairman. One of them is that it actually says that -- under the MMR section -- for rubella, one dose of MMR at least three months before pregnancy or immediate postpartum, but this I assume will be dependent on the discussion tomorrow where that may need to be changed.

DR. MODLIN: That's correct. We will be discussing this issue specifically tomorrow, which will be an easy

change to make, if necessary.

DR. SALISBURY: I was also interested to see that whilst two doses of measles vaccine are recommended, only one dose of mumps vaccine is recommended, and I wondered whether there was good evidence that seroconversion and duration of immunity with one dose of mumps vaccine was that much better than you got with one dose of measles vaccine.

DR. MODLIN: Sam, can you help us out?

DR. KATZ: I don't know of any data, David. Perhaps someone at Merck, Tom Vernon or someone, could help us, but I'm unaware of any data.

DR. MODLIN: Or Stan Plotkin?

DR. PLOTKIN: I think it's well-established that in actual experience, the efficacy of -- well, effectiveness of mumps vaccine has not been to the same level as measles and rubella. So there's at least some logic to a second dose of mumps in order to improve the efficacy.

Now, in terms of actual data comparing one dose and two doses in an effectiveness study, I'm not sure that I can recall that. I don't think I can bring that up,

so to speak, at this moment. But I would personally be in favor of two doses of mumps vaccine.

DR. MODLIN: Melinda, can you help us in terms of you knowing of the top of you head how many cases of mumps occur in adults in this country on an annual basis?

DR. WHARTON: Off the top of my head, I can't answer the question, but it's not many because there aren't many cases of mumps. It's annually down to a few hundred cases a year.

DR. MODLIN: So it may very well be that just our actual experience may help us --

DR. WHARTON: Well, I think that what we're seeing here is the residual of the previous MMR statement where ACIP recommended two doses measles vaccine and also recommended that, in general, that should be administered as MMR but, in fact, the Committee has never recommended two doses of mumps vaccine. And what you're seeing here is simply a literal representation of the existing ACIP recommendation.

DR. MODLIN: All right.

DR. LEVIN: How often --

DR. MODLIN: Myron?

DR. LEVIN: How often are we likely to see individuals that are lacking immunity to just one of these next -- because it would certainly simplify things if it collapsed at getting another dose of MMR or if you've never gotten two doses.

DR. MODLIN: It does, except it becomes an issue with pregnant women and rubella seronegativity, Myron, where we know that one dose of rubella vaccine provides virtually complete protection. I think that's the issue that's driven the one dose versus two doses, is my understanding. Is that right?

DR. SMITH: And we have a lot of issues regarding immigrants, too, that may have just gotten measles. I mean, they may be naturally immune to mumps or rubella, but as far as immunization goes, they may have just gotten the measles component.

DR. MODLIN: We've discussed this issue at some length at past meetings and this is where the two dose, one dose, one dose strategies generally occurred, and particularly around the MMR statement, which we redid two or three years ago -- about three years ago. Dr. Neuzil?

DR. NEUZIL: Just to make a general comment, we tried in every situation here to follow the MMWR recommendations, and people here are identifying some items that we did identify and others that we may not have that maybe this group needs to look at again. But for the purposes of this, we felt as if we had to follow what was published -- really to the letter, is what we attempted to do. So I think, for instance, the mening issues are important, but we can't disagree -- since we're saying this is the ACIP recommendations -- with the way it is written.

DR. MODLIN: That's a good point. We're raising many issues that relate to the underlying recommendations for the individual antigens and vaccines. Rich?

DR. CLOVER: I just want to underscore what she just said. I mean, it's really been a challenge, looking at inconsistencies and/or recommendations, without data that we've uncovered as we've gone through this process. And so an arbitrary decision -- well, it wasn't arbitrary. A decision was kind of made just to keep with what was in print. But I do encourage us, as we identify these issues, that we need to go back

at some point in time to re-look at them.

DR. MODLIN: Good point. Dr. Mahoney?

DR. MAHONEY: To get back to the question Dr. Neuzil had made earlier about how to deal with the Lyme, perhaps, again, in the spirit of promoting harmony between the childhood and adult Harmonized Schedules, some consideration might be given to putting in this red dotted line for selected -- these selected groups, to sort of separate them a little bit.

DR. MODLIN: Dixie?

DR. SNIDER: Thank you, John. Just to follow up on what Rich said, seems to me that one of the valuable functions that the ACIP serves -- and it becomes very transparent when you have the publication of a recommendation -- is the research gaps and the research needs. But what Rich is stating here is that when we do some other activities, too, like the development of this document, we identify other research gaps that don't necessarily get translated into a publication. And it would be useful, I think, to the agency -- to all the agencies, Carol's and Karen's and CDC, if we could have those things written down as important

research gaps that need to be filled.

And then having said that, I have a question for the people who are proposing this, and that is around the word "proposed", it came up earlier, and somehow that seems -- you know, as an internist, that seems a lot softer to me when the words that are used for childhood, which is "recommended," and if there's -- I wondered what the reasoning was to use what appears to me to be softer language --

DR. MODLIN: I was reading --

DR. SNIDER: -- when they're really not --

DR. MODLIN: -- "proposed" and "draft" in the same way and -- right here, quite frankly, Dixie, in the same way. I think we can change the title to be a little more directive. Dr. Salisbury?

DR. SALISBURY: Thank you. It was just to finish off my points that I'd netted from looking at this sheet. And on point ten, which is the meningococcal vaccine one, I found it a rather odd recommendation, really. It reads (Reading) Meningococcal vaccine, quadrivalent polysaccharide for serogroups A, C, Y, and W is recommended to control serogroup group C

meningococcal disease. That seems odd. I would imagine it was for control of disease from all four serotypes. So that, in itself, is slightly odd. And -

DR. MODLIN: Can we just cross out serogroup C?

DR. SALISBURY: I'm sure it can be easily -- easily amended. One of the prime indications that we have used in recent years is for contacts of group C cases, and I don't know whether that is what is included in that opening statement. It then seems to me to miss a very simple thing, and that's a bullet point that the travelers are included under occupational and other. And yet in numerical terms for the number of doses that get used, it's the travelers that seem to be one of the biggest groups for whom vaccination is indicated. And I would have thought for someone reading this it would be awful easier if they actually saw that point drawn into its own bullet point. I know it's a very minor bit of editing.

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

DR. NEUZIL: Yeah, those are all good points. I'd be curious to hear other people's opinion on the

outbreak control. We discussed that and decided as a group that this is really recommended for the individual practitioner and health care provider, and that perhaps outbreak control is a public health function that we don't necessarily want an individual health care provider making a decision about. That was our reasoning, but we're clearly open to -- to debate. That's --

DR. SMITH: I agree with you, Kathy, on that point, and also the childhood schedule that those are complex decisions that have to remain in concert with public health and I don't think we can spell out all of those for the various diseases in this kind of routine document.

DR. SNELLER: Dr. Modlin, may I make a statement on the

DR. MODLIN: Yes.

DR. SNELLER: We looked at the ACIP recs on the efficacy of the vaccine and it states clearly in the ACIP recs that this was recommended. It has been found to be efficient against group C and out -- preventing outbreaks. And Dr. Schwartz and I have gone back to

see whether -- I mean, there's a statement that says if the efficacy against other types is not -- is assumed to be just as effective. So we decided to keep to the word -- to keep to the printed word rather than having to quote published materials because what we were doing was summarizing the printed versions.

DR. MODLIN: Okay. It sounds like something that just requires a little bit of perhaps re-examination when we come around to --

DR. SNELLER: I think these points should be in the actual publication to identify these.

DR. MODLIN: Natalie?

DR. SMITH: Just another little point on that. On the foot -- maybe not so little. But on the footnotes, number seven under MMR, measles component, persons born in the U.S. are most likely have received two doses of MMR, and I'm not sure that's actually accurate, given especially that we're having outbreaks in California of measles in people who are in their twenties and thirties and clearly haven't had two doses of MMR.

DR. MODLIN: Other comments? Yes, Geoff?

DR. EVANS: I notice there's some more white space

on this series of recommendations, so let me again suggest that there be something about the reporting requirements and availability of both vaccine adverse in the reporting system as well as the compensation program. Just within the past week, even today, I've explained to people that just because you're an adult doesn't mean you're not eligible to file a claim for the compensation program because you've received a childhood vaccine, and I think still a lot of people don't know that.

DR. MODLIN: Yes, Dr. Foster?

DR. FOSTER: Steve Foster. You mentioned it earlier about not being -- having available a black and white copy, but actually most people may be actually taking something like this and photocopying it. So before the final colors are selected, you might want to throw one on the machine and see if it actually will copy.

DR. MODLIN: That's a good point, and actually that way we've been very careful to do that with the childhood immunization schedule, knowing that, of course, that occurs. And I'm sure that this will be taken into account before this is finally produced. Yes, Gary?

DR. OVERTURF: Under hepatitis A you have -- you have no indication for the CDC's recommendation for high-risk states. You have it for countries and travel to countries. I suppose if you're traveling to New Mexico, that might be considered a high-risk state. But I'm wondering whether you need to indicate that, because you were trying to follow the letter of the law in terms of putting all the indications down, and that's not indicated here at all.

DR. MODLIN: That's right. Dr. Neuzil, go ahead.

DR. NEUZIL: I'm not sure. I would honestly have to open up my hepatitis A recommendations again to remember this, but the universal in the states applies to childhood. Correct?

DR. MODLIN: That's right, two to 18, I believe.

DR. NEUZIL: Right. So I'm not sure it affects the age groups on our schedule --

DR. MODLIN: I think that's correct.

DR. NEUZIL: -- but correct me if I'm wrong.

DR. MODLIN: Where's Beth when we need her?

DR. NEUZIL: No, I think that's --

DR. MODLIN: I think you're correct. Yes, Lucy?

DR. TOMPKINS: Just a comment about the colors again. I think that anybody who is red/green color blind would not be able to distinguish the green from this purple stuff, and I think you should go to a different color scheme.

DR. MODLIN: Other suggestions?

DR. SMITH: Just on the harmonization issue again, it -- so is the idea that this schedule, one hopes, would at the bottom say approved by the various organizations, just like the childhood one does?

DR. MODLIN: Dr. Sneller, do you want to address -- You did indicate earlier kind of where we were going, but you want to kind of repeat where we're -- what the plans are for the next few months?

DR. SNELLER: I think that the only one that's pending is the negotiation with ACP, and Dr. Neuzil has a meeting scheduled for the 24th. And we do intend to put all the partners and the additional information like websites and the VAERS number and so on and so forth.

DR. MODLIN: So we might be able to finalize the ACIP portion of this in February. Is that right? Dr.

Zink?

DR. ZINK: Good afternoon. I'm Tom Zink with Glaxo Smith-Kline and I bring this question up because it was brought up earlier with the childhood immunization schedule. Is there room for a footnote about the new tool that Twinrix brings to the clinician if both of -- if the patient is worthy of both A and B at the same time?

DR. SNELLER: The working group had decided not to use any commercial names at this point. Maybe there's a decision later on.

DR. MODLIN: Well, I think it's certainly possible that if the working group decided it was a good idea to include the combination for whatever reason, you could use -- don't need to use the commercial name. Dr. Neuzil?

DR. NEUZIL: Well, I suppose we could make a similar statement, which I think is what you're saying. We could say license combination vaccines may be used whenever components are indicated and avoid the trade name.

DR. MODLIN: Do it in the same way that we do with the

childhood schedule.

DR. NEUZIL: Right.

DR. MODLIN: Okay. Rich?

DR. CLOVER: Just one comment about the process, because clearly the childhood immunization schedule is routine for the ACIP, AAP, and AAFP. This is a new schedule. So the approval process is probably going to be a little bit slower. Part of the thinking in some of the working group was to have the ACIP take the lead in what one would look like and then we would foster it to the other groups for their approval. Our full intent is to go after ACP, ACOG, and AAFP as the lead organizations, but there was some concern of how rapidly we get it approved with this being a new schedule for those groups.

DR. MODLIN: Okay. Yes, Jaime?

DR. DESEDA: Well, maybe I shouldn't be saying this at the time, but the fact that we're talking about meningococcal vaccine makes me wonder if we shouldn't mention that in the childhood schedule because freshman students who stay in dorms, this is recommendation from the

AAP -- you know, I think it should be considered under special situations or under the red line.

DR. MODLIN: You're suggesting that we include meningococcal vaccine under the red line in the childhood immunization schedule?

Perhaps -- Rich, do you want to respond or -- I'm sorry? We actually do not recommend it specifically for college freshmen. We encourage its use or encourage people to discuss it with their physicians and with college health providers, but we actually don't make that recommendation. And -- Well, I'll leave it at that.

Any other comments? Let me just congratulate you, Dr. Sneller and Dr. Neuzil and others, on a nice product so far and we really look forward to completing the work.

DR. SNELLER: If it's feasible then to have a presentation for the MMWR before January or should we present a draft for the -- during the February meeting?

DR. MODLIN: Oh, that was what I was asking before. I got the sense that it's going to be hard to publish this in MMWR as a Harmonized Schedule until it's truly been

harmonized. Is that right, Rich? And so I have a feeling that we'll have to -- almost certainly will revisit this as a committee before it's actually -- we can take a vote on it and it's approved by the other organizations.

DR. NEUZIL: I guess the issue is, though, as Rich said, in principle, if there are no major changes, it's easier for us going to the partner organizations, since they haven't done this before, is to assure them that this is unlikely to have any major changes at this point from the Committee. Is that fair?

DR. MODLIN: Speaking for the Committee, I would say yes. I think the Committee would like to finally have the opportunity to vote on the final product, but I don't hear any major -- drumbeats for major changes. Unless Dr. Clover has some.

DR. CLOVER: No, I don't have any changes, but the colors have been brought up several times and I'm not a color expert, but I would love some advice as far as what the colors should be because there are different issues in adults than there are in kids. And especially if you look at the one that's based upon

disease or health condition, the colors there are also important in our consideration. And so in going back to Rick's comment, the continuum, if we alter the colors in our form, do they need to be consistent with the childhood form? Please advise us.

DR. MODLIN: Okay. Dr. Sneller, thank you. The next item on the agenda is use of OPD to control outbreaks of polio. And here, Ben, I od have you as the primary presenter. Are you going to fill us in on what's happening in the Philippines?

DR. SCHWARTZ: I think what John was referring to is some cases of vaccine-derived poliovirus causing infections in the Philippines with, I believe, the most recent case occurring in July, several cases altogether, and this represents now one of several circumstances where vaccine-derived poliovirus has circulated, more close to us, in Haiti and the Dominican Republic, again, with the most recent case occurring in Haiti last July. So we know that poliovirus, either vaccine-derived or wild poliovirus, is still out there. And in the United States we have high immunity as a result of our successful vaccination program, yet

at the same time we believe that it would be important to maintain a stockpile of oral polio vaccine for use in a situation of a potential outbreak occurring. This was an issue that was discussed by the ACIP and voted on by the Committee and you recommended to us to maintain a stockpile of oral poliovirus.

What I would like to do in this presentation is to talk a little bit about our efforts to obtain that stockpile and talk a little bit about or progress toward reaching an investigational new drug application for OPV, a protocol for OPV use in an outbreak, and then some unresolved issues. And specifically, the questions I'd like the Committee to consider are, first of all, is the proposed investigation and vaccination strategy reasonable; and secondly, are there situations in the draft IND which I'll be presenting where IPV should be used rather than OPV. And the reasons are obvious, that IPV is a licensed product and also that it doesn't carry with it the risk of vaccine-associated paralytic polio. So where we can, clearly, we would like to use IPV, yet we, at the same time, have more experience with OPV for outbreak control, and again, that has been the

ACIP recommendation.

The recommendation for use of OPV to control an outbreak was published in the MMWR -- I think I got the date wrong, in that it was 2000 rather than 1998. There were several reasons advanced for that recommendation: first, the greater degree of seroconversion following a single dose compared with IPV; the decrease in intestinal replication of wild poliovirus following OPV in someone who's been infected with that poliovirus; the potential spread of vaccine virus to others, increasing immunity within a community, although in the United States, where sanitation is very good, that effect is likely to be minimal; and then finally, and perhaps most importantly, the successful experience that has occurred in other countries that have used OPV in outbreak situations.

In the United States, Wyeth-Lederle OPV remains the only licensed product, but no new doses of that product are being manufactured. There are about 850,000 expired doses of OPV remaining, and these are from several lots. Use of this product would require an IND in order for it to be administered, and quarterly

testing has been done on these doses on these various lots, the most recent test being done in September, and those tests have revealed that the vaccine remains potent. But FDA has data that indicates that the potency may soon drop off. Therefore ,use of this product would not represent a long-term solution to the stockpile problem. Therefore, CDC is contracting with another manufacturer for a long-term stockpile which also would be given under an IND because that vaccine is not licensed for use in the United States. The progress that we've made thus far toward an IND includes a teleconference with FDA in late August, discussing the draft IND for the Wyeth-Lederle product. In mid-September we received written comments from FDA and are currently revising the document based on those comments, and, simultaneously, we are working toward an IND for the other OPV product. I would like to move now into some of the specific recommendations included in the draft IND document, and I apologize for not getting those -- these to the Committee so that you would have time to review them before this presentation, but after we make the

revisions as suggested by the FDA, we will share the document electronically with the Committee and will look forward to any additional comments that you may have that you can't kind of give us off the cuff today, seeing it for the first time.

The initial step in an investigation would be to confirm the index case with laboratory testing. In other words, we won't base our implementation of this protocol only on a clinical case but would require laboratory confirmation. Information would be obtained from the case patient, including travel exposure and immunization histories, and at the same time we would begin to identify close contacts and obtain clinical and vaccination histories from those close contacts and obtain stool cultures from some of them. What we would propose initially is obtaining stool cultures from household contacts, other family members, day care contacts, and day care staff. In other words, young infants, those who are less than five years of age, where transmission of a fecal/oral agent would be more likely to occur. We are not at this time proposing that stool cultures for testing would be done

on classmates of an older child who may be a case, teachers for an older child, or on the health care workers who might care for these individuals. And I would be interested if there were any recommendations from the Committee for either more extensive or less extensive testing.

Pending case confirmation, IPV would be administered to close contacts of the case patient who had not been completely immunized, and this would provide the most immediate protection for those who would be most likely to have become infected. At the same time, there would be an investigation, an epidemiological investigation, done to identify the level of complete polio vaccination coverage in the surrounding community and also to identify whether there were any pockets in the community where much lower rates of vaccination might exist.

We had substantial difficulty in coming up with a definitive protocol outlining exactly who would receive vaccine during an outbreak situation, because those outbreaks may vary so much in terms of who's infected, how they became infected, what the community

is like, what the age is -- age or ages are of the cases and so on. Therefore, we felt three questions were particularly important in defining the vaccination strategies that would occur in response to a case. The first question is whether the case is a primary case; in other words, someone who's unvaccinated, incompletely vaccinated, or who is immunosuppressed and has a history of contact with the case or traveled to an endemic area. If the case is a primary case, it would suggest that spread within the community is unlikely to have occurred or to have occurred widely. However, if it is not a primary case or if there is evidence of one or more other cases, then significant levels of infection within the community are likely and the outbreak control strategy would be much more broad-based.

The second question that we would ask is what are the age groups affected, and poliovirus spread is most likely to occur between young children, although some past outbreaks -- for example, that which occurred in Israel in 1988 -- also involved adults, and clearly, that would have implications on the vaccination

strategy.

Finally, the specific outbreak response -- Oh, I'm sorry, I skipped the second point, which is what is the level of complete vaccination coverage in the community, is it greater than 80 percent or less than 80 percent? And coverage within a community of less than 80 percent would increase the likelihood that significant infection could spread within the community, again, mitigating toward a more broad-based vaccination response.

And then, finally, as I mentioned before, the specific outbreak response would depend on the epidemiological situation and the results of the cases, the community, and the environmental investigations.

This figure shows a first cut for what our proposed vaccination strategy would be, based on the characteristics of the outbreak, and I'd like to just walk through this slowly, or somewhat slowly. The characteristics of an outbreak may include the case being a primary polio case. In other words, someone who's unvaccinated, incompletely vaccinated with travel or contact with the case. There are no

secondary cases and there's no evidence of dissemination within the community. In that situation we would want to limit exposure to OPV to household and other close contacts who are less than 60 months of age, where IPV would be given to health care workers who might have been in contact with that case patient, and also to non-household close contacts who were 60 months of age or greater.

I'll pause after each one of these, and if there are comments or questions, I'd be happy to take them, unless you would rather I just go through them more rapidly.

DR. MODLIN: I think, Ben, maybe we should discuss the issue of using IPV as the appropriate vaccine for a first contact -- or for contacts of your first case. I guess, thinking it through, if the contact is immune for whatever reason, it doesn't matter whether you use IPV or OPV. That means they're non-immune, and if they're non-immune, it seems to me that OPV is likely to be more effective than IPV would in that setting, if that is your goal of protecting that individual. Sam?

DR. KATZ: I would second what you've said, John, not

only that it's more effective, but if you have a contact who is infected, injection with IPV is -- gives you the added liability of provocation paralysis.

DR. MODLIN: Other comments?

DR. SCHWARTZ: Okay. So I understand these comments to suggest in this case, all close contacts, rather than just the young children who are close contacts, would be better managed with OPV than IPV. Is that --

DR. MODLIN: The goal of the contact -- of immunization is to prevent disease in the contact, and that's -- you are making assumption the contact is non-immune.

DR. SCHWARTZ: Okay.

DR. MODLIN: IPV is a good booster, but as terms of providing primary protection with one dose, I think we would all agree that OPV is probably -- is preferable. Paul?

DR. OFFIT: I completely agree with that, although there are countries, I guess, that have never used OPV. Like, for example, Sweden, which did control endemic and epidemic polio in their countries in the 1950's with just an inactivated vaccine. But I agree with you, I

would think it wouldn't have been as quick to be --

DR. MODLIN: That's on a population basis and we're talking about a slightly different issue here.

DR. SCHWARTZ: I appreciate the input from the Committee.

The second scenario would be a non-primary polio case where no additional cases had been identified within the community and where more than 80 percent of the identified community had three or more doses of vaccine. In this situation, OPV would be given to household and close contacts who are young and I would take the same comment from the first line and include older close contacts, as well, as well as all children within the community who are less than 60 months of age and who are not completely vaccinated. In this setting, IPV would also be given to the health care workers and to unvaccinated or incompletely vaccinated persons who are greater than 60 months of age. The reason for using IPV rather than OPV in this population would be that their risk of vaccine-associated paralytic polio is higher than that for young children, and that they're less likely to participate in the

transmission of the virus within the community. But again, if the folks on the Committee feel otherwise, I would welcome that input.

DR. MODLIN: Again, let's take that -- it is, for reasons that Ben stated, the adult health care worker is going to be at less risk and therefore the risk/benefit ratio or the risk/risk ratio may be a little different with OPV. But still, the purpose is protecting the health care worker. And if that's the primary purpose, it seems to me that I would think that OPV would make more sense in this setting, as well, just for -- for starters. Myron?

DR. LEVIN: I would agree.

DR. MODLIN: Oh, okay. Paul?

DR. OFFIT: I would agree with that.

DR. SCHWARTZ: I thought health care workers washed their hands all the time and, therefore, would not be at risk. But perhaps that's not the case.

DR. MODLIN: Well, if that's the case, you wouldn't need to immunize them at all. I think if you're going if the purpose is to provide quick immunity with immunization, you might as well give it your best shot.

DR. SCHWARTZ: The third situation would be the same whether the case was a primary or non-primary case, and that would be in the setting either of additional cases or of community immunity of less than 80 percent. In this situation, the recommendations for use of OPV would be broader and would include unvaccinated or incompletely vaccinated persons who are greater than 60 months of age, based, again, on the epidemiological data, so that the specific age groups to be vaccinated would be guided -- vaccinated with OPV would be guided, in part, on the age distribution of the cases or, if the virus was identified from stool specimens, on the evidence of where infection existed. IPV then would be given to others who are not included under the OPV recommendation.

So what we tried to do for these three different levels of risk is to expand the use of OPV as we moved to a situation of greater risk within the community. We've already heard from the Committee that you think more widespread use of OPV would be warranted in the first two situations. Are there any specific comments on this third situation?

DR. MODLIN: Sam?

DR. KATZ: Not on that, Ben, but I assume that you are proposing this strategy for a time when we're still doing polio immunization in the United States. This is not after the global eradication --

DR. SCHWARTZ: Right.

DR. KATZ: -- and we have a susceptible, naive infant.

DR. SCHWARTZ: Right, that's correct.

DR. KATZ: Thank you.

DR. MODLIN: Other comments? Okay.

DR. SCHWARTZ: And then, finally, I would just like to share some thoughts about OPV use in young children in an outbreak situation.

First, the recommendation for use of OPV would be for those who are three days of age through 59 months, so that we would be including young infants who would not have been eligible to receive polio vaccine in a routine situation. The immediate action that would be taken where there was identified risk in the community would be to provide a dose of OPV to these young children, regardless of whether they had been fully vaccinated and had records available, whether they were fully

vaccinated by history but did not have records, partially vaccinated, or whether they were unvaccinated.

Where the actions would differ would be in terms of what the follow-up would be. Where someone who is fully vaccinated and had available records would not get further vaccination, those who did not have the records available at the initial contact with the health care system, they would obtain the records. Those records would be checked, and if they were fully vaccinated, they would not require a further dose. If they were partially vaccinated, these individuals would receive a second dose of OPV and then, if necessary, receive further doses from their health care provider and those doses would be IPV. And then if they were unvaccinated, they would also receive two doses total with OPV. And the question that I'd like to address to the Committee is, do you think that that's a reasonable recommendation for partially vaccinated or unvaccinated individuals, giving them two doses of OPV rather than just a single dose?

DR. MODLIN: And this is two doses spread four months

four weeks apart?

DR. SCHWARTZ: Four weeks apart, right.

DR. MODLIN: Comments? I see some general nodding of agreement.

DR. SCHWARTZ: Right.

DR. MODLIN: Any reason why -- I don't want to be picky here, but why three days as opposed to one day? I'm just curious as to the rationale for three days of age. Most infants, of course, are going to have passive acquired -- well, at least these days will have passive acquired immunity.

DR. SCHWARTZ: Actually, I don't have the answer to that question.

DR. MODLIN: Stan, do you want to weigh in on this? You've had probably more experience with newborn weights than anybody?

DR. PLOTKIN: May I weigh in on a few things?

DR. MODLIN: Sure, go ahead.

DR. PLOTKIN: First, the assumption here, it seems, is that you're using trivalent OPV. To answer the trivial question, if you are using trivalent OPV, you need two doses to have 100 percent seroconversion.

Okay. But more to the point, if you're going to IND's so that you're going through the whole process, why not go the monovalent, because now you have the situation where VDPV is a well-established phenomenon. It is -- We now know that it is not a rare event. And so if you introduce three serotypes in an epidemic situation, you are taking a risk.

Now, admittedly, in the U.S. with high levels of immunization, the risk of VDPV spread is less. Nevertheless, as I said, if you're going to an IND, why not go to an IND for monovalent material?

And the second reason for going to monovalent is the one that I just mentioned, that you need two doses of trivalent in order to be sure of seroconversion against the three types. So if you had a Type 1 outbreak, let's say, and you gave TOPV to population at risk, you wouldn't be sure that you would have immunized them all against Type 1 with the first go-around. So it seems to me that you have an opportunity here to reduce a couple of risks.

DR. MODLIN: Stan, doesn't that assume that you know the type of virus --

DR. PLOTKIN: Yes.

DR. MODLIN: -- that's causing the disease in the first place, for which for that first case or for these first few cases, it's going to certainly result in a lag in terms of --

DR. PLOTKIN: Oh, no, no, no, no. John, with modern methods, the lag is going to be 24 hours.

DR. MODLIN: Okay.

DR. PLOTKIN: I mean, you're going to know which serotype it is very, very quickly, as soon as you have a virus isolate, and maybe even before, using PCR. But two other points. One is that it's well known that the risk of VAP is higher -- was higher in adults. So now if you're talking about immunizing adults -- health care workers, et cetera -- you have the issue of informed consent, which may certainly influence the choice by the health care workers and -- all of whom, of course, should have been immunized against polio and therefore could receive IPV or OPV, as the case may be. And lastly, I agree with John. Three days -- you know, why three days? The birth dose commonly used in the third world -- you know, why not go -- to the newborn?

I mean, that was shown years and years ago that you could immunize newborns.

DR. SCHWARTZ: I appreciate all your comments. Let me try and address some of them, as I remember them. I think that the risk of spread of vaccine-derived virus in a highly immune population would be unlikely. I believe that the lots that are available from Wyeth-Lederle, the OPV lots that currently exist, are trivalent. This may make a difference when we talk about the future IND that is being established and whether those products could be kept in the monovalent form. With respect to requiring two doses for 100 percent seroconversion, I think I would ask the question of whether what we're trying to do here is trying to achieve 100 percent seroconversion, and those who are totally unvaccinated indeed would receive two doses; or whether, in the context of trying to stop an outbreak, a single dose, because it decreases intestinal replication and shedding as well as increasing immunity within the individual, would be satisfactory. As far as the three versus one-day issue, I think this might have been on the

recommendation of our international polio folks, but we can go back and talk with them some more about the data supporting use from birth, from one day of age versus three days of age.

DR. PLOTKIN: I think that's a good point that you just made about blocking the intestine. Indeed, you may be able to do that, but in relation to VDPV, a point I think should be borne in mind is that the likelihood is that if there is an introduction of polio in the U.S., it will be in an under-immunized population. And that specific population may be, in fact, a fertile ground for VDPV spread. So I would still make the point that you want to reduce the possibility of that from happening.

DR. MODLIN: Other comments? Suggestions? Sam?

DR. KATZ: I like Stan's proposal for monovalent for another reason, and that is, as far as we know -- aside from vaccine-derived strains -- there is no more Type 2. I mean, the WHO program has shown that there is no more Type 2 circulating anywhere in the world.

DR. MODLIN: Except for feral vaccine viruses.

DR. KATZ: That's what I said, except for the

vaccine-derived strains, so that selectively using Type 1 or Type 3 might have an advantage. And the other thing is, in an individual who is -- if you do have a vaccine-naive individual, if you feed oral vaccine, Type 2 replicates from the vaccine virus much more advantageously than 1 or 3, so you might be not protecting against what is the paralytogenic strain that your original case has. So I would give a lot of attention to Stan's suggestion of monovalent 1 and 3 being available as the first line.

DR. MODLIN: Dixie?

DR. SNIDER: Well, just in regard to that, I guess I wanted to ask Ben for clarification of whether he's asking for ACIP guidance with regard to the procedures for the remaining Wyeth-Lederle vaccine or -- and if that's the case, then there are obviously certain answers, or whether this would apply to both the old vaccine and any new vaccine, or whether he'd be coming back to the Committee with a new set of recommendations for use of any new vaccine.

DR. SCHWARTZ: I certainly appreciate the guidance of the Committee in whatever areas they decide to provide

it. I think it is important that we hear from the Committee about the monovalent vaccine because we are in the process of negotiating with the other manufacturer, and we can certainly include this in our discussions with them.

In terms of the specific protocol, we feel that it's likely that the protocol that we put together will be the same, both in this IND as well as in the other IND, although if there are issues of monovalent versus trivalent vaccine, we can certainly take those into account. So I certainly do appreciate all the comments that I'm receiving now.

DR. MODLIN: Ben, there's just one other comment I might make, then I'll let Neil have the microphone. That is that we need to keep in mind that even though clearly vaccine is -- I certainly wouldn't argue it's a preferable way to respond to an outbreak or potential outbreak, we need to remember that there are other ways to prevent polio and that immune globulins are also effective. And if for some reason you find yourself in a situation where you have no vaccine, plain old immune serum globulin or even IVIG is likely to be

effective in certain situations. Neil?

DR. HALSEY: I think you have to take greater consideration into the use of IPV in several different situations. I don't really agree with what Stan said earlier about the issue of not wanting to use IPV because of provocation polio. The first thing that's going to happen if there's a community -- such as my own city of Baltimore where immunization rates are not high -- if there is a case of paralytic polio and you really know that, I mean,there should be a -- an immediate demand to get children who are incompletely immunized or un-immunized vaccinated right away. And you don't want to turn them away from the clinics because you're afraid of paralytic polio from, you know, provocation polio. People should be informed that they should use IPV for children who are behind in the schedule.

There's also no reason that I know of, from the limited studies that are available, that you can't give both at the same time. I mean,we did one study with both at six months. Other studies have been done here by CDC staff, giving both IPV and OPV for either the first

or the third dose, and that seems to enhance the immune response. There's no evidence of any interference. So you need to be very careful about the messages that go out, and I would encourage catch-up as rapidly as possible for incompletely immunized children in that community with IPV. That's going to be available at site, at multiple sites throughout the city where this occurs. I don't know how long it's going to take you to mobilize and get the OPV, you know, from CDC to the community and then distribute it and so forth. There will be days of a delay, anyway.

DR. SCHWARTZ: I appreciate those comments. We also felt that the potential benefit of providing IPV to close contacts immediately, while a case was being confirmed, outweighs the potential risk of provocation polio. And also we felt that, since we were not discouraging all injections or all vaccinations, that there was no particular reason to discourage use of IPV in selected circumstances.

DR. MODLIN: Other comments? Tom?

DR. VERNON: Tom Vernon from Merck vaccine division. Ben, the practical implications of the 80 percent as

a measure of population coverage, how is 80 percent arrived at? How would it be measured if I were the epidemiologist there? Would I try to use the National Immunization Survey for the state or otherwise? And what would I define as the community in which 80 percent is measured?

DR. SCHWARTZ: You ask good questions, and I think all of those would be up to the team that was conducting the investigation in terms of how they would define the community and the population. As you know, there may be pockets of religious groups who may object to vaccine, surrounded by larger groups where the coverage is higher. So defining what the outbreak community is would be an important step to take. And as was done in the Netherlands, vaccination of a sub-community or an outbreak community, if you will, where the coverage is low -- less than 80 percent -- with OPV, with use of IPV in assuring complete vaccination in a broader community around that, may be a very reasonable approach.

With respect to your question about 80 percent and where that figure came from, I think we used it as the

proportion vaccinated whereby there appears to be good herd immunity within the community. I don't think that that's a particularly magic number, but that it's a reasonable guideline for public health personnel to use in deciding what the best response is to the outbreak.

In terms of how it would be defined, NIS is a possibility, or community surveys, or data that is present in the local or state health department may also be useful.

DR. MODLIN: Any other comments? Ben, is that adequate?

DR. SCHWARTZ: I do appreciate the input. I'd also like to mention that Joanne Kono, who has been the lead epidemiologist working on this in NIP, has taken a new position at CDC and will no longer be working on this, but certainly she has provided us a wonderful basis to move forward from. Thank you.

DR. MODLIN: Thanks, Ben. I understand it's going to be a little bit of time before we can make contact with Dr. McCormick for the next -- for the discussion of the IOM report which is coming up, so we're going to take

about a ten to 15-minute break before we start with the next item on the agenda.

(RECESS FROM 4:56 P.M. TO 5:13 P.M.)

DR. MODLIN: Can I ask everybody to please be seated so we can finish up the last item on the agenda? Could you please take your seats so we can get started?

(PAUSE)

DR. MODLIN: The last item we'll be taking up today will be the report of the Institute of Medicine Immunization Safety Review Committee which was just released to the public about two weeks ago, early in October. And we have Dr. Kathleen Stratton here, who is the Executive Secretary of the committee. Is that correct? Okay, fair enough. And I also understand that we've got Dr. Marie McCormick patched in by phone. Dr. McCormick, can you hear? Yes, thank you. In advance of this, Joel Kuriski [phonetic], did you have any -- or Dave Johnson is here. Dave, did you have any comments that you wanted to make before Dr. Stratton gives her presentation?

JOHNSON: We wanted to go straight into that presentation, then we'll take it from there.

DR. MODLIN: Sounds good, thank you. Dr. Stratton?

DR. STRATTON: Well, actually Dr. McCormick is going to give the presentation. I'm the PowerPoint operator, and you-all have a handout of far more than Marie is going to cover, unless she needs to go back and cover some things. So, Marie, tell me where you want me to start on the slides and we'll go from there.

DR. McCORMICK: I'll start with number one.

DR. STRATTON: That's up.

DR. McCORMICK: Let me begin by saying that the next sort of six slides in your handout -- five slides in your handout are -- is material that has been presented to this Committee before. It's really the information, for those who may not know, of how this committee was set up and what its charge is. As you'll notice, one of them, however, is -- we do have some choices citing both biologic plausibility and the hypotheses that we are being presented that indicates a relationship between thimerosal and neurodevelopmental disorders, and come to some conclusion about the causality and we'll finally the significance of the next step.

Biologic plausibility ranges from not plausible to established, and anywhere in between. However, there is no agreed-upon hierarchy of evidence or associated terminology that does exist for being able to do this hierarchy. It is a domain of intellectual and research inquiry and requires less stringent standards than proof-of-principle.

In thinking about the relationship between thimerosal and neurodevelopmental disorders, the committee reviewed a lot of evidence. First, they looked at what was known about the toxicokinetics of mercury and [inaudible] ethylmercury and methylmercury. They were also looking at the health effects of high-dose exposures to thimerosal, ethylmercury or -- and to methylmercury, and also look at the VAERS reports. There were no published epidemiological studies that we could examine. However, we did look at and had presentations on the unpublished studies of the VSD Phase I and II look at this issue.

Finally, we also looked at the health effects of low-dose exposures to thimerosal and methylmercury, looked at investigations related to mercury and heavy

metals in children with autism, and looked at the application of methylmercury exposure guidelines to thimerosal exposure from the vaccines.

To do this, the committee reviewed the published literature and information supplied by interested parties. We had an oversight at that meeting, commissioned background paper and comments, again had analysis of the VAERS reports, looked at some of the unpublished data and that had caveats in the report when weight given to such data. We had public access responsibilities in terms of people being able to contact the committee, and peer review of the report. I would say that not all sources of data were equally weighted, and I would also state, on behalf of the committee, that these [inaudible] published literature and unpublished data represent a fair commitment on that part. We actually had four three-inch ring binders of material that the committee went through, and I will say that the committee members did read the materials.

At the end of this process, the committee concluded that, although the hypothesis that exposure to

thimerosal-containing vaccines could be associated with neurodevelopmental disorders not that -- and it rested on [inaudible] information, primarily from analogies with methylmercury and levels of maximum mercury exposure from vaccines given in children, the hypothesis is biologically plausible. No direct evidence supports the hypothesis that thimerosal exposure from childhood vaccines in the recommended childhood immunization schedule has caused neurodevelopmental disorders. And the evidence behind that that is that no-dose thimerosal exposure has not been demonstrated to be associated with effects on the nervous system. Neurodevelopmental effects have been demonstrated in prenatal but not postnatal exposures to low doses of methylmercury. The methylmercury toxicologic information, particularly at low doses, is limited. Thimerosal exposure from vaccines has not been proven to result in mercury levels associated with toxic responses.

Signs and symptoms of mercury poisoning are not identical to autism, ADHD, or speech and language delay. Autism is thought primarily to originate from

prenatal injury. And no evidence that ethylmercury causes any of the pathophysiological changes known to be associated with autism, and there are no well-developed pathologic markers, markers of ADHD, or delay of speech or language that could be compared to effects of ethylmercury on the nervous system. Indirect information supports biological plausibility. High-dose thimerosal exposures are associated with neurologic damage. Literature establishes that methylmercury, a close chemical relative, as a toxicant to the developing nervous system. Some children who received the maximum numbers of vaccines on the childhood immunization schedule -- had thimerosal-containing vaccines on the childhood immunization schedule had exposures to ethylmercury that exceed some estimated exposure limits based on methylmercury federal guidelines. And susceptible or vulnerable to mercury -- and some individuals may be susceptible or vulnerable to mercury exposure due to genetic or other differences. The committee concludes, in terms of the causality argument, that the evidence is inadequate to either

accept or reject a causal relationship between exposure to thimerosal from vaccines and the neurodevelopmental disorders of autism, ADHD, and speech or language delay.

The committee bases the causality conclusion on the following: the available case reports are uninformative with respect to causality; there are no published epidemiological studies examining the potential association between thimerosal-containing vaccines and neurodevelopmental disorders; the unpublished and limited epidemiological studies provide only weak and inconclusive evidence regarding the hypothesis that exposure to thimerosal-containing vaccines may lead to certain developmental disorders.

We then have to go on to think about significance assessment of the relationship -- the potential relationship between thimerosal and neurodevelopmental disorders. First, the significance assessment concludes that immunization is important to continue against serious vaccine-preventable diseases. Neurodevelopmental disorders are pervasive and impose a significant

burden. Mercury is a well-know toxicant. It is not possible to predict if removing thimerosal will decrease prevalence of neurodevelopmental disorders. And there's no reason to believe that switching to thimerosal-free single-dose vial vaccines will pose a risk to children. Replacing thimerosal with less effective preservative in multi-dose vials may increase the risks. And decreased immunization due to fears may increase the prevalence of vaccine-preventable diseases.

So, in other words, there are a number of reasons to consider -- continue to consider the issues that thimerosal raises.

The reasons for continued public health attention are that thimerosal is used in millions of vaccine doses over several decades. There is a need for more evidence on the risks and benefits of thimerosal-containing products in use in the United States and elsewhere. Future concerns about thimerosal in the face of great uncertainty and how to make [inaudible] in the face of great uncertainty, and also to restore, maintain, and build trust in vaccines.

In terms of the committee recommendations, the committee supports the prior decisions in 1999 by ACIP, AAP, and AAFP to call for removal of thimerosal from vaccines as soon as possible as a precautionary step in the effort to minimize children's exposure to mercury.

In terms of thinking about this as a precautionary principle -- precautionary principles, when an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically.

In addition, the committee recommends the use of the thimerosal-free DTaP, Hib, hepatitis B vaccines in the U.S., despite the fact that there might be remaining supplies of thimerosal-containing vacs available.

We recommend that full consideration be given by appropriate professional societies and government agencies to removing thimerosal from vaccines administered to infants, children, or pregnant women in the United States.

Further, the committee recommends that appropriate

professional societies and governmental agents review their policies and about the non-vaccine biological and pharmaceutical products that contain thimerosal and are used by infants, children, and pregnant women in the United States.

The committee also recommends that policy analyses be conducted that will inform these discussions in the future. In particular, the committee recommends a review and assessment of how public health policy decisions are made under uncertainty, and whether the policies by which [inaudible] could be improved. The committee recommends a review of the strategies used to communicate rapid changes in vaccine policy, and it recommends research on how to improve these strategies. In terms of countries outside of the United States, the risks and benefits of the vaccines and practical considerations in other countries may lead to different conclusions regarding continued use of thimerosal-containing vaccines in other countries. And finally, the committee recommends a diverse public

health and biomedical research portfolio in terms of the risks and benefits of vaccines.

We'll move a little bit further and go on to slide number 45 with our recommendations for clinical research. The committee recommends careful, rigorous, and scientific investigation of chelation when used in children with neurodevelopmental disorders, especially autism, recognizing that chelation itself is not necessarily a benign intervention.

In addition, the committee recommends research to identify a safe, effective, and inexpensive alternative to thimerosal for countries that decide to switch from using thimerosal as a preservative.

And finally, the committee recommends research in appropriate animal models on the neurodevelopmental effects of ethylmercury.

DR. MODLIN: Dr. McCormick, thank you. I want to mention that the ACIP has formed a work group to discuss the implications of the IOM report and that work group has been active over the last week to two weeks. It's been chaired by Dave Johnson. The other members of the work group are Paul Offit, Bonnie Word, Natalie Smith,

Lucy Tompkins, myself, Gary Overturf, Stan Gall, Georges Peter, Rick Zimmerman, Joe Kuritski, Melinda Wharton, Karen Midthun and Lance Rodewald.

I'm actually going to turn things over to Dave to moderate the rest of the session. And I assume, Dave, that you'll probably want to have the members of the Committee and others address questions and comments to Dr. McCormick and to Dr. Stratton.

DR. JOHNSON: Thank you, John. First of all, we would like to take a few minutes to entertain questions and maybe have some answers or comments back from Drs. McCormick and Stratton. So I would open it up to the ACIP Committee members for questions about the IOM report or their process.

Good, we'll proceed ahead. It sounds like we had a thorough presentation then and we understand the process for the IOM report and what their conclusions and recommendations were from the IOM report.

As John mentioned, we did get together on several occasions by conference call over the last couple of weeks to discuss the implications and to try to come to some sort of recommendation for the larger

Committee. There are several issues that we'd like to bring up to further our discussion this afternoon and this evening. And I think, Joel, we wanted to have Dean Mason give us just a very brief update on vaccine supply as it relates specifically to thimerosal-containing vaccines, so I'll turn the panel over to Dean for just a moment or two.

MR. MASON: I want to basically cover two subjects. One is the surveys that we've done related to the amount and number of doses of thimerosal-containing vaccines remaining in our provider inventories, and also a very brief update on the DTaP supply situation, since the most significant portion of thimerosal-containing vaccines remaining nationwide are DTaP vaccines, and our present shortages may or may not influence thinking in that regard.

The first thing just to show very quickly is a picture of the progress being made in reducing thimerosal-containing vaccines in the United States. If we had gone back a little before April, the left side of this table, the thimerosal-containing vaccines and toxoid side, would be at a more pronounced. But

basically, in April of last year we had about 11 vaccines -- I believe that count is right -- 11 or 12 vaccines that were thimerosal-containing. And if you look at that picture now -- next slide, please -- if you look at that picture now, this is, of course, referencing only through CDC's contracts. Not all vaccines on the market, but through our contracts we are down to six products through our contracts that have to containing vaccine, none of which are part of the routine pediatric schedule targeting all children. This does not include tetanus, diphtheria, DT pediatric, other products that may contain thimerosal that we do not have CDC contracts for.

In order to evaluate a rough evaluation, if you will, of what was out there in real time with respect to thimerosal-containing product, we did a convenience sample of provider offices nationwide. This was a cross-sectional survey conducted the week of September the 10th, and we focused on DTaP, Hib and hepatitis B pediatric containing vaccines by -- as in the different states. They were doing vaccines for children or AFIX visits to provider offices. We asked them to do a

physical inventory, if you will, of provider refrigerators to record the number of doses of these type of products that were in the refrigerator. We later performed an analysis to determine if those were t-containing or t-free, based on lot numbers and cooperation of the vaccine manufacturers.

The results were across 16 states and three large urban areas, 225 site visits where inventories were conducted, the proportion of these -- 22 percent were public clinics, 31 percent private pediatric offices, pediatricians, 47 percent were family practitioners. Of the 65,909 doses that were evaluated, 5.5 percent of those products contained thimerosal. Now, in terms of -- Well, I'll hold off on that comment. Next slide, please.

If you're interested in where does this fall, the greatest number of doses of vaccine are the DTaP. The greatest proportion of t-containing vaccines is the relatively seldom-used DTaP/Hib combination vaccine which, as you're aware, is licensed for the fourth dose. We had -- These are the proportionate breakdowns reflecting the percentages of the t-containing by

antigen type.

Another opportunity we felt that we could do within the time frame necessary was a broad sample or a convenience sample of the t-containing product in two major depots with which multiple states contract for their vaccine distribution. These two depots are GIV and Delco. Each of them has contracts with between eight and 12 states whereby they store the vaccine and they ship the vaccine on behalf of those states as provider orders are made. We wanted to evaluate the t-containing products in these two depots, representing a multiple number of states.

And what this shows you is of the vaccine that was in the depots, only one percent -- which was considerably less than what we found in the provider offices -- only one percent of the total products, these selected vaccines, were t-containing.

Our explanation for that is that the depots have fresher vaccine, if you will. Theirs is the vaccine coming out of the manufacturer plants, whereas the provider inventories could reflect inventories that they had ordered several

months -- maybe even six, seven months prior to our analysis.

Of the t-containing product, 80 percent was DTaP vaccine, 14 percent was DTaP/Hib, and six percent was hepatitis B pediatric vaccine.

Now, to move over to what our DTaP supply situation is at the present time, in February of this year the ACIP was presented with information about the considerable back order of DTaP vaccine. In February 167,000 doses almost were on back order through CDC's contracts. This is not national supply. This is supply that we can evaluate through our contracts, which represent about 55 percent of the national supply.

In this analysis, in June the back order situation had considerably improved. It was down to 268,000 doses. However, in -- shortly after that, Aventis Pasteur announced that they would not be able to supply DTaP vaccine through the public market, and all of our supply dependency reverted or moved over to Glaxo Smith-Kline. In October, and this is very current, only several days old, you can see that we're at

786,000, I believe, 580 doses, so we're approaching more quickly than we like what we faced in February, which we were quite concerned about. Also you'll note that only in the space of a month, or actually about three weeks, between September and October our back order situation has increased by 50,000 doses. Instead of improving, it's deteriorating.

Now, when we talk about back orders, the CDC contract requires that manufacturers ship product within 15 days of the receiving the product -- receiving the order. Therefore, anything over 15 days means that it's a back order situation in violation of our contract and represents supply issues to the states. If we added, by the way, that vaccine which is under 15 days, our figure would be about 1.4 million doses back ordered at this time.

What is the effect of this on the grantees? This is self-reported information from 56 of our 64 grantees. The majority of those not reporting are Pacific trusts or Pacific commonwealths. The DTaP inventory in the central storage depots of the states of the grantees, in September we had four grantees reporting zero

inventory in their depots for DTaP supply, meaning all the doctors in that state, if they were to order, they could not get DTaP. That has further deteriorated whereby in October 15 of our grantees are now reporting zero inventory of DTaP, and indeed, 42 of our grantees are reporting inventories of equal to or less than 15 days' duration. So over 60 percent are in a critical situation with respect to inventory.

What's the projections for now through December of this year? The average national need for DTaP based on a four-year analysis is about 1.44 million doses per month. That's for all providers. We -- The company informs us that between October 1st and December 31st they feel they can fill about 1.64 million doses per month. If that, in point of fact, is true, then it won't completely address our back order and build inventories, but it would relieve some of the pressure that we are experiencing at this time. In point of fact, only about 61 percent of the orders that we are passing through to the manufacturer are being filled in a time-honored way at this time.

What's the outlook? We know that there are spot

shortages already occurring among provider practices. This may continue for the next three to five months, based upon our evaluation. The DTaP that we are being supplied is totally from Glaxo Smith-Kline. Aventis Pasteur is continuing to fill orders in the private sector, though they're filling no orders for CDC. They are expressing that they are limiting those orders to 80 doses or less per doctor per order per month. They will change that based upon justification of the doctor. We will -- Aventis estimates that they'll be able to start -- restart filling orders through our contract not until the second quarter of next year and we will continue to monitor our orders and work closely with the provider for the public contract, Glaxo, and try and prioritize our supply so that those most in need will be prioritized. Thank you.

DR. JOHNSON: Are there questions for Dean on current supply? Georges?

DR. PETER: Dean, thank you for that helpful information, and the information comparing September to October is particularly useful. I was wondering if you have any plans or any possibility of repeating the

survey in the providers' offices between September and say early November to determine whether the supplies are being rapidly utilized in the providers' offices.

MASON: We have the potential to do that. We have to go hat in hand to the states and ask that their labor forces out there piggyback this onto the visits they already have scheduled with the doctors' offices, but if this is something that the Committee has an interest in our continuing, we'll continue to do that evaluation.

DR. JOHNSON: Any other questions for Dean? Bob?

DR. CHEN: This is not a question but just a follow-up on Dean's presentation. We -- He did not present an alternative approach that we've been trying out and that is, instead of the labor-intensive look of convenience sample, can we use the reports to VAERS of actual use of different lots out there to estimate what's the remaining amount left from different lots. And from those projections, the initial look is very consistent with what Dean showed in terms of very small amounts being left out there, and that would be a fairly inexpensive way of repeating the analysis down the

road.

DR. JOHNSON: Thank you, Bob. We would like to take up to 20 minutes now for brief presentations followed by questions and answers from each of the four manufacturers that has an interest in this. And we'll start off with Glaxo Smith-Kline, and I don't know which representative is going to come from each manufacturer, so I hope they'll step forward.

DR. ZINK: Okay, good afternoon. I'm Tom Zink, representing Glaxo Smith-Kline. I'm the vice president of immunization practices and scientific affairs. And I'd like to thank the Chair, Dr. Modlin, and the Executive Secretary of course, Dr. Snider; Director of the CDC NIP group, Dr. Orenstein; and certainly Dr. Wharton, as well; all the distinguished members here at the ACIP and all the friends out there monitoring things today. Greetings to you all. I guess I'd like to -- Before I go into the thimerosal, I would like to not spring a surprise necessarily because I think Dean and my associate, Jane Quinn and Scott Harword, on the DTaP supply issue are working very, very hard together. And I've been informed

yesterday afternoon that CBER released 400,000 vaccine doses for us to help address the back order. And we think, and we've been told, that in another couple of days they'll open up another 400,000 for us to release again.

Our usual lot runs around 440,000, so that's where we stand, about -- within another week or so. If you pull together the graph tomorrow, perhaps it'll look a little better than it did this afternoon.

So in regards to the thimerosal issue, I'd like to quote Yogi Berra. He's one of my favorite quotable fellows in American history. He used to say you can see a lot if you just watch. And so I think that what Yogi was really trying to tell us is that you can learn a lot if you observe. And so what have we observed at GSK? The practice of immunization is one of the greatest achievements in the history of public health and disease prevention, we think. Recent events have made it clear to us at GSK vaccines that there is a continuing public concern regarding the use of thimerosal in vaccines. We observed, as well, that there is an absence of any reliable scientific evidence

demonstrating a causal link between thimerosal in vaccines and neurodevelopmental harm. So what have we learned from the observations? We've learned that -- and believe -- it is of the utmost importance to preserve public trust in our nation's immunization programs. So even in the absence of reliable scientific evidence of a causal link between thimerosal in vaccines and neurodevelopmental harm, what can we do?

Well, we at GSK first can and must be clear. The only GSK vaccine that contained thimerosal as a preservative in the U.S. is Andrax B adult and Andrax B pediatrics. Our Infanrix, DTPa and Havrix hepatitis A vaccine have no thimerosal as a preservative and never did.

Number two, we have worked diligently with the FDA to remove thimerosal as a preservative for our Andrax B brands, adult and pediatrics. And thirdly, we no longer distribute any vaccine in the U.S. in any presentation -- vial, pre-filled syringe, any presentation -- that contains thimerosal as a preservative.

Finally, we acknowledge that residual supplies of adult and pediatric Andrax B, with thimerosal as a preservative, may still be in circulation somewhere, perhaps in a practitioner's refrigerator or in a depot. So we are instituting a voluntary exchange program for adult and pediatric Andrax B with thimerosal as preservative. This will be at no cost to our customers. It includes only GSK Andrax B products, both adult and pediatric, of course, that have preservative thimerosal. And we will be conveying this to our customers within the next 24 hours, if it hasn't already occurred while we talk.

So, in closing, even though there is no reliable scientific evidence that demonstrates a causal link between thimerosal in vaccines and neurodevelopmental harm, this action is quite simply being taken to assist those health care practitioners who wish to have an alternative to help manage the current public concerns about vaccines with thimerosal as preservative; number two, to assure that there is no disruption in vaccine supply; and three, to help build and maintain the public's confidence in vaccines in our nation's

immunization programs.

Thanks for the opportunity to tell you what we're up to.

DR. JOHNSON: While you're still there, are there questions or clarifications that you would like?

(NO RESPONSE)

DR. ZINK: Thank you.

DR. JOHNSON: Next we'll call upon Merck to give us their perspective. Tom?

DR. VERNON: Tom Vernon from the Merck Vaccine Division. David, in fact, you took my by surprise. I was not expecting to give a report as such. I thought we would be responding perhaps to specific questions from the Committee.

The products from Merck, the Recombivax, the hepatitis B vaccine, contained thimerosal up until the latter part of 1999 when, in response to the concerns raised, there was a very rapid move to make the vast majority of our pediatric line Recombivax HB completely thimerosal-free. The contract for all thimerosal-free pediatric line with the Centers for Disease Control was discontinued in -- I think it was

April 1 of the year 2000.

We continued to distribute a syringe formulation of five microgram, which is our pediatric line Recombivax hepatitis B, until last month. A syringe formulation that is intended for clinics, school clinics, the employee programs, and the like, that has also been discontinued. That particular formulation constitutes a very small percentage of the total pediatric line. But as of this moment, there is no distribution of any thimerosal-containing vaccine.

GSK has raised the issue of being responsive to customers about a return policy. This has been under consideration. Over the last several days we've been talking with many, including your subcommittee, about that. A final decision has not been made on that, but it is -- has been discussed and we are going to be listening carefully to your deliberations.

DR. JOHNSON: Thank you. Are there questions and follow-up to that statement? Thank you very much. Wyeth is next.

DR. PARADISO: Thank you. Peter Paradiso from Wyeth-Lederle vaccines. I, first of all, would like

to congratulate the IOM on their report, which I have had the opportunity to read and study. Obviously, we're gratified that, as expected, there was no link identified between thimerosal in vaccines and neurodevelopmental disorders.

We have, as Wyeth-Lederle vaccines, responded as rapidly as possible to the Committee's recommendations regarding thimerosal over the past several years, and certainly will continue to do that. Our Hib titer vaccine is free of thimerosal, as is Prevnar, and those are our two pediatric base vaccines, and I'm sure the Committee will continue in their recommendations to follow the scientific approach that they've used so far and the public health interest in making their recommendations, and we'll abide by those. Thank you.

DR. JOHNSON: Finally, Aventis.

DR. HOSBACH: Good afternoon, this is Phil Hosbach from Aventis Pasteur. And Dave, I, like Tom, was not prepared to make a statement, but I was prepared to answer questions. But in light of what's going to occur in future discussion, I just want to update everyone or at least remind folks of what we've done

at Aventis.

In March of this year, we had approval for Tripedia with reduced amounts of thimerosal, similar to Smith-Kline's hepatitis B vaccine. So it's now termed preservative-free. So all products coming out of our plant for routine pediatric use under recommendations is now considered thimerosal-free, and that includes IPV, Hib and our DTaP and TDaP/Hib combination vaccines.

We, too, are waiting with anticipation to see what the ACIP will say. We'll take whatever you have into consideration and under advisement. We also want to let you know that we continue to struggle a little bit with our DTaP production because it was a quick changeover from a thimerosal-containing vaccine to a preservative-free vaccine, and we're also coping with the loss of not only one manufacturer in that arena, but also the loss of a manufacturer in Td where we're allocating tetanus vaccines.

DR. JOHNSON: Thank you. Jon?

DR. ABRAMSON: I guess very important to us in summation is understanding, after all of this, do we

have a shortage? Are we going to have a shortage of DTaP where we cannot meet the needs of our kids? And I still, after all of this, do not understand where we are.

DR. JOHNSON: I'm not sure that I have a simple answer to that. I don't know if Dean would like to take a stab at that. I may kind of divide up the question between do we have a shortage of DTaP or will we have a shortage of DTaP for children and will we have a shortage of DTaP because of a thimerosal-related issue.

DR. ABRAMSON: Right.

MASON: I think, with that respect, whether it's thimerosal-containing or thimerosal-free, if you define shortage as the doctors' inability to serve all children who are eligible for DTaP at the time of their visit, we are experiencing -- in different parts of the country -- that type of circumstance at this time. Exactly when the time frame for that being cleared up will be is open to debate. We optimistically would say that it will be corrected before the end of the year, but the projections that we've stood before this Committee and given in recent past have not borne true

in practice.

DR. JOHNSON: John?

DR. MODLIN: Just a follow-up question to Jon's question and for Dean and perhaps Walt, the question is with identified proportion of remaining doses that are thimerosal-containing that you've identified where we have at least a guesstimate, what's the likelihood that those remaining supplies will contribute to the alleviation of any shortage? I know it's an unanswerable question, but I guess a feeling for how important those remaining supplies may be.

MASON: I suppose, Dr. Modlin, I would turn it around and say what will be the issues faced if we discontinue immediately the use of all the product in the inventory if we're having problems filling the inventory as is, how much more of a problem will be have if we place a moratorium on that particular t-containing DTaP.

DR. JOHNSON: Now, rephrase the question.

DR. MODLIN: Walt, we're going to default to you.

DR. ORENSTEIN: I think if you look at the -- what's in the provider offices, about ten percent -- nine percent, I think, if I recall the numbers correctly --

of their DTaP was thimerosal-containing. So I think if you have an immediate cessation, I think that would be a substantial problem. Obviously as each day and each week goes on, it becomes less relevant. The shortage will be independent of thimerosal. It's only as of the time we did it where I think a ten percent drop -- plus that's probably not at even nine percent, but we don't have -- I think Dean said that some states had as much as 16 percent, is that --

MASON: Sixteen percent was the highest in the range that I saw.

DR. ORENSTEIN: Sixteen percent, so -- and there's likely practices with substantially higher, so I think but as I said, I think that will be a transient issue. The problem on the DTP -- DTaP shortage will be independent of what -- of thimerosal.

DR. JOHNSON: I think your question, John, and your response, Walt, are a good jumping-off point to tell you a little bit more about the deliberations of the work group and to move us along in our discussion as an entire Committee. We did have some very rich

discussions on our conference calls over the past week and a half, and essentially, we deliberated or considered six different options. I want to mention those to you and then mention sort of what was the product of our deliberation.

The first option was immediate cessation in use of vaccines containing thimerosal, right now; come out with a strong recommendation to stop using thimerosal as a preservative containing vaccines.

Second option was along those same lines, but maybe less definitive, expressing a preference for thimerosal-as-a-preservative-free vaccines.

Then a series of other options, the first based on establishing a date, such as a January 1st, 2002, after which a preference or a recommendation for use of only t-free vaccines. An age group was another option that we considered, focusing on either children less than six months of age for t-free vaccine administration, or less than 12 months of age for t-free vaccine administration. We considered the notion of doing this by vaccine and saying okay, it appears that we have very adequate supplies of thimerosal as a preservative

in Hib vaccines or free in Hib vaccines and in hepatitis B vaccines, but with DTaP that may not be the case, so let's have a preference or a recommendation for Hib and hepatitis B vaccines that are t-free.

And then the sixth option was to essentially continue with what is the current ACIP statement developed in 1999 and renewed or furthered in 2000 and actually in 2001.

We, at one point in our deliberation, felt like we had a pretty good consensus on the work group around one of the options. It became clear thereafter that we didn't have as full a consensus among all the contributing parties that we might have liked. So what we'd like to suggest is that we have a process for adopting a joint statement and that we set up some principles to discuss with you now for developing that joint statement. And I'm going to turn a few minutes over to Roger Bernier to talk with us about a process, and then I'm going to review some principles and ask you for your input on principles for a joint statement. Roger?

DR. LEVIN: John, while he's coming up, I didn't

understand the significance of something that was said by GSK, that 800,000 new doses of vaccine were just released, is that -- is that -- did I hear that right and is that --

DR. MODLIN: Dr. Zink, do you want to clarify or -- for Dr. Levin?

DR. ZINK: Say the question again, please.

DR. LEVIN: You announced that the FDA had just released a large number of units of vaccine, and are we counting that in our concern about a shortage or did I get that wrong?

DR. ZINK: No, Dean -- is he still here?

DR. JOHNSON: He might be behind the projector.

DR. ZINK: I'm not sure. I don't believe that Dean had that figure because he -- and I think Karen's shaking her head no, too. Did you have the 400 that was released yesterday afternoon in your graph of the 800,000 that are -- or near 800,000 backlog?

MASON: Right, we did not reflect pending lot releases in our estimates.

DR. ZINK: And it just was released yesterday and we have another pending lot in two days, perhaps, a day

and a half or so.

DR. LEVIN: because that would certainly change the equation a lot in a short period of time.

DR. ZINK: Right. You know, the process --

DR. LEVIN: Providing you can move it out quickly.

DR. ZINK: Right. And -- well, I think it's the best way to say it. It -- Those lots are released and we're working diligently and the line are producing and -- but they still need to be checked through protocol, and that takes some time, as well. But we do have that to report in terms of pending lot, and Dean did not know that, even though we met with Dean -- I guess it was yesterday morning -- we didn't have the information ourselves. So the lot release -- the question was, what is the size of the lot that may be released in two days, and it's my understanding, again, 400,000 or thereabouts. Yes?

DR. ORENSTEIN: I was just going to ask, Tom --

DR. ZINK: Yes?

DR. ORENSTEIN: -- what the real key is is how much that contributes to the general need and how many doses you

are putting out into the system, and so, for example, how many doses -- I think Dean said we needed I think 144 million doses --

MASON: A month.

DR. ZINK: A month.

DR. ORENSTEIN: -- a month. How does that contribute and how many doses, for example, will you have out in October total, and not just -- It's very difficult, at least for me, to understand what a single release of 400,000 or another 400,000 means if it doesn't influence the rest of your production during October.

DR. ZINK: Sure, yeah. I think Dean might have a better handle on that actually because he's been studying just the trending and so on. Do you -- You're nodding at me like you have that answer.

MASON: I think the projection is that 38 percent of the product that's going to be delivered between October 1 and the end of the year will come out in October, so it's not -- so the front -- The good news is that it's being front-loaded. The bad new is that that 62 percent that will come out in November and in December -- and this is if everything goes perfectly.

And I don't want to be a nay-sayer, but you know, we have had a continuing setbacks in what our projections versus our experience have been in the recent past, and that's no reflection on Glaxo, which stepped to the plate and is indeed providing beyond what they had originally agreed to provide on the CDC contract. It's just a reflection on the situation. But 38 percent of that figure will be distributed in October if all goes well.

Now, in terms of equitability among the states and in terms of how much of that goes to the private sector and to the public sector, there's all sorts of questions in this regard. We obviously -- 800,000 doses is -- will certainly help. But we're facing 1.4 million doses as of today in total vaccines that are sitting waiting to be filled and 67 percent of that is over 15 days duration, and that's just for the public sector.

BERNIER: I'm Roger Bernier from the National Immunization Program and I'd like to describe a process that we have discussed for moving forward. The reason for this is that perhaps it's a little bit misleading. We're not asking you today -- will not ask the ACIP to

vote on one of the options that Dave Johnson presented to you. We feel that we're not quite ready to do that. And if we engage in that kind of discussion, we probably would not reach closure. So as an alternative to that, we also realize that we would prefer to develop a joint statement, because that was how we proceeded when the thimerosal episode began in July of '99. We also had a second joint statement which included the American Academy of Pediatrics, the American Academy of Family Physicians, the ACIP and the public health service agencies. We did the second statement in July of -- or June of 2000 and we feel that we should end the transition by developing a third joint statement. Could I have the first one -- second? Now, there is widespread agreement. Not everyone is unanimous that we should respond to this IOM report. We are thankful to the IOM for the good work that they have done because remember, we have asked for this because there are issues of public trust around screening and prioritizing the many allegations that are surfacing about vaccine safety. And because of concerns that we've had about public trust, we had asked the IOM to

help us with this, and we're grateful for the work that they've done to try to help the immunization community with some of these issues.

Now, responses will be generated to all the recommendations of the IOM. As you recall from Dr. McCormick's presentation, there were several. But today the focus is on the recommendation -- the one recommendation they made to use thimerosal-free or vaccines with only trace amounts for DTaP, Hib and hepatitis B. This IOM recommendation, in case you haven't fully realized it, is different from the existing recommendation of the ACIP that was reaffirmed that you could use either t-containing or t-free as recently as June of 2001.

Could I have the next transfer? Oh, go back one second. I'm sorry, there were two on that slide. The second point, about which there is widespread agreement, is that following a review of the IOM report, we should issue a unified policy position, as we have done in the past. And basically, because of the controversial nature of this, to put it most succinctly, I think, the feeling has been on the part

of many that the government does not want to be issuing recommendations without the support of the pediatricians and the physicians, and the physicians and -- family physicians and pediatricians don't want to be out there making recommendations independently of the government. So there's a really strong-felt need to try to maintain a unified position on this issue. Next slide.

Well, this is ironic, because as you can sense, we aren't totally in agreement. There's a lot of differences of opinion. And instead, what we're calling for is a unified policy. It might be -- seem a little strange, but perhaps the -- because there are so many divergent views and so many strong feelings, I think it does re-emphasize the need for all of us to try to stand together, because otherwise this could complicate the delivery of immunizations and could lead to drops in immunization coverage. So we want to make a very strong effort to try to reach that kind of unified position.

Well, how do we do that? We've just said we're not going to vote on options today. The idea that we have

for this is to try to use a process that will result in a joint statement. And the approach that we propose today is to create a framework which includes a description of all of the points of agreement that we have on this controversial issue, and that we use these points of agreement as guiding principles, if you will, which we would then charge a drafting committee to use these guiding principles and this framework to actually develop the joint statement. And that was what we propose to accomplish in the time we have for discussion today. You should now be receiving, if you haven't already, a copy of this framework, which includes five main general principles that we believe there is widespread agreement on. And we say this not without any evidence, but based on the conversations that have taken place over the last two to three weeks since the release of the IOM report. The ACIP work group that Dr. Johnson chaired also had liaison members from the other organizations, so we have heard from a fairly wide group of people and have heard a widely representative set of views. So we would like to have your input into this framework this afternoon to either

add or subtract or fine tune this document and then we will charge a drafting committee to create the -- develop the joint statement.

We're going to start this evening. If we're lucky, we may have something to show you tomorrow morning, which the ACIP could then review and then we will share with the other four organizations that we are trying to reach consensus with. That's the AAP, the AAFP and the Public Health Service, which includes the Food and Drug Administration, the NIH, the NIP and HRSA, at least those four we think will want to participate directly, and maybe another agency or so that feels that it wants to get involved, but at least that's what we mean when we say PHS. It's really four -- four different -- at least four different groups.

I think I'm jumping ahead here, Diane. Let's move on to the next one.

David Johnson, after I complete my presentation, then will lead the discussion on these -- on this framework document as soon as I finish.

Go on to the next one. I may have covered some of these already. Okay, I got that, too.

We plan to call what we develop either tonight, or we would like to commit to doing it within a week, the provisional joint statement. And then following that development, we will share that with all the four organizations and also we're prepared to share this with vaccine manufacturers and other key stakeholder groups to harvest their comments on the provisional joint statement. We will then incorporate -- you want to move on, Diane? We will incorporate those comments into a final -- into a final statement. I think we're still one behind, go ahead. Yeah, a courtesy copy of this provisional joint statement will be shared. So let's say that either tomorrow or in a week or so we will have this provisional joint statement. We'll then get your comments and we'd like to commit to trying within 30 days to then get the final approval for this document from the four organizations that we're talking about. Next?

And then we would plan in approximately 30 days to publish this document, put it up on the internet and publish a notice to readers in the MMWR, and that will represent the joint statement response of these

organizations to the IOM's report.

I think the last one is a timetable that I've already described about how we might accomplish this.

So that's the idea. We think we can make progress on that this afternoon, and I'd like to ask Dr. Johnson if he could now lead the discussion on the document that you have, if you'd like to try to suggest revisions or modifications.

Just one other point. We made a distinction between sort of key guiding principles of which I believe there are five on the document. But then there are other things that people felt were very important points to make in the statement, even though they're not in the same genre of being a guiding principle, but they are very important points. I think those are on the back of your sheet, and people may have others similar to those that they would like to make. Thank you.

By the way, we've done this twice before so that's how we know we can do it again.

DR. JOHNSON: Before I start to talk about these so-called guiding principles and communication -- major communication points, before I start to get your

feedback on these, are there questions on the proposed process? That was pretty clear and straightforward what Roger presented, but I want to make sure there was no question on the proposed process for making a provisional joint statement and arriving at what we hope would be a final joint statement in fairly short order. Please.

DR. VERNON: If I may, David, speaking for the four -- the four companies, I would assume that stating that a courtesy copy will be provided is not a signal that there would not be an opportunity for input into the discussion as it goes forward.

BERNIER: We have -- certainly meant by that that we would consider the -- your comments, but not be under obligation to accept them. But we certainly intend, by inviting them, to also give them fair consideration.

DR. VERNON: Absolutely, thank you.

DR. JOHNSON: Okay. I have -- you have these in front of you. We'll also put them up on the screen as I go through them briefly, and let me try to get through all of the five guiding principles and then our two major communication points and we'll start to get your

feedback, your additions, your refinements to these. The first is, we have a general agreement that it is important for us to come out with a single unified policy position for completing the transition that was started in July of '99, reinforced in June of 2000. The second one, still on this slide, the main purpose of this joint statement is to state how the transition from using vaccines that contain thimerosal to using vaccines without thimerosal or only trace amounts should be completed, should end. Next.

The transition -- we have general agreement -- should be completed as rapidly as possible to eliminate the theoretical risk of harm from thimerosal-containing vaccines. And as rapidly as possible, of course, is something that would have to be I think considered and maybe clarified.

The transition policy should cause children to experience no delay. In my thinking, this is a particularly important principle. The transition policy should cause children to experience no delay in receiving their scheduled DTaP, Hib and hepatitis B or any other vaccination. So the transition to t-free

vaccines should not cause children to experience delays in receipt of vaccinations.

The transition policy should pay particular attention to the current and anticipated vaccine supply at various levels, whether we're talking national, state or in the community, maybe even more particularly in a provider's office, and should not seriously jeopardize vaccine availability, even at the provider level.

In addition to the five guiding principles, there's important communication messages. The transition should be completed in such a way that we're emphasizing that this is precautionary in nature and not driven by evidence of harm to children from these vaccines that contain thimerosal as a preservative. And we should continue to emphasize that message that we've put out in previous joint statements that these vaccines that contain thimerosal as preservatives that we're phasing out of are still considered to be safe and effective, no less safe and effective now, in October of 2001, than they were in July of '99 or thereafter.

Those are the five guiding principles and a couple of

communication messages. I think I saw Bonnie's hand first of all and then John's.

DR. WORD: The question I have or comment is on -- I'm trying to find the point, where it is -- oh, it's number two -- no, number four, thanks. When you talk about there's no -- experience no delay in receiving scheduled -- and my question is, can that be changed to or influenza vaccination, because there are some children right now, even though we haven't -- now we're thinking of things in the future, but right currently there are some children that yearly influenza vaccines are a part of their routine schedule.

DR. JOHNSON: Thank you for bringing that up. That certainly was an important point in our work group discussions that even without anticipating what this Committee or others may suggest vis a vis broader influenza vaccination for children, there are clearly children for whom we are strongly recommending influenza vaccination right now. The products that we have available in this country do, for the most part or exclusively, I think, to this point -- contain thimerosal as a preservative. We do have, in that

guiding principle number four, or any other vaccination. Are there others who would like us to clarify any other vaccination to explicitly state influenza? John?

DR. MODLIN: I was going to say exactly the same thing that Bonnie did, and since there are children for whom influenza vaccine is clearly strongly indicated, I think it needs to be included -- either here or we say somewhere else as a guiding principle that this statement does not apply to influenza vaccines. You could do it either way.

DR. JOHNSON: Paul?

DR. OFFIT: Right, in -- on number three you say that the transition should be completed, as stated in July of '99, as rapidly as possible to eliminate the theoretical risk of harm from thimerosal-containing vaccines. Am I correct in understanding that that theoretical risk is based on the fact that it was possible that children could receive enough thimerosal-preservative-containing vaccines that they would have exceeded the EPA's guideline for, you know, for a safe limit, but not obviously above WHO or

FDA or, for the most part, ATDSR? Is -- How many children is it that you all are anticipating are going to be receiving vaccine - - who are receiving vaccines now that exceed the EPA guideline? In other words, the -- is that -- when you say theoretical risk, is it that guideline that you're referring to? And if so, how relevant is that now to what's going on out there?

DR. JOHNSON: I have some thoughts, but Dixie, you may want to respond to that specifically.

DR. SNIDER: Well, I'll -- Yeah, I'll respond to that. I mean, I think that the -- that was one issue, but one communication point I would like to include is what progress we've made in terms of removing thimerosal from vaccines and how little would be contained in -- let's say if you had to have one DTaP containing thimerosal. But I think the more important concern that many people have is the fact that vaccines aren't the only source of mercury. And so the issue in the larger context, if I understand it, from the AAP, Environment Health folks, had to do with the overlay of vaccine mercury on top of all the other exposures. And so that was a consideration, at least in the

discussions that we had at the AAP board meeting about the, quote, theoretical risk. It was vaccines in combinations with other exposures.

DR. OFFIT: I think once you, I guess, go down that path, however, you bring up the notion then that any quantity of mercury that is -- to which the child is exposed in addition to what is the environmental exposure is potentially harmful. And that's where you start to separate then thimerosal preservative-free vaccines from thimerosal-containing vaccines. Because you know, the fact is that thimerosal is part of the process for many vaccines, and then you're left trying to explain the difference between, you know, microgram or nanogram quantities to the -- either the provider or to the parent. You know what I'm saying? It's -- If that's the reason, then I think we've started to enter into a very slippery slope.

DR. JOHNSON: Paul, to finish this part of our discussion, would you prefer modification of that guiding principle that changes the last clause to something along -- to reduce -- to further reduce the amount of mercury that a child may receive, not only

from vaccines, but from the environment generally?

DR. OFFIT: Well, I mean,-- I just -- If you're going to talk about trying to reduce mercury, then I think we should take, you know, thimerosal completely out of vaccines, including any trace amounts of thimerosal, if you're worried about any excess amount. Which is obviously not a practical thing to do and would seriously compromise the current, you know, vaccination programs that we have. So I just -- I guess I worry about this in the sense that we're saying we're trying to eliminate a theoretical risk, which I think has largely been eliminated.

DR. JOHNSON: Maybe not right at this moment, but I'd call upon you to try and think of how you'd modify this guiding principle for the drafting group then, if you could do that.

DR. SNIDER: Yeah, and David, one of the other things, though, that I was going to say that I think needs to be part of the communication is, again, this issue of benefit/risk and, although it's implied in some of the statements, it clearly needs to be communicated -- since I assume that we're not going to react immediately

by saying we're, as of tomorrow morning, going to go to thimerosal-free vaccines -- that we judge that the risk of -- from some of these statements, delays and so forth, that we judge that the risk of harm to children from their not getting vaccinated far exceeds any risk, if there is any, from the thimerosal. And that needs to be stated, I think, very, very clearly in the --

DR. JOHNSON: Dixie, I think then you've suggested maybe a couple of other communication points then to go along with the joint statement that we hope we can arrive at. A communication point about the remarkable progress that's been made in removing thimerosal from vaccines, and a statement that emphasizes once again the benefit of vaccination versus the theoretical risk or something to that effect of use of thimerosal-containing vaccines.

Jon, you had your hand up?

DR. ABRAMSON: Yeah, I want to get to the point number three, as rapidly as possible. I bring you back to 1999. It's a different set of circumstances. In 1999 we were exceeding at least one -- well, we were exceeding one of three guidelines. We knew that. We

are not any longer doing that.

Number two, the IOM report notes that we have a problem and we don't know how to deal with crisis effectively. Why are we putting ourselves in the crisis mode again at this point when we've effectively dealt with the problem of exceeding any of the guidelines? If the problem is, as the COEH might suggest, that we also eat fish, then why are we not dealing with that issue? Fish is a bigger problem by far and away thana the remaining thimerosal in vaccines. So I don't understand -- I don't understand, why are we in crisis mode again?

DR. JOHNSON: You've raised two points and maybe a question. I see Walt's hand. I'll turn to him first.

DR. ORENSTEIN: I think we have a new report, and we have a report from a group we've asked to review the issue, and I think we need to have a response to that report which basically called for, as I understand it, a fairly rapid changeover, and so I think there is a need to have some sort of response, and quickly, as this recommendation from the IOM comes out -- is disseminated more widely.

DR. JOHNSON: I would characterize it a little bit differently than crisis mode. I don't consider this to be a crisis. But I do agree with Walt that we're obligated to have a timely response to this and to lay out a course of action thereafter.

DR. ABRAMSON: Again, we have laid out a course of action, and that action has been very effective and will soon take care of the problem, no matter what. We are really turning a blind eye to a more major issue, which is the total mercury consumption of our population. And again, I still do not understand -- I understand the IOM came out with a report, but it is a report. It's a series of recommendations for consideration.

DR. JOHNSON: Yeah, a number of us in our other roles try to address mercury and mercury exposures from other sources. I don't know that this Advisory Committee can grapple with that head-on. I do think we are faced with a report from the Institute of Medicine that calls essentially for immediate cessation of vaccines or use of vaccines that contain thimerosal. If we don't do something to say we're underscoring our current position and continuing with that, we hastening our

transition, if we don't address that in some way or another, I think we leave many questions open. And I saw -- Rich and then Gary and then Paul.

DR. ZIMMERMAN: Rick Zimmerman. I also think that it's -- and I'll have a similar opinion with this with my colleague sitting next to me. There is an issue. There are times there are emergencies. And our Academy, AAFP, is prepared to really move ahead and very quickly with communications that are of an urgent nature in assisting. And we have to make sure, though, there are other things that are not quite as urgent. And I sense in the time laid out that, you know, there's still this sense of urgency. And in the days of terrorist incidents and anthrax and many other things, I think we need to -- not everything is an urgency or an emergency. And if everything is an urgency or an emergency, then nothing is because you can't prioritize. And we stand willing to quickly communicate on those things that are really urgencies and emergencies, but we need to be careful not to make everything in that category.

DR. JOHNSON: Thank you. Gary?

DR. OVERTURF: One of the things I'm concerned about with the approach in here is that we're actually -- by reacting the way we're reacting, with a statement, it sounds like we've done nothing. And so there needs to be a re-statement that our initial plan was, in effect, a very good one and it's been highly successful. I agree with Jon on this, and maybe that's all that needs to be re-stated. And a re-statement that the goals, which are mutually agreed-upon by us and the IOM report, will be met in a reasonable time. We may be able to come up with some predictions based on what we know about in terms of what thimerosal-containing vaccines are still present and which vaccines -- and how long it will take to liquidate those, because it sounds like it's going to be a very short time, based upon the fact that we have a shortage. We're arguing about an issue here of whether we want to use a remaining supply, a very small remaining supply, and whether that's consistent with our original plan and whether it's really consistent with the IOM report. And it seems the IOM recommendation, they said as rapidly as possible or let's not use them. I think there's a

subtlety here that I kind of lack any real understanding for. It seems to me that we have done what -- and by reacting to this, it sounds like we didn't have a plan that was reasonable. And we did have a plan that was reasonable, and it's in process and it's being carried out. And the issue is -- is really a very minor issue in the total context of mercury exposure.

DR. OFFIT: I think -- I'd like to think that we learned something from what happened in July of 1999 because what we did was we recommended hepatitis B vaccine be delayed for newborns who were -- you know, till six months of age for mothers who were, you know, clearly either -- who were clearly hepatitis B surface antigen negative. But what happened was is that nine percent of hospitals just suspended their newborn hepatitis B immunization program. I mean, it wasn't -- this wasn't just a few hospitals or a few doctors making this decision. It was nine percent of hospitals. That's sobering. And I think what's sobering about that is that we sent a message that hepatitis B vaccine which contained thimerosal was dangerous to newborns. And so now we have an Institute of Medicine report that asks

us as a policy -- or puts forward a policy decision that says we should stop giving, you know, all thimerosal preservative-containing vaccines now. And I think -- I worry that the message that we're going to be sending out there is that thimerosal, as it's contained in preservative levels in vaccines, is harmful to children and that, you know, it will spill over to include vaccines like influenza and it may cause children not to get, you know, pertussis vaccines that they need because physicians are going to feel I can't give these vaccines because they're dangerous, when there's no new science that suggests that it's dangerous. That's my fear.

DR. JOHNSON: Dixie?

DR. SNIDER: Just in terms of the need to respond, I think it is important for ACIP to respond to the IOM report, with whatever words the Committee feels are correct to put down on paper. I think that in the vacuum of ACIP not making a statement, then it puts pressure on the ACIP in the sense that those who may not regard the Committee highly anyway would exploit silence as complicity in not addressing the concerns

of a conflict-free scientific committee which, in many people's eyes, has great credibility. So I think it's important to say something.

Also, I think federal agencies would feel some pressure to make their own statements about this issue, and the directors of those agencies or the directors of the departments of those agencies may feel that it's important to make statements. And so I think it's preferable for ACIP, myself, to work hard with the other groups that Roger's mentioned. And it seems to me the proposal he's made, you know, to make it joint so that we're all on the same page, has some great merit. I would not personally want to characterize it, like -- I agree with David, I wouldn't want to characterize it as crisis, and I certainly don't have any problem with people wordsmithing the principles and -- of not wanting to have language -- like as soon as possible that you know, maybe creates the perception in people's minds that there is something dangerous about a thimerosal-containing vaccine.

But aside from that, I do really feel it's important for this Committee to weigh in and weigh in strongly

and work with these other groups to say something in the weight of the IOM report.

DR. JOHNSON: Sam?

DR. KATZ: I think it's very important that we make a statement and use the guidelines that Roger Bernier has outlined for us, which don't say we have to say tomorrow or January 1st or what. That's what will come in the discussion of a consensus group. But there are already people who have made statements, and if we don't respond, I think we refute the IOM. Mr. Burton has made a statement. The National Vaccine Information Center has made statements. There are all sorts of things on the internet already saying, as you know, there's a consortium of hundreds of lawyers who are instituting suits on the basis of neurodevelopmental disorders due to thimerosal. I think if we do not support the IOM, not by saying we're doing it tomorrow, but by coming up with something reasonable that we'll discuss later, we leave ourselves in a situation where we lose public confidence, public perception, which David Salisbury has accentuated so, public trust. And it has to be a statement that includes us all because

You know, the public doesn't say well, CDC says this and FDA says that and ACIP says this and the Academy of Pediatrics says that. It's the vaccine establishment. And I think the vaccine establishment has to speak with one voice.

If we deny the IOM statement, then what happens to their statement on MMR and autism? Well, they'll throw that one out, too. And what happens with the next one on vaccines and immune overload and the others that come along? I think we have to, with temperance and with a very well-crafted statement, come up with something that will be supportive of their stand, but modified by what the realities are of what we can do and how quickly.

DR. JOHNSON: Neil, then I'll go to John.

DR. HALSEY: Neil Halsey. I would agree with what many people have said, that enormous progress has been made in the last two years. And the problem is going to virtually go away completely within a few months, I believe.

But it's also hard to believe that it is still possible for some children to receive all three of the vaccines

in question that contain thimerosal in some clinics. It's a very small number, but it's still possible. So Jon, what you said is not quite true with regard to the fact that there are no longer children who are exceeding the federal guidelines with regard to exposure. We don't know that.

And you certainly are in the situation where you can separate the vaccines, as you talked about, but you didn't put that in your principles. There is no shortage of Hib or hepatitis B vaccine at this time, it appears, that do not contain thimerosal as a preservative. And so you are in a situation where you can reduce dramatically the potential for some children in some clinics.

You also -- One of the principles you have is in direct conflict with one of your already-established recommendations. That is, in the presence of a shortage of DTaP, that you delay the fourth dose, and you need to take that into consideration when writing your formal recommendations.

DR. JOHNSON: Let me just respond to that very quickly and we'll get to the other comments. I would argue

that we're stating in the fourth principle that the transition policy, the transition to t-free vaccines, should not delay the receipt of any childhood vaccines. A shortage otherwise may indeed do that, and that may be the unfortunate situation that we find ourselves in. Dr. Brooks? Yes, please.

DR. BROOKS: I just wanted to concur with what everyone else had said, and you know, I remember the discussion on thimerosal was quite -- there was quite a lot of dialogue, and I think it's important, like Dr. Overturf said, to put in the statement that we did respond and where we came from and where we're at right now because I think that would increase the credibility of the group on the joint statement as per se.

DR. JOHNSON: Thank you, and I certainly have that down as an additional communication message, the actions that were taken a couple of years ago and the great deal of progress that's been made. Georges?

DR. PETER: Well, I was going to agree with Sam and I could never say it as well, but I think two additional points need to be understood is that in the recommendations from the IOM is the -- is one that

states a review and assessment of how public health policy decisions are made under uncertainty. The second is the review of strategies to communicate rapid changes in vaccine policy, which implies that we have not always been effective in communicating rapid changes. And I think we have the opportunity now to indeed respond expeditiously but rationally in a way that demonstrates that we are able to make public health decisions rationally and appropriately. And I think we need to bear in mind those points. And not to take steps to respond by the organizations is to basically ignore it, which will not be well-received in terms of public trust and will be used against us, as Sam said.

DR. JOHNSON: And I would argue, Georges, that this process that we have outlined that tries to come up with a joint statement addresses both of those points you brought up in the IOM report. Bob?

DR. CHEN: Yes. As long as Kathleen and maybe Marie is still on the line, I think there's a nuance in what the IOM said that is probably important to clarify for the group that will convene to discuss, and the nuance is the use of the term "inadequate evidence to accept

or reject", which in some of the discussions so far people have translated to say that there's no evidence to accept a causal relationship. And I think the two, in the IOM parlance, is actually not synonymous and it's probably useful for Kathleen to clarify that for the group that will be discussing the --

DR. JOHNSON: Thank you, Bob. Jon, yes?

DR. ABRAMSON: I again want to make the point. My point is not that we shouldn't respond to the IOM report. The third principle is a transition as rapidly as possible. Indeed, to me, if I read it, meaning something close to crisis mode, and that is a very different statement than should we respond to the IOM report. We should. We absolutely should respond to the IOM report.

DR. JOHNSON: Thank you. Yes, please?

DR. STRATTON: Bob asked if the IOM would respond, and he's absolutely right that the IOM has always viewed the category two -- the level two categorization to very literally mean there is not enough evidence to say that the causal relationship is proven or disproven. And that is based on epidemiologic evidence, and in this

case it is true that the committee felt that the only epidemiologic evidence neither proved nor disproved a potential relationship. So Bob is right that it's a two-sided statement. Is that what you were asking, Bob?

DR. CHEN: And that is different than no evidence.

DR. STRATTON: It is very different from no evidence, absolutely. Although one unpublished study is pretty close to no evidence, very close to no evidence.

DR. JOHNSON: On the phone line did we have a comment?

DR. McCORMICK: No, I would agree. We discussed that study in great detail with the epidemiologists on the committee and really felt that the conclusion was that the data were -- even the [inaudible] relationships that were established were really quite weak.

DR. JOHNSON: Thank you. Jon, I want to come back to the point that you've made because I think that's been brought up several times in our discussion of these principles for the drafting group to use. We seem to focus on number three more than any others. Paul, I'd asked if you'd have some alternative language. It seems to me that "as rapidly as possible" is kind of

the catching phrase or the phrase that causes some irritation here. Yes, Peggy?

DR. RENNELS: Expeditiously?

DR. JOHNSON: Gary?

DR. OVERTURF: Well, this -- because --

DR. JOHNSON: Expeditiously is a possibility? Okay.

DR. OVERTURF: This also gets back a little bit to Paul's point, which is that the other part of that statement is to eliminate the theoretical risk of harm from thimerosal-containing vaccines. And in that theoretical risk is the assumption that there was a total dose that was a problem. And actually, that total dose was reduced within months after the statement. And somehow there has then gone -- the risk has now gone from that theoretical maximal dose that the vaccine contributed and it somehow needs to go down to zero. And we all know in a sense that's true, because there are other risks. The only reason why we could eliminate these risks in vaccines is because it was there. And so theoretically, you could eliminate that single risk. But we haven't eliminated all risk. And it seems to me so that when we talk about as rapidly

as possible, that actually was achieved, that the theoretical risk which was based upon one out of three recommendations about the total dose of mercury was reduced almost immediately. And although I agree with Dr. Halsey, you can't say that every child has met those goals, I think the great likelihood is that the vast majority of children have met those goals, and they met them very quickly, and it was as a result of that same policy, which was to remove them as rapidly as possible, which was the policy we had two years ago.

DR. JOHNSON: John?

DR. MODLIN: I just wonder if we ought to go on to public comment here fairly quickly and then wrap up. We may want to take one more comment. I saw Dr. Reilly, and then I would suggest doing that and we can --

DR. JOHNSON: Thank you.

DR. MODLIN: I know people don't want to wait much beyond 7:00 o'clock.

DR. JOHNSON: Thank you.

DR. REILLY: I would like to make a cautious statement on behalf of the manufacturers. I think very clearly the manufacturers will and have followed the

guidelines of the committee and responded very positively. But what I would like to draw attention to is the level that we've already reached. We have had the guidelines from July '99. I think they've been very effective guidelines from the Committee, and I think the Committee is to be complimented on the clarity in the guidelines that were put in place.

I think the manufacturers should be complimented on their response to that guideline and the work they've done to remove thimerosal. And I would like to put -- you know, we're talking about the number of five percent of the inventory has been put up as a bench -- you know, our best estimate at the moment. Just from general knowledge of the way we operate, the maximum likely inventory out in the field I think at any time is probably two months. And in fact, with -- in the era of shortage, it's likely less than that then. So we're talking about five percent of two months' inventory. And I think we should give consideration to the fact that the existing guidelines and the existing response by the manufacturers has brought us within 98, 99 percent of the target. And we have to ask ourselves

whether the continuation of those guidelines is sufficient to achieve the objective of a final transition as rapidly as possible, and I would suggest that there is strong -- strong evidence, in terms of thinking, that our consistency and our achievement may be the important message to be communicated.

DR. JOHNSON: John, I'll turn the time over to you to conduct the public comment.

DR. MODLIN: Okay, fine. We have three individuals who have asked to -- Stan? I'm sorry, I think we probably ought to --

DR. PLOTKIN: Can I make public comments?

DR. MODLIN: Yes, you may, but we'll call on you fourth. We've got three ahead of you. Absolutely. The first individual is Lynn Redwood of Safe Minds. Let me please plea that you keep your comments to three minutes or less.

MS. BERNARD: I'm actually the second speaker listed. I switches places with Lynn. This is Sally Bernard. I'm the executive director of Safe Minds, and we're a parent advocacy group that's been involved with the thimerosal issue for a number of years.

And I'd first like to thank Glaxo Smith-Kline for issuing a voluntary recall of thimerosal vaccines for their products. They're definitely to be commended for that action. I'd also thank the IOM for a balanced set of recommendations that we are very supportive of. From a parent's perspective, a parent group's perspective, I would say it's very important for this Committee to state a strong -- a strong and decided preference for vaccines without thimerosal and for this to be done with a sense of urgency, and not just as rapidly as possible, but to do it right -- right away. I think there will be a negative public reaction if that doesn't happen. I think there's a danger for this idea of a shortage to be perceived as an excuse for not acting.

If you don't do that, you will be in violation of the IOM recommendations. If you look at the recommendations, they did not say to do it as rapidly as possible, they just said to do it, use thimerosal-free vaccines, period.

And I would also like to ask for consideration for a parent representative to be part of this working group

so you can get the voice of the parent in your deliberations. Thank you.

DR. MODLIN: Ms. Redwood?

MS. REDWOOD: Lynn Redwood, president of Safe Minds. I know I've been before you a number of times in the past, and I just basically wanted to share some information with the Committee today.

In light of the recent IOM report on thimerosal and neurodevelopmental disorders, we, along with numerous other organizations, are petitioning FDA for the recall of all remaining infant thimerosal-preserved vaccines.

And again, I would like to thank Dr. Zink for their responsiveness to the public concerns over thimerosal by their voluntary recall, and I'd like to ask the other vaccine manufacturers to consider doing the same.

Additionally, I just wanted to let the -- actually ACIP Committee and IOM committee be aware that Safe Minds is in receipt of numerous documents, including a never-before-released VSD document, that reflects the original study protocol. When this document was reviewed by independent statisticians, statistically

significant associations were found with increasing levels of thimerosal exposure, with neurodevelopmental delays, including autism. We are premature in saying that there is no evidence of there being causation because if you look at this data very closely, the evidence is there.

There are also major discrepancies between this unreleased document and the documents that were presented to ACIP in June of 2000 and to the IOM in June of 2001. We're in receipt of numerous other internal documents which call into question the entire VSD process, one which characterizes the process as letting standards be dictated by our desire to disprove an unpleasant theory.

Therefore, Safe Minds is calling for a Congressional and a Department of Justice investigation into the generation and manipulation of these reports. Since ACIP relies on this data to set policy, we would like to ask for your support in these investigations.

We would also like to ask IOM to review -- In their review of thimerosal they relied on the VSD data in the assessment of causality, and we would like to ask the

IOM to support our efforts and consider re-looking this data once our investigations are complete. Thank you.

DR. MODLIN: Thank you, Ms. Redwood. The next speaker is Terry Polling.

MS. POLLING: Hello. My name's Terry Polling, and I am a parent. In addition to that, I was a registered nurse for 14 years and I've been an attorney for seven years. My husband is a neurologist and a scientist and he just finished his residency at Johns Hopkins. And we became involved in the issue of vaccines when our daughter, who is now nearly three, was about six months old. Up until she was about six months old, she received the routine vaccines, at birth, two months, four months and six months, the DTP, Hib and the hep B all contained mercury in her case. She didn't have any medical problems whatsoever, no developmental problems during that time. The only known problem was some eczema. From the time she was about seven months old till she was nearly 18 months old, she had developed otitis media chronically and chronic rhinitis, so she -- I was unable to have her vaccinated. I'd always been someone who was very much

an advocate of vaccine, so this bothered me tremendously that my daughter was not vaccinated for nearly a year. However, she did not receive a disease of any sort other than her chronic otitis media and her chronic rhinitis.

At 18 and a half months, because we were so behind on the vaccines, the pediatrician recommended that she receive all nine vaccines at one time. Needless to say, two days later she developed an encephalopathy, a rash all over, and she's never been the same. She has a diagnosis of autism.

The reason I bring this up is one of the issues that was brought up was whether or not we should wait to give the DTaP for the two-month turnaround time to give thimerosal-free vaccines. In my daughter's case, who one might argue is susceptible or could be in that minority group of children who is susceptible to a vaccine that could cause autism, she did not receive the disease not receiving the vaccine. Therefore, I would say in most cases, if we're going to rely on scientific evidence and we're using the idea that we do not have scientific evidence to show a causal

relationship between neurodevelopmental problems and vaccines, then we have to look at what scientific evidence do we have for coming up with the age of birth, two months, four months, six months, 12 months and 15 months. Is there any scientific evidence that shows that if you do not get vaccinated with the DPT at -- or DTaP at six months of age, you are going to develop one of those diseases within two months? I think not.

The other issue that I wanted to bring up was that Mr. Zink from Glaxo Smith-Kline -- and I would like to also commend Smith-Kline for removing the thimerosal from their vaccines -- is that he said to see -- you see a lot if you just watch. And I believe in this case he used that to show that there was no reliable evidence of a connection between thimerosal and neurodevelopmental problems. However, we also did not see any evidence showing that there was no causal connection, and that is because, until now, no one has been looking. And I think that that's a point that everyone needs to think about when they go in their deliberations.

In addition to that, we have seen an increase in

thimerosal-containing vaccines, and we have seen an increase in the number of type of neurodevelopmental problems in children, and we do know -- not just from a theoretical standpoint -- that thimerosal is neurotoxic. And I would just like you to take these things into consideration when you go back and you deliberate, as policy-makers, what policy you're going to put forward to the public because I do think you will have a backlash reaction, coming from both a professional and as a parent, if you do try to say that we're taking all the thimerosal out of vaccines because we think that, to be safe, we should take them out, but go ahead and be the guinea pig. Because I think now, when you're going out there to try to find that control group and that experimental group, if you give informed consent, you're going to have very few people wanting to be that experimental group. Thank you.

DR. MODLIN: Thank you, Ms. Polling. Stan Plotkin?

DR. PLOTKIN: Well, I don't want to prolong this. I'm sure everyone is anxious to go to the bar or wherever. And especially since my point is a philosophical one, and in the emotional atmosphere it's hard to stand back

and try to be rational about things. But basically, the point I wanted to make is that the principle -- the philosophical principle invoked by the IOM is the so-called principle of precaution. This is an importation from Europe which, unlike automobiles and some other things, may not be a totally desirable importation, because it can lead to actions which are, in fact, based on nothing but a certain concern. And I would point out that that was the same principle that resulted in the partial withdrawal of hepatitis B vaccine by the French authorities, despite the studies that, in fact, showed no relationship between hepatitis B vaccination and multiple sclerosis.

So in opposition to that principle, and this has been discussed ad nauseam here, is the idea of risks and benefits, and that for every action there are risks and there are benefits, and that we ought to be careful of unintended consequences of our actions if we act on the principle of precaution without taking into account what effect that has on other parts of the vaccine equation.

DR. MODLIN: Thanks, Stan. Dr. Zink?

DR. ZINK: I'd just like to set the record straight. Our program isn't a voluntary exchange program for vaccines and Andrax B, all products.

DR. MODLIN: Thank you. Dr. Wexler?

DR. WEXLER: I have a public comment. This is Deborah Wexler. I'm here on behalf of the California Department of Health Services, immunization branch.

DR. MODLIN: Deb, before we do that, let's -- why don't we finish up. I'm sorry, I thought you --

DR. WEXLER: Sorry.

DR. MODLIN: -- going to be talking about the -- about the issue at hand. Maybe we could finish up with you just as soon as -- I wanted to turn things back over to David just to kind of wrap up and make some relate the next steps in the process.

DR. JOHNSON: I think over the course of our few minutes of discussion here, we've heard clearly some additional communication principles that we'd like the drafting group to deal with. And I think we've heard some modifications to guiding principle number three that we can take into account. We do have a group in formation right now that includes representatives from

AAP, AAFP, ACIP, and then NVAC and the Public Health Service in terms of, of course, CDC, HRSA, and FDA. And we will try to get that group together this evening to begin that process, and hopefully be able to report out something tomorrow morning. But I wouldn't give you an ironclad prediction about that.

DR. MODLIN: Okay. This means that if you feel like you will have something for us to look at, that we will reconvene the Committee at 8:00 o'clock tomorrow morning and spend 30 minutes on this, although we'll probably have no longer than 30 minutes to spend on it because of the rest of the agenda. If we can't complete the ACIP review of this tomorrow, then it will almost certainly mean a conference call sometime in the future in advance of the next meeting.

I'm going to bring the thimerosal/IOM report issue to a close. I'm sorry, Mike, I think -- It's late and -- Do you have a burning comment?

DR. DECKER: Just two very quick procedural questions.

DR. MODLIN: Okay, sure.

DR. DECKER: Can you name the persons on the drafting committee? That's the first question.

DR. MODLIN: Dave, I think --

DR. JOHNSON: We haven't approached all of them yet so I'd prefer not to --

DR. MODLIN: They've not all agreed to --

DR. DECKER: And the second is, if you can't meet this challenging goal of having a report ready for Committee deliberation tomorrow and you have to go to a conference call, will it be handled in a way so that there's the same full public participation that you would have at this meeting?

DR. MODLIN: It would have to be, by -- according to law, we're required to -- if we have a conference call that's a meeting of the Committee, it has to be held in public.

THE COURT REPORTER: Could I have your name, please?

DR. DECKER: Michael Decker.

DR. MODLIN: Okay. I'm going to draw this one to a close. Deb has a quick announcement to make about a

DR. WEXLER: About a new video. This is -- We're changing topics. Immunization Techniques, it's on everyone's table and there are many copies still left

in the back. It's been two years in the making. Dr. Natalie Smith is the featured lecturer on it. It's a 35-minute video on how to give an immunization and it's excellent. We haven't had anything this good since 1988, I think was the last time this was done. And I think -- just to let you know, every clinic in the United States I believe should have a copy of this. Inside it has some teaching guidelines so that -- it's designed to teach your clinic staff how to give a shot appropriately, how to give IM, subcu injections, and there's actually a skills checklist so that you can review your staff's immunization techniques and make sure they're doing it right. So I just wanted the ACIP and people here to be aware of this new video, know that you can order it. There are order forms in your packet. We distribute it also not in a pretty box, but for $10 less. And the last thing I wanted to tell you about is this poster which is on the back table. It's for hanging in the clinic to show actually visually where you give a subcu injection, where you give an IM injection, and I can't tell you how important this is because so many injections are given improperly in the

United States now. And this is the kind of tool that we all need on the front lines so that we are doing it properly and know what we're supposed to be doing and our staff in our clinics are adequately trained. So I just wanted people to bring this information back to their settings.

DR. MODLIN: Deb, thanks. Let me state that I've already passed the video and the poster on to our own people, who are enthusiastic, wildly enthusiastic, about having it as a teaching tool.

We'll see you at 8:00 in the morning when we'll continue the thimerosal discussion.

(Whereupon, the meeting was adjourned at 7:10 p.m. until the following day at 8:00 a.m.)

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C E R T I F I C A T E

STATE OF GEORGIA

COUNTY OF FULTON

I, PAMELA T. LENNARD, BEING A CERTIFIED COURT REPORTER AND NOTARY PUBLIC IN AND FOR THE STATE OF GEORGIA AT LARGE, HEREBY CERTIFY THAT THE FOREGOING IS A TRUE AND COMPLETE TRANSCRIPTION OF SAID PROCEEDINGS; AND THAT I AM NEITHER A RELATIVE, EMPLOYEE, ATTORNEY, OR COUNSEL OF ANY OF THE PARTIES, NOR A RELATIVE OR EMPLOYEE OF SUCH ATTORNEY OR COUNSEL; NOR FINANCIALLY INTERESTED IN THE ACTION.

WITNESS MY HAND AND OFFICIAL SEAL, THIS, THE 8TH DAY OF NOVEMBER, 2001, IN ALPHARETTA, FULTON COUNTY, GEORGIA.

PAMELA T. LENNARD, CCR, CVR

NANCY LEE & ASSOCIATES

CERTIFICATE NUMBER B-1797
(CCR SEAL - NOTARY SEAL)

NANCY LEE & ASSOCIATES

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

convenes the

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

VOLUME II - DAY TWO

The verbatim transcript of the ACIP Conference commencing at 8:07 a.m. on Thursday, October 18th, 2001, at the Marriott Century Center Hotel, Atlanta, Georgia.

C O N T E N T S

(continued)

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

(By Group, in Alphabetical Order)

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Professor of Pediatrics and Medicine
Dartmouth Medical School
Lebanon, New Hampshire

Executive Secretary:

Dixie E. Snider, Jr., M.D.
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Kevin Reilly
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Radnor, Pennsylvania

P R O C E E D I N G S

8:07 a.m.

DR. MODLIN: Good morning. Our first order of business will be to review the progress that's been made by the joint working group on the provisional third Joint Statement on Thimerosal-Containing Vaccines from the AAFP, the AAP, the ACIP, and the Public Health Service agencies, including CDC, FDA, HRSA, and NIH. And Dave or Roger are going to lead the discussion. We do have a draft working document that is being passed out.

DR. JOHNSON: Thank you, John. We do have a document that's going around. We'll talk about that in just a moment, and I think Roger spend a few moments sort of walking us through that. I want to tell a little bit about the process last night.

In the spirit of openness, I want to mention the folks that got together in sort of the nature of our deliberations, if you will.

We had Gary Overturf from AAP; Rick Zimmerman from AAFP; myself and Paul Offit from ACIP; Karen Midthun and

Norman Baylor from FDA; Geoff Evans represented HRSA; we had Joel Kuritski, Roger Bernier from CDC; Sam Katz, Georges Peter participated as well. We had what I would call a very free-flowing discussion for about the first hour and a half and I think it was a nice process of compromise to try to arrive at a statement that each of the organizations represented or the representatives from the organizations thought that they might be able to take to their organizations in a deliberative process over the next several weeks and get approval from those organizations to sign on, as it were, to this joint statement.

I think our job was made considerably more easy last evening with the expressions that we heard yesterday by the manufacturers and with the ongoing efforts by the manufacturers over the last couple of years to try to achieve the goal of reducing or eliminating thimerosal in vaccines. We want to recognize those tremendous efforts toward that end. We particularly appreciate Glaxo SmithKline's effort, willingness to facilitate the process of completing the transition, and we also want to thank Merck and Wyeth and Aventis

for their expressions of willingness to continue to work to complete this transition to thimerosal as a preservative-free vaccines.

Now, I think we've had an opportunity for the statement to go around. So if Roger is available, I would like him just to walk through this statement and then I'll talk a little bit about the process we would like in terms of review and deliberation by ACIP over the next several weeks. I want to emphasize that we are not suggesting or asking for anything but maybe a little bit of discussion this morning, comments back over the next couple of weeks, and then some mechanism for us to sign off on this a bit later in November.

Roger?

DR. BERNIER: I'm sorry, we're not prepared with -- I don't think -- Patrick, did you make any overheads? I don't think we have that. So I guess what I would just like to reiterate, what Dave just said, that as we have sort of constructed this process, the idea is that this is a provisional joint statement. And this statement is the one that we want to elicit review and comments. It's not the one that we would ask for approval at this

time. So now the ACIP is one of four organizations -- AAFP, AAP, ACIP, and the Public Health Service -- that would presumably approve this joint statement in about towards the end of November. What we tentatively decided last night is that we would like to invite comments on this version -- that's why it's called "provisional" -- and have those back by -- I think we said November -- November 5. We will then incorporate comments into the draft and we will issue a final joint statement on November 15 which we will circulate to the four organizations and ask them to approve the final version by November 30.

The idea is that these -- this joint statement would appear perhaps earlier, but the intent was to publicize it approximately around the time of the new Harmonized Schedule for January so the we would be conveying the impression that this change is being made as part our routine immunization activities. There was a strong view that we not give a sense of urgency or crisis to this -- to the completion of the transition. So we would like to somehow integrate it into the announcement, not put it on the Harmonized Schedule but

sort of make it more public at that time, and then give people one to three months at the most to implement it, and say that after March 31 of 2002 then at that point that would be the official end of the transition period. It's possible that for many providers this could be accomplished much sooner but the idea was no later than March 31st. We're very grateful for the cooperative spirit that I think we saw from the AAFP and from the AAP who thought that with a date towards the end of the first quarter that they would be able to convince people to sign on and to support this kind of approach.

So we're hopeful that the people who were there last night will be able to make additional comments that are important to their constituents, that we will integrate those into the next version that you will get by November 15th and, hopefully, we'll have a final by the end of November.

I don't have much more to say, John Modlin, but if you want, we could read it together or just leave it. I'm not sure how we want to proceed.

DR. MODLIN: I don't think we have the time, or perhaps

not even the will, to engage this morning, but what we might do is invite some comments or questions regarding the process itself. I certainly would prefer to encourage everybody to obviously read it carefully and get your comments in writing to David or to Roger.

DR. JOHNSON: Probably ought to go to Roger.

DR. MODLIN: To Roger Bernier, by the time set of November 5th, and I think we can certainly do that. Are there comments or questions regarding the process itself? Stan?

DR. PLOTKIN: Just a question not about words, but do you mean to exclude influenza vaccine? Because in the last paragraph, it uses the term "vaccine" without any modification or specification. And if read literally, it would mean that you wouldn't be able to use influenza vaccine after March 31st.

DR. BERNIER: That's clearly not the intent.

DR. MODLIN: Good point. Why don't you put it in writing, Stan, seriously, or we'll --

DR. JOHNSON: We obviously do need some assistance in terms of crafting the exact words. One of the points that we did discuss last night was to explicitly state

in this document that we were focusing on the three vaccines that are routinely used for all children that have contained thimerosal as a preservative DTaP, hib, and hepatitis B, and that the exception -- one of the explicit exceptions to this would be, I think for the present time, influenza vaccine because our supply contains thimerosal as a preservative.

So, yes, if we haven't made that clear, if there's any inconsistency in our wording, we do need to change that and would appreciate those comments.

DR. MODLIN: Yeah. Again, this is the first draft and, obviously, I think comments would be appreciated, not only on content and policy, but on wordsmithing as well.

Any other comments regarding the process? Dave?

DR. JOHNSON: Maybe just to point out then that we are probably looking at sometime in November. I guess our suggestion from the drafting group last night would be a later November ACIP conference call --

DR. MODLIN: Yes.

DR. JOHNSON: -- meeting if that would be possible so that we could have an open and formal discussion, if

you will, of what we would hope would be a final statement at that point and then a vote on that.

DR. MODLIN: Okay. I suspect we could probably begin working on that now. Gloria, you heard? Okay. Any other comments -- I'm sorry. Dixie?

DR. SNIDER: Yes. I know Marty Myers is not here, Steve, but we do need the help of the NVPO to engage all the PHS agencies and coordinate those responses back to Roger, as well.

DR. MODLIN: Good point. Roger, thank you very much. John --

DR. CHEN: Bob Chen.

DR. MODLIN: I'm sorry.

DR. CHEN: If you don't mind --

DR. MODLIN: Sure.

DR. CHEN: -- this is perhaps in a semi-non-official capacity, if you don't mind. I found it ironic yesterday at the session. About a year ago, I gave the last update on vaccine safety to the group and I mentioned that one of the challenges of working in vaccine safety is that whatever our finding is, usually one side or the other side does not like our findings.

And I found it ironic yesterday that both sides found our findings unacceptable. And I wanted to just kind of follow up on that a little bit.

I think in terms of the, let's say, vaccine community, I guess I would caution that we have spent many years building the VSD as kind of our only major infrastructure for testing hypotheses. And as Sam Katz mentioned, if we -- if we reject -- we should take our rejections of VSD findings with a grain of salt because similar to the IOM, if we reject IOM findings on this particular study, then we would have to reject IOM findings on MMR and autism, et cetera. So just kind of we want to be cautious. That being said, this was a screening analysis of administrative data, and at no point did we ever feel that this finding alone is adequate, that we have always pushed for the more definitive validated study.

And then for the parents advocate groups, I think we very much emphasize with your desire to better understand -- I don't know if they're here -- but with your desire to understand whether thimerosal is related to autism or to neurodevelopmental defects. I

think that is not -- Our job in public health is not to hide results, and I think in the spirit of kind of post-September 11th, et cetera, trying to create a more harmonized humanistic world, conspiracy theories and kind of attacking personal integrity of researchers is just not going to get us there. I would urge you to just reconsider your tactic and just -- there are certain things that just doesn't make sense. For example, in the U.K., as David Salisbury pointed out, the amount of thimerosal content in the U.K. schedule has basically been unchanged since the 1950's and, yet, they've also experienced the similar rise in autism as has been seen in the U.S. So thimerosal and autism, that bit of data, again, while not definitive, is something that raises an issue. I want you to be cautious.

And then I think that comes back to ultimately, in terms of -- this clearly is a controversial and tricky issue and that -- the IOM had proposed kind of a larger research agenda to answer many of the difficult questions that will hopefully resolve some of the controversy, which I think at this point may be

unnecessarily controversial because it is possible to get to the truth and let's work together towards getting at that truth.

DR. MODLIN: Bob, thanks. Let's move onto the updates from each of the PHS programs, and we'll start with the National Immunization Program. Walt?

DR. ORENSTEIN: I just want to cover a few things here. One is to give you the latest estimates we have -- Can people hear me?

UNIDENTIFIED SPEAKER: No.

DR. ORENSTEIN: It's on now? All right. I wanted to cover a few things we're doing. One is an immunization coverage update. We have released the first quarter of 2001 figures. Second is the FY 2002 budget as best we know it. Discussion of the study that we have -- that we are working on with IOM on vaccine financing, a new private provider survey, the Vaccine Health Care Center Network, CISA, and if we have time -- I'm not sure we have time for the others.

Let me just go over the numbers. What you can see here is calendar year 2000 and calendar year 2001. Now, when we need to remember that these data are data when

they were collected. They are not dates of birth of the individual children. I don't know, Patrick, if you've been able to get those dates. Okay. I think these are 19- to 35-month-old children, and what you can see here is that for polio, we've kept roughly the same coverage rate; for hib, roughly the same; MMR, roughly the same; hepatitis B, we're over 90 percent; and varicella has gone considerably up, now with 75 percent, the highest we've ever had for varicella immunization coverage. Again, many of these data were collected or -- or many of these children were immunized prior to the disruptions in the immunization system that occurred in 1999.

This just shows some of the data from DTP and the combined series. For DTP-3, we're close to 95 percent. We're still considerably lower for DPT-4 as we have always been, roughly at 82 percent, and this is the major driving force behind the combined series that are low. And sometimes these numbers are often used when we want one single number for immunization coverage, but they clearly do not reflect the overall immunization efforts and are driven by the lowest

coverage antigen, in this case the fourth dose of DTP. There are now -- the House and Senate committees have passed budgets for immunization. They are not the same, and I'll try to go over them. The FY 2001 317 budget was $553 million. The President asked for 22 million more. Of those 22 million, 14 were for vaccine purchase, four for vaccine safety, one for extramural research, one for global polio, and then two million for mandatory salary increases.

The House-passed version was $25 million above the President's request, and the Senate-passed version was $62.5 million over the President's budget request. It's not clear yet to us what that money is going to break down on, but we believe either all of it or the great majority of it will go for state grants for both vaccine purchase and for infrastructure, but that's not clear yet. Obviously, we don't get two numbers. This will have to be adjusted in conference and then the President will have to sign the bill. So we don't know what our budget is, but we wanted to let you know what our status is.

DR. JOHNSON: Walt --

DR. ORENSTEIN: Yes.

DR. JOHNSON: -- quick question. Not to quibble about words, but you had "Senate Mark" as opposed to "Senate Passed." Is that an actual difference? Have they not passed that in the Senate?

DR. ORENSTEIN: That, I think, has been passed at least by the Senate committee. Patrick? (NO RESPONSE)

DR. ORENSTEIN: He's not here. I believe that's just by the committee. I don't know if it's the whole Senate. I do not know that.

This is the -- It may be the whole Senate. I don't know and I'll try and clarify that. Many people have been concerned about financing of immunization. We have previously contracted with the IOM to do a report on financing of the public sector. This has been very helpful to us and we've heard about "Calling the Shots." We've now contracted with them to look at the private sector, as well as public sector, and we've asked them to focus on five areas: the roles and responsibilities of different groups, including the federal government, state and local governments, private insurers, employers, et cetera, overall in the

immunization system; what the best finance strategies would be; what their current needs are; how best we ease into the introduction and financing of new vaccines -- this particularly crisis portions in my opinion with the financing of pneumococcal conjugate vaccine, particularly coming in in the middle of budget periods, and we've been asked -- we've asked to address that as well as future vaccine prices. The study director is Rosemary Chalk who is the same person who was the Project Director for the "Calling the Shots" report.

We have entered with the Gallup organization an annual longitudinal survey of a nationally-representative sample of physicians. These are family practitioners and pediatricians, plus the ability to do rapid, ad hoc surveys of physician attitudes and practices. So we feel this is an important part of the armamentarium. This will involve issues that deal with knowledge, attitudes, practices relative to childhood immunization, including vaccine safety.

We have also -- for the sake of time, we've entered into the military in developing the equivalent of what we're called the Clinical Immunization Safety Assessment

Network, or CISA. This is academic centers of excellence in partnership with CDC serving as sources of clinical expertise in adverse events following immunization. Basically, these are centers that would help us in setting definitions of adverse events, reviewing adverse events, setting up protocols for potential therapy of such events. And contracts have been awarded to the Johns Hopkins University with the University of Maryland, the Boston Medical Center, the Kaiser Research Institute Foundation with Stanford and Vanderbilt, and New York Presbyterian-Columbia.

And then measles is still extremely low and continuing low, and I think we've had success on polio eradication. Obviously, the recent events, it's difficult to gauge what they will mean for overall polio eradication, although even before all of these things started on September 11, Afghanistan, for example, had reached certification level standard and had conducted outstanding NID. So what will happen in terms of September 11 remains to be seen, but we are continuing aggressively in polio eradication.

Thank you.

DR. MODLIN: Thanks, Walt. Questions for Walt? Bill?

DR. SCHAFFNER: Yeah. Walt, I was interested in the Gallup survey you were undertaking and mindful of your comments at a previous meeting that you were increasingly interested in adult immunization issues. I wonder if you might, at some point, also consider surveying physicians' attitudes about adult immunization? I dare say those findings are going to be even more revealing than physicians' attitudes about childhood immunizations.

DR. ORENSTEIN: I think we view this as a start, Bill, and I think we certainly have intentions of trying to expand it.

DR. MODLIN: Jon?

DR. ABRAMSON: Walt, can you give some update about financing for studies that involve vaccines such as anthrax and smallpox? Particularly I know that you're doing a dosing thing for smallpox, but does it involve children? Where are we with those issues?

DR. ORENSTEIN: Those are actually being conducted through the NIH. I don't know if, Carole, you want to

comment on that.

DR. HEILMAN: I tuned out for a minute.

DR. ORENSTEIN: Okay. The question Jon asked about the dosing studies with the smallpox vaccine stockpile and whether children were involved in those studies.

DR. HEILMAN: No. Actually, we have looked at that in the age range of 18 to 30 years old and we're planning to do a second study, but still focusing on that age range. The longer-term plan is to absolutely go down into the pediatric and go higher into those that have been already vaccinated or in the elderly as well, but those will be done in an incremental way.

DR. MODLIN: Any other questions for Walt?

(NO RESPONSE)

DR. MODLIN: Walt, thank you very much.

DR. ORENSTEIN: Thank you.

DR. MODLIN: The update from the FDA, Dr. Midthun.

DR. MIDTHUN: As I mentioned yesterday during the July Advisory Committee, Vaccines Advisory Committee of FDA, the biologic license application for Aviron for their live-attenuated influenza virus vaccine was presented and I went over the brief summary of that of

yesterday. So I won't discuss that further.

Also, since the last meeting here, we approved Evans' supplement for thimerosal-reduced formulation of their influenza virus vaccine. And then the other update is that we also have another Vaccines Advisory Committee scheduled for this November, the 28th and 29th. And the topic of that meeting will be to discuss efficacy endpoints for human papilloma virus vaccine studies.

Thank you.

DR. MODLIN: Thanks, Karen. Questions for Dr. Midthun?

(NO RESPONSE)

DR. MODLIN: Thanks. The Vaccine Injury Compensation Program, Dr. Evans.

DR. EVANS: Good morning. You all should have the usual monthly statistics sheet in front of you through September of this year and you'll notice that under "Claims Filed" we received actually more this year, this calendar year -- excuse me, this fiscal year than we had for several, probably owing to the media interest in the program. We received 212, about 17 per month,

and of course, the claims that are under the pre-88 column have been dismissed because they're no longer eligible for filing.

As far as new vaccines, vaccines that have been added to the program since it was enacted, we still have a steady state of hepatitis B claims that are still in a fairly long process of being adjudicated awaiting for the IOM report that's probably going to be coming out in the six months that will at least look at one of the major areas of hypotheses, that being hepatitis B vaccine and neurological disorders. This will be done by the Immunization Safety Review Committee.

Hib vaccine, very low numbers, the same thing with varicella. And rotavirus, we've received 11 claims to date, one of them including the family through -- that experienced a death following rotavirus vaccine from intussusception.

A very low number of acellular pertussis claims and we've received none for pneumococcal vaccine so far, which isn't surprising since it was just recently added.

Under "Awards," a little over a billion dollars paid

to date for both pre-88 and the post-88 program, and the Trust Fund continues to grow.

You should also have in front of you a Notice of Proposed Rulemaking that came out this summer which several important things are being proposed, the most important there being changes for rotavirus vaccine, and I'll get into this in a minute, basically adding an additional category to the Vaccine Injury Table, along with the injury of intussusception with a time interval from zero to 30 days.

Also, there are some technical changes having to do with the hib vaccine, the polysaccharide vaccine, that I'll get into and removing residual seizure disorder from the AIDS interpretation, and to begin the process of adding pneumococcal vaccine to the table so that it has its own box category on the Vaccine Injury Table. I explained that at the last meeting. We probably have about a three percent residual understanding, but as pneumococcal vaccine is actually listed on the table today, but it's in a general category of vaccines that are now recommended by CDC for routine administration rather than having its own separate box. As far as

coverage, it doesn't make any difference. That dates back to the effective date of when the excise tax went into effect.

Rotavirus vaccine, as you know, was added to the table back in March of '99 and then we went through the experience of having the post-licensure data showing intussusception with a statistically-significant association from zero to 14 days. In deliberations in front of the Advisory Commission on Childhood Vaccines, it was agreed that the window for adding it to the Vaccine Injury Table should be expanded somewhat to give the benefit of doubt and they agreed that zero to 30 days would be more appropriate since, obviously, a case on 15 days could be very likely to be related also. So that was unanimously approved as was the idea that there would be a distinct category for the specific type of vaccine that the intussusception was found to be related to, that vaccine product, and that was the live, oral, rhesus-based. So in the future, if additional vaccines were to be licensed that had a different -- which will, we expect, have a different derivation, that would simply be added under the

general category. And then if there was any additional evidence that showed intussusception, then that certainly could be added as a table injury at that point.

I should add parenthetically that just the fact that it's under the general category of rotavirus vaccines means that anyone could file for intussusception under that category and they would simply have to prove it rather than having the presumption that it's listed as an injury under that new type of rotavirus vaccine. And that would not be difficult, of course, if there was evidence that there was no association.

I just wanted again to remind people that because of the particular nature of -- the unique nature of rotavirus and intussusception, the fact that most of the infants that unfortunately suffered this adverse event went onto to have it but, fortunately, recovered in a very quick fashion, under the law before year 2000 they would not have been eligible for compensation because you have to have six months of continued effects. And with the legislation passed in 2000, the fact that anyone that files a claim for any vaccine

under the program, if they have both hospitalization and surgical intervention, would be qualified to receive compensation if their effects did not last more than six months.

And although this specifically was done because of the rotavirus episode, this does apply to all vaccines under the program.

These were the bases for the changes, the technical changes I referred to. We -- In adding hib polysaccharide vaccine to the table back in 1997, we did so with the understanding that the IOM had found that early-onset hib disease was related to the polysaccharide variety of hib vaccine. And by that time, of course, hib was not being utilized and, in fact, use, for the most part, stopped as of 1989. When you add a new vaccine or a condition to the program, you have eight hours -- eight years of retroactive application. We're a little bit more generous than eight hours. And by the time they were able to add it to the program, that eight years nearly exhausted itself. So we had never received a claim for the polysaccharide vaccine, so we're removing it really

because it has no effect at this point.

We're also removing Residual Seizure Disorder because there's no longer any condition listed on the table for that. And these are both being removed from the qualification for AIDS to interpretation also.

Pneumococcal conjugate vaccine, again, is also part of this reg, so it can officially be added to the table for its own category. And

that -- we'll see if there's any particular public comment as far an injury that should be listed for it. We don't expect any at this point.

A quick couple of notes on legislation. Of course, the attempt to lower the excise tax, the Jim Bunning legislation, the House and Senate is ever present. There's also the Weldon-Nadler Bill that I've referred to in the past that continues to receive attention in a very quiet manner. It's more attention from the Government Reform Committee, as it turns out, than the House Commerce Committee which really has oversight of our program. And the important thing to realize about this legislation is that it would set forth a non-scientific standard for deciding whether claims,

both for table and non-table injuries, have any relation to vaccines. Of course, this would be extremely problematic for the program. And it also creates a statute of limitations that would really be almost limitless. So this is legislation that hopefully will be admitted in the months to follow when we get some additional kinds of changes based on comments from various stakeholders in the program. It also turns out that the Government Reform Committee, who has had a hearing on the program in September of 1999 and issued a report in October of 2000 with these three main points that it made in the report, is actually scheduling another hearing, and it was actually scheduled for the 24th, which has now been changed to the 25th. And since they're coming back from -- they went out of session yesterday and I understand that they're supposed to be coming back on the 24th. So it's not clear whether this is going to take place, but we received a letter from Representative Burton, and the questions and the concerns are pretty much along the lines of what's been reflected in the screen and what we've heard in the

past. So I'm not sure what new ground this might be covering.

A quick reminder -- and this goes back to the flu discussion yesterday -- when you add a vaccine to the Compensation Program, it has to qualify based on these two major areas. It's an administrative process, but it has to be a vaccine that is recommended by CDC for routine administration to children even if adults receive it and it also needs, of course, an excise tax with the coverage and the filing deadline as shown there. If we were to make a general use recommendation for the inactivated flu vaccine, understand that individuals of any age group would be eligible to file with the Compensation Program. So there's meaning beyond just the children that would be receiving this vaccine. And we, of course, would go forward with rule-making to add it and it would be up to Congress as to whether an excise tax would be enacted.

Q It some trepidation, I thought I would at least mention this because there's not a lot that I can say, mostly because I don't -- we really don't now very much. But I can tell you that the Compensation Program has only

received one claim alleging thimerosal-related injury. And of course, as many of you know, there have been articles, there's been some ads in the newspaper -- I know USA Today has had some -- where they refer to a litigation group that has entered into class action lawsuits in various cities across the country. Now, this is somewhat surprising to us because our understanding that if it's a covered vaccine, you must first file with the Compensation Program. So it's not clear how they're going to be able to go forward on this basis, but we have not really heard very much from the manufacturers or any of the other interested parties. So we really don't know the current status of these suits or if motions have been filed or if there's been any actions on these motions. And maybe some of the manufacturer representatives might want to comment to add any information to that that they feel comfortable with. It's also not clear what the effect of the IOM report may be. But I thought at least I would mention it because I know there have been concerns raised. The Academy is concerned about this, of course, because the practitioners are vulnerable. And practitioners, I

understand, have been named in these lawsuits. So I think I will end there.

Questions?

DR. MODLIN: Thank you, Geoff. Questions or comments? Sam Katz?

DR. KATZ: I wonder, Geoff, if you would clarify the new regulation or new requirements that you mentioned regarding intussusception. If I understood correctly, it only covers those cases where surgery was involved. Maybe I misunderstood. And then you said there was a general application of the surgical intervention. My patient had a seizure, fell down, and fractured his arm, went into the hospital, had an open reduction of the fracture. Is that a covered thing? My patient had an abscess at the site of the injection, had surgical drainage and antibiotics in the hospital. Are you saying that those sorts of things are now covered?

DR. EVANS: The answer is yes. Although I would --

DR. KATZ: How ridiculous could we be?

DR. EVANS: I would also add that those kinds of scenarios are probably very rare but, yes, that is the

way -- there was concern at the time that -- We understood through the grapevine that they did not want to make this seem as though this was a particular vaccine and commercial kind of legislative relief and they wanted to make it more general.

DR. KATZ: I would like to think that the liability lawyers think it's unusual as you state.

DR. EVANS: But the scenarios you've painted, of course, we've never had cases like that. And the first part of your question -- Sam, did I answer the first part of your question?

DR. KATZ: Yes.

DR. EVANS: Okay.

DR. MODLIN: Other questions for Dr. Evans, comments?

(NO RESPONSE)

DR. MODLIN: Hearing none and seeing none, Geoff, thank you very much.

The next update is from NIH, Dr. Carole Heilman.

DR. HEILMAN: I'm going to talk to you about two activities that have been of importance to you this particular ACIP and that's influenza research activities and some of the things that we're still doing

on thimerosal. I want to give you a brief update. I'm obviously not going to tell you about everything on influenza research, but I just want to tell you our web site in case you do want to know more about what we're doing. Obviously, we do have a very robust influenza program but, again, for things that are of particular interest to you, I just want to highlight under epidemiology activities, that we do have a contract that looks at a lot of the ecology of zoonotic influenza viruses, and this is through Rob Webster in Hong Kong. This has been very crucial contact in identifying the H5, H7, and H9 zoonotic infections that have occurred.

In addition, yesterday you heard a little bit about some of the activities on community-based strategies and herd immunity. Those are also areas that we're actively involved in.

I want to focus a little bit more now on some of the vaccine development activities that we have in terms of the public/private partnerships that we're evolving.

The NIH has very good relationships with industry, and

one of the areas that's been very obvious is -- has been the development of the live-attenuated influenza vaccine with Aviron and now Wyeth-Aviron through a CRADA agreement. But more recently, we have done something called the Challenge Grant Program, and this is the program in which we challenge industry and we did a 50/50 percent -- 50 percent sharing of costs in areas of high importance that industry -- in vaccine high importance but in which industry had not taken a very aggressive role. And I wanted to tell you, within that particular program, we actually have two activities going on. One is the development of the DNA-based influenza vaccine; and the second one is the production of non-egg vaccine substrates, which down the line will be very important.

This program has received a lot of very positive feedback from industry and I just wanted to highlight that we'll be coming out again with this program, calling it now partnerships instead of challenges in FY '03 and influenza vax and development roles will be highlighted in that particular activity.

And finally, we do have, again, research to try to --

as again, Linda Lambert talked to you a couple of rounds ago, about trying to figure out how to be responsive to potential shortages through a half-dose study and also looking at novel ways of delivering influenza. Obviously, the live-attenuated via the intranasal administration is one example of that.

Let me now move into the second area, and that's the studies -- a little bit of an update on the thimerosal studies.

If you remember, we had presented to you, again a couple of ACIP's ago, that we were looking at -- had taken the opportunity that thimerosal was being phased out and did a very quick study to try to identify how much mercury was actually in infants after they received their vaccines, and this was done at the University of Rochester. And we also talked with you about a second area that we were focusing in on, and that was the evaluation of the kinetics of the mercury and the tissue distribution in infant macaques, and that's what I want to update you on, both of these activities.

With respect to the clinical study -- this, again, was done at the University of Rochester with Mike

Pichichero and John Treanor's group and also through the Naval Medical Center -- again, just to remind you, this was a very quick study in which we were looking at 22-month-olds, 26-month-olds, and 20 control infants. Again, these are the vaccines that the children received.

On average, those that were two months and younger received about 46 micrograms of mercury total and those that were over six months received about 111 micrograms of mercury total. And the -- and what we did was to look at whole-blood, urine, and stool samples, and these were done at various times during a 30-day period. So it was not a longitudinal but it was just a point estimate all the way. And we also had some opportunity to look at formulations of breast milk and maternal hair, et cetera, and the assays that were done -- and again, not important because you don't have the graph right here of how we assigned it. But the bottom line of this was that in the full-term infants with -- receiving the vaccine regimens within a 30-day period of time, all of the serum thimerosal mercury levels were below EPA safety guidelines. And the blood mercury

levels in these infants were lower than was predicted if, indeed, we considered the half-life of methylmercury, which is a 45-day half-life, and those were, again, the studies that I showed you.

Most recently, we evaluated the stool samples and this was actually very surprising because we found a lot of mercury in the stool samples, and the mercury was found in the area of about -- a half-life of about six to eight days. So I'm not really quite sure what this means because we haven't seen this kind of pattern in methylmercury in animal model studies, but we are looking very carefully. But it does suggest that mercury, by way of thimerosal, is actually eliminated quicker and eliminated by this particular mechanism. But again, whether or not there are kelators in the formulation, I don't know, but this is a different pattern than you do see with methylmercury. So that's being explored.

So I just want to tell you what we're doing on follow-up studies. Again, we're confirming -- going back and confirming all this data. This will be published shortly, but we're also considering about doing a more

expanded pharmacokinetic study in Argentina or some other place where, indeed, they're still delivering the thimerosal-containing vaccines in which we can do the appropriate study pre-vaccination, looking at the levels post-vaccination at various time points and, again, to do a complete look at the whole range of activities. A much more appropriate and elegant kind of study.

But we're also looking at the question about just the pharmacokinetics in infant macaques to understand the distribution of methyl versus ethylmercury. And this is just the study design. I briefly presented it to you, but we will be looking at one-week-old infant macaques. We will be looking at IM-plus vaccines over a period of four weeks. We're going to sample a whole variety of things, monitor their kinds of behavioral patterns, collect a number of specimens, and then see what we see.

Right now, where are we at that? We have already tested the infant formula and food for mercury levels in terms of background and found that those were very low. We've already analyzed the brain tissue from

normal infant macaques for mercury level and, again, low and nondetectable levels, and we began breeding females this summer so that we can indeed do these studies.

So that's all I wanted to let you know.

DR. SNIDER: Carole?

DR. HEILMAN: Yes.

DR. SNIDER: Dixie Snider. Could you just say to the group what you said in some other meetings about NIH response to the research proposals in the IOM report.

DR. HEILMAN: It's especially -- Yes. A lot of these things that have -- that I'm telling you have actually been identified already in the IOM report as areas that we should be continuing research on. There is one other area that IOM mentioned and that has to do with our DTaP study that we did in Sweden, in particular. And we've been working with our Swedish investigators to try to see if we can't -- we still -- we actually are still following those children under IND and looking at neurological outcomes, particularly HHE outcomes with those children. The questions will be, can we redo the consent forms, get all the ethical

clearances, et cetera, to be able to now link that particular activity with an autism database. So we're working with our Swedish investigators to actually try to accomplish that.

So we are, again, being responsive to the IOM activities.

DR. MODLIN: Other questions for Dr. Heilman? Bob Chen?

DR. CHEN: It's not a question, but just to add to Carole's response in terms of what are the other research that we're currently doing in response to the IOM suggestions and research on the EPI side.

What we have done with this last fiscal year's funding was to fund a pilot study into what will be the logistics necessary in terms of different studies in terms -- if we bring these children now back at an age about six to eight years of age at these different domains of neurodevelopmental function, what are the best standardized tests and, logistically, how would one do a whole battery of these in one single visit. So that is one funded study, and based on that, we will kind of hopefully have a good sense of whether the cohort

approach, which has been our sense, will be the best approach or multiple simultaneous case-control study which was what the IOM suggested would be the best approach. And we have applied for NVPO unmet funding for -- for the follow-up study with that, as well as Carole mentioned in terms of the follow-up on the previous DTaP trials in which those in Sweden and in Italy, in which you have the randomized arms, and see if we could follow up with those cohorts, all by it with possibly lowered thimerosal exposure than in the U.S. settings. So those are what's happening there.

DR. MODLIN: Thanks, Bob. Further comments, questions?

(NO RESPONSE)

DR. MODLIN: Thank you very much.

MS. REDWOOD: Could I ask a question of Dr. Heilman, please?

DR. MODLIN: Certainly.

MS. REDWOOD: Dr. Heilman, I was just curious about the amounts of mercury that you found in the stool, what those levels were, and if it would not be that the mercury had to have been, at some point in time, in the

blood for it to have gotten to the stool. It wouldn't just go from an IM injection to the stool, but possibly you missed those blood levels.

DR. HEILMAN: I'm trying the numbers. Just a second.

MS. MURRAY: May I have your name, please?

MS. REDWOOD: Lynn Redwood.

MS. MURRAY: Thank you.

DR. HEILMAN: I do apologize, but I don't have the actual numbers with me. The paper, as I said, will indeed be published very shortly and this is research that was done by John Treanor. So I'm just reporting on the summary on it.

MS. REDWOOD: Weren't they around like 50 to 80 micrograms or so per gram?

DR. HEILMAN: As I said, I don't have those numbers.

MS. REDWOOD: Okay, thank you.

DR. MODLIN: The next update is scheduled to be from the National Vaccine Program, and Dr. Myers is not here.

DR. PETER: Steve is here.

DR. MODLIN: Steve?

MR. SEPE: Yeah, thanks. Good morning. I have a brief report from the National Vaccine Program Office.

Georges Peter will then provide an update for the Committee on the activities of the National Vaccine Advisory Committee.

The first update I have is in regards to the National Influenza Pandemic Preparedness Plan. The plan was last submitted to the Department in July of 2001. Revisions were made based on Agency input, and it is currently back in the Department and we're awaiting response from the Department regarding additional comments.

What is currently up there is the plan plus 16 accompanying annexes. And as I said, we're awaiting review at the Department level and, hopefully, we can get this plan approved in the next few months.

The NVPO coordinated the preparation of a report to the House and Senate committees on appropriations regarding the delay in submitting influenza vaccine for the 2000-2001 influenza season. This was a multi-agency effort. The report was submitted in August and explains the basic procedures for yearly influenza vaccine production and distribution, problems encountered in influenza vaccine production

during the 2000-2001 season, actions taken by the Department in its operations divisions, continuing issues in influenza vaccine supply, and recommendations being implemented by the Department to improve vaccine distribution in the future.

The Secretary has specifically requested that the NVPO and the Interagency Vaccine Group see vaccine supply as a high-priority. One thing which has already been done is the NVAC, the National Vaccine Advisory Committee, has convened a work group on vaccine supply, which Georges will provide you an update on.

Finally, the -- we have prepared and the Secretary has signed a recommendation to all DHHS agency health clinics to only give influenza vaccine to those at high-risk initially. That recommendation has been distributed throughout the Department and into the Agency health clinics. So, hopefully, they will -- they will respond and only give vaccine to high-risk individuals initially.

Georges?

DR. PETER: Thanks to Geoff Evans, I have a PowerPoint presentation. Well, Steve Sepe has provided you with

an update on the activities of the National Vaccine Program Office and I will concentrate on the activities of the National Vaccine Advisory Committee meeting. We were scheduled to have a two-day meeting in Washington on October 2nd and 3rd, but because of the events in Washington at the time, we decided to postpone the meeting. But we realized the necessity of convening because of certain priority issues, namely the IOM report which has implications and challenges for the NVAC. We met by teleconference, which was announced in the Federal Register and was successful during a three-hour period of time on October the 2nd. The major issue initially was the presentation by Kathleen Stratton of the report that we heard yesterday from Marie McCormick, and two particular recommendations on the public health response required NVAC review. The first is public health policy decisions under uncertainty, which is indeed the exact language of the IOM report; and secondly is strategies to communicate rapid changes in vaccine policy, both of which the IOM report noted needed review and perhaps improvement. As a result, we will be forming a work

group to examine the basis under which these decisions are made, as well as how they are communicated. And this work group will be formed during the course of the fall.

Second is related to recommendations for topics to the interagency vaccine group for the IOM safety review committee. As you know, this contract is for three years. A total of nine topics will be examined, and our role is to make recommendations for future topics to be examined by this committee.

The next that the IOM report, as you know, will examine is the possible dangers of multiple antigens, i.e., is immune overload a realistic possibility or not. We have made a recommendation to the interagency group that the next topic following that one would be the putative association of hepatitis B vaccine and neurological disorders.

The second aspect that we are examining is what topics would follow and we've established a matrix for consideration of future topics we would recommend for consideration to the interagency group for future review by the IOM.

I discussed yesterday at length the workshop on intussusception and rotavirus vaccine. We will review that report at our next meeting. I think our role is a different one from yours in the sense that our role is to foster the development of new vaccines, how do we enhance public sector/private sector collaboration, and indeed this report has perhaps implications that we need to consider because the challenge is how do we foster the development of a rotavirus vaccine -- this is a specific example -- for the international community and, indeed, we recognize that as a very high priority which has been already stated by the World Health Organization and by GAVI. The Standards for Adult Immunization Practices, which has been reviewed by the working group of the ACIP and numerous partner organizations, including the American Academy of Family Physicians, the Infectious Disease Society of America, the American College of Physicians, and other organizations, has been submitted to JAMA and we have an expectation of publication in perhaps early December. I think these will be a definite improvement and update from those

that have been in existence since 1990.

We have companion standards on child and adolescent immunization practices. We had some debate about calling them pediatric standards and, if so, did we need to have adolescent immunization standards, but we have combined the two of them. These standards have been approved by the National Vaccine Advisory Committee and are now -- have been reviewed by ten key partner organizations. Their comments have been -- will be assimilated. The document will be further submitted then back to them for final approval and we look forward to publication -- a promulgation of these standards, I would believe, early next year.

Another major topic that we've been asked to review is the question of immunization recommendations, and of course, these can vary from an elective immunization to universal recommendations with or without mandates. And by mandates, I mean school immunization laws. And in order to examine and establish a framework for states to make these decisions, our work group has organized three meetings. The first was in Nashville on September 10th and 11th, and of course, the second day

was cut short by the tragic events in New York and Washington. The next meeting will be in Denver on the 8th and 9th; and the third will be in Boston on December 4th and 5th. And the format of those meetings is to examine how public health policy is established when implementing vaccine recommendations at first, the national; second, the state; third, the local; and fourth, the consumer prospective. And indeed, a report will be issued. We're not going to say whether or not immunization -- whether school laws should be utilized but, rather, establish a framework by which decisions can be made and the public health agencies can utilize in assessing which vaccines might warrant school immunization laws, which are better fostered by other means such as universal recommendation without state laws, which ones are better based upon elective utilization.

Vaccine supply was already mentioned by Steve Sepe, and we do have a work group which has prepared, together with NVPO, a list of concepts which include options and strategies for addressing this problem. This topic is a major priority with the Department and we are planning

a workshop, hopefully in early 2002, in which to examine this question in greater detail, which, of course, would involve multiple organizations, including industry who are a key partner in this issue.

The plan for pandemic influenza preparedness has already been mentioned by Steve and is fairly far advanced. And finally, the NVAC work group on introducing new vaccines was in response to the crisis in the private sector over vaccine financing when pneumococcal conjugate vaccine was introduced, and our work group has indeed begun to look at the various issues, but I think the most important development is that an IOM committee will be specifically examining the financial elements, and I think we will await that report, too, before indeed we make any further recommendations. But it does -- our work group does address a major issue, how do we expeditiously and efficiently introduce new vaccines so that their value becomes recognized as soon as possible.

I believe that is the end of my presentation. I would be glad to answer questions.

DR. MODLIN: Questions for Dr. Peter?

(NO RESPONSE)

DR. MODLIN: Thanks, Georges. And the final update will be from the National Center for Infectious Diseases. Dr. Alison Mawle.

DR. MAWLE: I believe I'll do it from here since I don't have a PowerPoint presentation.

DR. MODLIN: Okay.

DR. MAWLE: I just wanted to update the Committee on a publication that came out since the -- I guess it was about a month ago. I think probably many of you are familiar with the emerging infectious disease plan, The Strategy for the 21st Century, which was actually published three years ago this month. NCID took the leadership in putting this document together, though it's a CDC-wide document. In that plan, there were a series of target areas that were essentially put in there to expand our focus. The one you're probably most familiar with is antimicrobial resistance, because I think that's the one that's really been out there in the news the most. However, one of the others was vaccine development and use. And all of those target areas, we've been putting

together brochures for our constituents -- I mean, this is a general brochure -- that will give some idea of what we're actually doing specifically in those target areas over the area of the plan -- at the time of the plan, which essentially will be sort of five years. So I just wanted to bring that to ACIP's attention and just very briefly go through some of those activities because you kind of think after three years we might have got somewhere with them, and indeed we have.

The way each of the target areas is organized is the same as the plan. There are four goals: surveillance and response; applied research; infrastructure and training; and prevention and control. So I'm not going to go through each one in detail, but I would just like to highlight one from each area that NCID has been involved in.

So under surveillance and response, one of our focuses has been to develop molecular immunologic tools for surveillance of organisms that cause VPD's, and I think I presented to you in detail before the establishment of the varicella molecular biology lab and you'll probably hear a little bit about that during the

presentation this morning. But from absolutely no lab capacity, what, three years ago, we now have a state of the art varicella lab which is able to track strains and is collecting a worldwide series of varicella strains which we seriously hope will be able to tell us what happens when you bring the vaccine in. Under applied research, we have -- one of the areas was to investigate natural acquired protective human immune responses to diseases such as malaria. And we've actually had a very active malaria immune response program for a long time. We have a field station in Kenya and we have in Kenya in a longitudinal cohort of mother and infant pairs that have been under active surveillance and we've studied their immune response at least five years, if not longer. And that is an ongoing study. From those studies, we have developed a prototype peptide vaccine, which is known as Fabach I [phonetic]. It's multi-epitopes from just different stages of the malaria parasite, and that is currently being put into GNP production for Phase I trials in conjunction with the malaria vaccine initiative. So that's been a very successful area.

Under infrastructure and training, establish laboratory networks for diagnosis and molecular epidemiologic study of VPD. One of the areas we've been most active in is in Africa. The lab capacity in Africa for diagnosis of a lot of diseases of interest is, as you're well aware, woefully underserved. The Division of Bacterial and Mycotic Diseases has been very focused on the laboratory diagnosis for meningitis, and they have a -- put together a protocol for lab diagnosis of hib, pneumococcal disease, and meningi. They have been doing training -- They have been setting up a network all over Africa. They have done two trainings, one in the English-speaking -- the English-speaking countries and one for the French-speaking countries. Those protocols are available through the web, and we are hoping that that will be a part of the integrated disease surveillance that has been set up in Africa as a separate entity but is also connecting with some of the GAVI goals and targets for Africa.

And lastly, under prevention and control, obviously, eradication of polio still remains one of the number

one goals. As you're well aware, NCID has the Wells reference lab for polio but the other area that we have a major focus on, along with NVPO and other government agencies, is now lab containment of polio after eradication. So we're very involved right now in doing the surveys within the U.S.

DR. MODLIN: Is that it?

DR. MAWLE: That's it. If anyone wants a copy of this, I'm going to put some on the back.

DR. MODLIN: Thank you. Are there any questions for Dr. Mawle? Stan?

DR. PLOTKIN: Yeah. May I ask an obvious, though jarring, question? What are plans for surveillance of biowarfare agents? Is there a surveillance plan for the possibilities that now exist?

DR. MAWLE: In what context? I guess that I would say that everything you hear on news is --

DR. MODLIN: Allison, you need to use the microphone.

DR. MAWLE: I'm sorry. I think what you're hearing on the news right now is our surveillance plan in action. Are you asking --

DR. PLOTKIN: Is there a published surveillance plan

for agents -- the variety of agents that might be anticipated?

DR. MAWLE: If you look at CDC's web site on bioterrorism -- or bioterrorism response, I should say -- I think you'll find there's a list of agents and you'll find a fairly detailed response of our approaches to that. I mean, I think you're aware of the select agent rule, and if you're talking about surveillance within this country, all movements are tracked of any of those agents between labs.

DR. MODLIN: Dixie?

DR. SNIDER: Yes. I might just add that CDC has been working very closely with the Counsel of State and Territorial Epidemiologists, and we have bioterrorism preparedness folks and Health Alert Network folks in the various states with whom we have been maintaining close contacts. We're providing them information on a routine basis in reinforcing, for the most part, messages that we have already crafted and, as Allison mentioned, are on the CDC web sites, reinforcing that and considering how we might broaden the messages to include laboratory workers and practicing physicians

and infection control folks and delineate for them more clearly their individual roles and what they might be on the lookout for and what they should report. Obviously, it's a tricky issue in terms of trying to pick up things early and still be specific enough that you aren't just getting reports of influenza as it begins to occur.

So these are some difficult issues, but we are working with the appropriate authorities at the state level to so that they can further work with their constituencies to maintain the appropriate enhanced awareness that we all recognize needs to be maintained.

DR. MAWLE: I would like to say just in terms of what's published, the lab networks that include the different state labs, there is a MMWR that I think was published last year that details that surveillance network, and obviously, CDC is the focus of that.

DR. MODLIN: I think we can say also that we are reactivating the bioterrorism work group of the ACIP as we speak, and the intent is that the group will serve or be available to serve on a consultative basis to the CDC as needed.

The work group has been chaired by Chuck Helms. Chuck is not here, but we will be getting the group together literally immediately. You may recall that this group has been very active in the recent updates of the anthrax statement and the smallpox statement which was just published this past summer and has been working on a consultative basis with a similar group from the Department of Defense as well. So I just thought I would mention that.

Any other comments for -- or questions for Dr. Mawle?

(NO RESPONSE)

DR. MODLIN: We're scheduled to have a break now. I think since we're about 30 minutes ahead of time, I'm going to ask if Susan Reef and Stan Gall are ready to go. And I understand that Susan will be making the presentation on a proposal to decrease the time interval recommended to avoid pregnancy after receipt of rubella vaccine on the basis of the data for -- the need to make this decision.

DR. REEF: Good morning. I'm going to first give a presentation and then followed by a discussion of the practicalness of it by Dr. Stanley Gall.

Today I would like to present -- provide the Committee data to consider for reducing the time period for avoiding pregnancy after receipt of a rubella-containing vaccine. First, I would like to provide background data and then the data from clinical trials.

The current recommendation says to avoid pregnancy for three months after the receipt of rubella-containing vaccine. And from discussing with different people on the Committee at this time, in the '70's, it was based on the isolation of vaccine-like virus from the eye of one fetus in a mother who had been inadvertently vaccinated with HPV77 duck embryo seven weeks prior to conception. Currently, this vaccine is no longer used in the United States and these findings have never been reproduced.

I want to present additional data today that shows no evidence of infants with CRS after inadvertent vaccination in the mother.

Just a little background. Rubella is considered a mild febrile rash illness in both adults and children. However, rubella infection in pregnancy can result in

miscarriages, still births, fetal deaths, asymptomatic infections in infants, and then a group of birth defects known as Congenital Rubella Syndrome, or CRS. Some of the defects include cataracts, hearing impairment, and heart defects. And the goal of any rubella vaccination program is the prevention of intrauterine rubella.

As you've heard many times probably in advertisements for CRS, it is timing is everything: timing of the maternal viremia that subsequently infects the placenta and then the fetus; and the most important determinant for fetal outcome is the gestational age at the time of infection.

Other key issues have to do with the timetable for organogenesis. And week three to six is by far the most critical time period for the development of heart, CNS, and eyes. Eyes can go out to week eight and also for hearing, it can go out to the week 16. So that's why many times you see just selective hearing impairment.

Through clinical trials, it's been known that viremia occurs usually seven to 11 days after receipt of the

vaccine and usually clears well before 21 days. Many experts back in the early '80's considered the high-risk period for CRS and inadvertent vaccination to be one week before conception to four weeks after, and it has to do with -- the one week before has to do with viremia at the time of conception to six weeks after conception.

Exactly why is this important for the United States? As you know, reported cases of rubella are at a record low level and so is CRS. Most of the rubella cases now occur among foreign-born adults and most of our CRS cases in the U.S. are born to foreign-born mothers. It's estimated about 40 percent of our CRS cases could be prevented, but they occur due to missed opportunities. And as noted, the high-risk population for rubella is women of childbearing age. And basically, rubella is occurring in that population. And one issue we really want to look at is eliminating as many barriers to receipt of rubella vaccine as possible, and one way to do that is by decreasing the time interval from three months to one month.

Another group that we need to look at is women that are trying to get pregnant and are undergoing fertility treatments. They, too, are a risk population, and for them, timing is everything for them also. And three months sometimes is just too long to wait even though they're susceptible, and Dr. Gall will talk about that. I just want to quickly review the rubella vaccination policy. In 1969, the rubella vaccines, the HPV's, there was duck embryo and dog kidney, and Cendehill vaccines were licensed. At that point in time in the ACIP recommendations, it was to avoid pregnancy for two months. In 1971, the Vaccine in Pregnancy Registry was established. In 1977, the time period was extended to three months on the basis of the one case I talked about in an aborted fetus.

In 1979, Cendehill and HPV vaccines were replaced by the RA 27/3 vaccine which is basically the vaccine that has been used since that point in time in the U.S. and is probably the most used vaccine worldwide. After much consideration, the registry was terminated in April of 1989. At that point in time, 321 susceptible pregnant women had been evaluated. As noted, no CRS

cases were observed. And in the 222 infants that had had blood samples, only six had subclinical infections and were followed for at least two years or more and there were no adverse outcomes or abnormalities noted. Also noted is that there were four infants that had non-CRS congenital abnormalities, which was in the RA 27/3 vaccine. And this is similar to what you would see in the background rate of two to three percent for serious malformations.

And something to note is for products of conception, 17 out of the 85 products of conception that they got for the HPV and Cendehill vaccine, 20 percent of those products of conception you could isolate rubella virus from; whereas, only three percent from the RA 27/3.

I just want to go over the combined data for risk of CRS in infants born to susceptible women who are inadvertently vaccinated. This is three months before and during pregnancy.

The first column is the countries -- the U.S. data, Germany's data from Gisela Enders, Sweden, and the U.K.'s data. There is approximately 680 women to date that we have data available for that have been studied

and that have delivered live births. Of all those women, 13 out of 343 that we have serology for, there was an infection in 3.8 percent. What's most important is this is between one week before to four weeks after, as I discussed that being the high-risk period. We have available data for 293. I just want to point out, in the first study of Gisela Enders, they looked at a period of two weeks before to six weeks after, which basically captures also the high-risk period. So I put that together.

Of these infants and of the 680, what's important is, none of these infants had CRS.

And I would like to thank Dr. Gisela Enders for providing this data for us. She, after I asked her, went ahead and analyzed her data like she had never done before and provided it for us to look at and also for Ms. Pat Tookey, who provided us data from their national CRS system.

I just want to look at the risk of CRS in infants from what is the observed risk and what is the maximum theoretical risk. When you look at the three-month waiting period, the observed risk is zero with a .5

percent being the maximum theoretical risk or the upper confidence interval for 95 percent using binomial distribution. For looking at only RA 27, three -- it was .9 percent. Going down and looking at the high-risk period for all vaccines, it was 1.3 percent which is lower than the background rate for serious malformations or birth defects. And then for the -- looking at just only RA 27/3 only, it's 2.3 percent. I just want to also emphasize that the observed risk is zero. So the risk for CRS is still theoretical, albeit small because of the limited numbers.

I want to talk about additional supportive data. Throughout the western hemisphere, mass campaigns are being done in adults, both males and females. In the Caribbean, they have conducted mass campaigns in almost all their islands and they have followed women -- 241 women who gave birth to children after they were inadvertently vaccinated during the campaigns, and of those, they have found no cases of CRS. In another study that has not been published but has been presented in Canada by Mother Risk, they had 81 live births through which they found no infants with CRS. So the

issues with these studies are that, at this point in time, we do not know what the immunity status of these women are.

Another important piece of information from Dr. Gisela Enders is the periconceptual wild rubella. The question is looking at the -- around periconception who is at risk for getting for CRS infants. And what's important is they evaluated 61 pregnancies five weeks before to six weeks after the last menstrual period. Lumping together the before to one to 11 days, which is before conception, 38 women were evaluated of which zero women with wild disease had infants that were infected or had placental infection. However, 14 out of 23 after conception basically had infants that had CRS or had documented fetal infection looking at the products of conception. Important with this data also is women that were three to six weeks from the last menstrual period, it was almost 100 percent [inaudible] and the kids had CRS.

I just want to quickly summarize that no infants with CRS have been born to women that had been inadvertently vaccinated. Looking at the combined data from the

U.S., Canada -- U.S., U.K., Germany, and Sweden, the maximum theoretical risk is 1.3 percent. Currently, our recommendations in U.S. is based on one fetus using -- from a vaccine that was used back in the '70's and is currently no longer in use.

And the final is that rubella in the United States occurs among adults, and that includes adult women, and this is a high-risk group. And optimizing our strategies and decreasing barriers will be key in assuring immunity among these age groups. I just want to show you what the current wording is in the ACIP MMWR. At the end, it talks about -- of course, MMR and its component should not be administered to women known to be pregnant, and it goes down and it talks about measles and mumps vaccine. You should wait for 30 days after being vaccinated; however, for three months after administration of MMR or other rubella-containing vaccines. And looking at it, if the Committee agrees or after considering just putting that "becoming pregnant for 30 days after receipt with measles, mumps, or rubella vaccine."

Thank you.

DR. MODLIN: Susan, thank you for a terrific presentation. Stan, did you want to follow up?

DR. GALL: I can do it from here.

DR. MODLIN: Your preference.

DR. GALL: John, first of all, I would like to thank you for putting a mundane topic like rubella on the agenda after thimerosal and influenza and meningococcus and all the others. However, I certainly appreciate Susan's presentation which was excellent and I think brought the new facts out that need to be considered. I think the crux of the situation is that mumps and measles recommendations is to wait one month and rubella is three months. That makes MMR three months. And that certainly impacts on clinical situations. I probably get two calls a month from clinicians wondering why the discrepancy between measles and mumps versus rubella. In particular, in IVS centers that's a big issue. Women want to get pregnant as soon as they can. They now are tested and come up rubella-nonimmune and need to wait when really the sign says it's really not necessary. I think in your handout the epidemiology of rubella is certainly

changing with the increase in immigrants, and 92 percent of the congenital rubella syndrome being in foreign-born women. And therefore, the delay of three months is something that some of these people will not do and they will end up becoming pregnant and unfortunately contracting rubella.

So I think that the data suggests that a change in the recommendations would be appropriate.

Thank you.

DR. MODLIN: Thanks, Stan. Dr. Salisbury?

DR. SALISBURY: As my leaving note, if I could, Chairman, is just to say that we made this change in the U.K., a reduction from three months to one month, about ten years ago and we have seen no change whatsoever from the zero that Susan told you for the number of CRS cases after an inadvertent immunization.

DR. MODLIN: That's certainly helpful. It's suggesting that perhaps we've been a bit negligent on this side of the pond.

Victor?

DR. MARCHESSAULT: [Inaudible] and we still have no problems with that.

DR. MODLIN: I have to admit, I will take some personal responsibility having maintained the rubella registry back in the mid-'70's perhaps for the three-month period and will say that I, myself, have absolutely no will take no hombrage.

Jon or Gary, any comments from the Academy?

DR. ABRAMSON: No. I think the data are pretty compelling.

DR. MODLIN: Okay. Any further comments or questions? Yes?

DR. STRICKUS: Ray Strickus, NIP. Susan, just for completeness sake, what proportion of women after vaccination with RA 27/3 will excrete vaccine virus beyond 28 days after vaccination? What proportion will be excreting virus -- or have viremia, not excreting virus -- excuse me, have viremia at 28 days or more beyond vaccination?

DR. REEF: What I have seen in the literature is that it's -- they clear it before 21 days, is what I've seen. Does anybody have any additional data?

DR. MODLIN: Stan may.

DR. REEF: Stan?

DR. PLOTKIN: Yeah. The -- In terms of recovery of virus from blood, I have never seen any beyond 21 days and that is exceptional. It's usually seven to 11 days. I would support this change and, in particular, one piece of evidence that's quite interesting was published in the German paper where they were simply testing situations where vaccination had occurred around pregnancy. And they did recover from one infant rubella virus -- This, as Susan pointed out, is a rare circumstance but does occur -- and they -- this was a persistent infection, but the interesting point was, even in this rare situation, the infant was normal and was followed for a couple of years and continued to be normal.

So even under that extreme situation, there appears to be essentially no risk of Congenital Rubella Syndrome.

DR. MODLIN: Okay. This does require a change in our recommendation and I assume that this would be published, Susan or Melinda, as an update once -- if and when it is finally accomplished.

DR. WHARTON: I think that this could be a brief notice to readers.

DR. MODLIN: Okay. Dixie, do people who are conflicted with Merck have to abstain? This is largely a safety issue regarding MMR vaccine.

DR. SNIDER: I think maybe -- Yeah.

DR. MODLIN: Maybe for the purposes of keeping us completely squeaky clean, we will ask how many individuals are conflicted with Merck?

(SHOW OF HANDS)

DR. MODLIN: Dr. Rennels, Dr. Offit, Dr. Clover. So we still have -- and Dr. Levin. So that means we almost certainly will not have a --

DR. SNIDER: That will require the ex officios to vote on this issue.

DR. MODLIN: Okay. Could I entertain a motion that the -- David?

DR. JOHNSON: I move that the ACIP recommend a decrease in the time interval from vaccination to pregnancy down to one month.

DR. SMITH: I second it.

DR. MODLIN: Okay. The motion has been made by Dr. Johnson and seconded by Dr. Smith that the interval for immunization -- interval that we recommend that women

wait before becoming pregnant after immunization be decreased from the current three months to one month. Any further discussion?

(NO RESPONSE)

DR. MODLIN: Okay. Those in favor? Those in favor would be: Dr. Word, Dr. Brooks, Dr. Johnson, Dr. Smith, Dr. Tompkins, Dr. DeSeda, Dr. Modlin, Mr. Graydon, Mr. Sepe, Dr. Groom, Dr. Diniega, Dr. Heilman, and Dr. Evans.

Those opposed?

(NO SHOW OF HANDS)

DR. MODLIN: Those abstaining? Those abstaining: Dr. Rennels, Dr. Offit, Dr. Clover, Dr. Levin, and Dr. Midthun.

Thank you. Susan, thank you and Stan for bringing this to our attention.

Yes?

DR. ATKINSON: One quick question --

DR. MODLIN: Yes, Bill?

DR. ATKINSON: -- a mundane topic. Bill Atkinson, NIP.

The general recommendations are currently being edited

by MMWR. Obviously, there's a big section on pregnancy and vaccines and in there we can make this change. Just one clarification. You just voted on a month. The 1998 MMR statement defines a month as four weeks or 28 days. So can I have the permission of the group to actually make this consistent with everything else and make this actually four weeks or 28 days rather than one month?

DR. MODLIN: Do we have to vote again?

DR. ATKINSON: I don't know.

(LAUGHTER)

DR. MODLIN: The answer is yes.

DR. ATKINSON: Good. So we'll put it in. We'll make sure it's in the general recs, which should be published in January.

DR. MODLIN: Paul?

DR. OFFIT: Just one quick comment. For younger members of the audience who may not realize that the person who developed the RA 27/3 vaccine is actually sitting in this room. I mean, this is one of the great modern success stories. We saw as many as 20,000 cases of Congenital Rubella Syndrome per year in this country

and now see, you know, often less than 10. That was Dr. Stanley Plotkin. So thank you, Stanley.

(APPLAUSE)

DR. MODLIN: Paul, thanks. And with that, we will take a break and ask that everybody return at 10:15.

(RECESS FROM 9:44 A.M. TO 10:19 A.M.)

DR. MODLIN: Could I ask everyone to please be seated? Since we are ahead of schedule, Dr. Van Beneden and Dr. Whitney I don't believe are here yet. So we're going to -- Are you-all ready to go, up and ready to go? Terrific. So we will. We had Dr. Seward and her group prepared to fill in, but we'll stick with the original agenda and the next item on the agenda will be an update on pneumococcal conjugate vaccine and will be led --

DR. WHITNEY: Good morning, everyone. Dr. Van Beneden will -- Can you hear me?

DR. MODLIN: Yeah.

DR. WHITNEY: Good morning. I'm Cindy Whitney. Chris Van Beneden won't be here today. She has been called to New York. So I'm going to start off by talking about some surveillance data for pneumococcal disease and then I will do the section that Chris was

going to talk about, about a new surveillance system we're starting.

We've seen a decline in invasive pneumococcal disease in the U.S. in the year 2000. And I think what I have to tell you today is really some good news that suggests that this decline is really in effect of the pneumococcal conjugate vaccine.

As you recall, pneumococcal conjugate vaccine, or Prevnar, was licensed in February of 2000. In August of 2000, the AAP published their recommendation for use. In October of last year -- so we're in the one-year anniversary now -- the ACIP's recommendations were published. And in the latter half of last year, various state agencies and federal agencies purchased vaccine. So it really was in the last -- it was the second half of last year that the vaccine was coming into use more widely.

So when we think about when the effect might have occurred, it's probably in that second semester.

So just to remind everybody what we came up with. ACIP recommended the vaccine be given to all children less than two and then to a subset of children two to

four years who had certain chronic illnesses and immunocomprising conditions. And then we came up softer wording for children two to four who had various -- had these three situations so that physicians could consider giving vaccine to these children. So, again, when we think about where the vaccine effect might be, it's going to probably be strongest in children less than two and then there will be some effect, but probably not strong, in children two to four.

So what are the potential vaccine effects that we might see? And here are some of the findings that were found in some of the pre-licensure research. There was a lot of efficacy against invasive disease due to serotypes contained in the vaccine. There was possible protection against vaccine-related strains and this was seen with both invasive disease and otitis media. The vaccine showed -- The vaccine had some effect in reducing carriage in the vaccine-type strains and also probably reduces transmission of those strains. However, there was some data to suggest that there is replacement carriage with non-vaccine-type strains and maybe even a little bit of replacement otitis media

with strains that aren't in the vaccine.

So what are our surveillance objectives to try to measure this effect? First, we're going the look at invasive disease due to vaccine serotypes in young children and possibly in older age groups as well to see if there is a reduction in transmission. Second, we're going to assess the effect on vaccine-related types and then we're going to look at types that aren't in the vaccine to see if there's been any effect on replacement disease.

The system we're using is called ABC's, or Active Bacterial Core Surveillance. There were seven states that participated in this system between 1998 and 2000, which is the data that I'm going to be showing you: Portland, Oregon; San Francisco County in California; the twin cities in Minnesota; Atlanta, Georgia area; Rochester, New York; the entire state of Connecticut; and Baltimore, Maryland.

Here are the ABC's methods. A case is defined as pneumococcus isolated from a normally sterile site. The surveillance personnel actively contact clinical laboratories to identify all cases in a catchment area

and then audits are conducted to ensure that complete reporting is ascertained on all the cases. Isolates are collected for susceptibility testing and serotyping at reference laboratories and then we do a little chart review to get some clinical information. So now the results. This is a table of invasive pneumococcal disease cases by year and age group. The age groups are on this side and across the top I'm comparing the number of cases in the year 2000 to the average number of cases that we saw in 1998 and 1999. So, for example, in less than two, there were 800 cases on average in '98 and '99. In 2000, we only had 634. So it was a 20 percent -- almost a 21 percent reduction in the average number of -- in expected cases. And you can see in the two- to four-year-old age group -- again, this is our catch-up group -- there's a 15 percent reduction; and in this age group, which is five to 39, which I wanted to look at because I thought it might indicate some transmission within a household, there was also a reduction of the same magnitude. In these older age groups, there was really almost no change in the number of cases compared

to the previous year, and when you use the age 65 as the referent group, the changes in less than two are highly significant and you almost reach significance for this group here.

So I'm going to show you now some other data that suggests these changes are due to the vaccine. The vaccine purchasing was done at different times by different states, so you might expect that this effect would be more strong in some sites than in others, and that's exactly what we see. In California, which is a small surveillance site, we really picked up no effect, but in some of these other ones, some of which are very large, there's a very big reduction in the number of cases in the year 2000.

Also, as I indicated before, you might expect that the change in the number of cases would be strongest in the second half of the year and that's exactly what we're seeing. Again, this is a table by age group and the percent change compared to '98 and '99. Here's the first semester in this column and the second semester in this column. If you look at kids less than two, there's only a small reduction in January to June but

almost a 40 percent reduction in the latter half of last year. And in these other age groups, it's about 20 percent and there was a little bit of a change in the 65 and older. But when you look at the -- using that as a referent group, again, this change in less than two is highly significant.

So I think that if you just look at the case counts, the data is already pretty convincing, but let's go ahead and look at what we know about the serotypes. And for the rest of the presentation, I'm just going to focus on the latter half of last year.

This is a graph that just shows the number of isolates we've typed by their serotype. And the black part of the bars show the vaccine types. The gray, the darker gray, is the vaccine groups. So it's strains that are related but not exactly in the vaccine. And the lightest gray is other groups, the non-vaccine-type strains. So as you can see, in children less than two, there really has been this marked reduction in the vaccine serotype strains and it's hard to tell if there's really been any change from this kind of figure in the other groups or the vaccine-related strains.

And if you look at the age 65, there's been a little bouncing around over the three years but really no obvious change in the distribution of the serotypes. So let's take a closer look at the vaccine serotypes. So this is very similar to the last table I showed you. Again, this is by age group. This is the average number of cases in July to December of '98 and '99. Here's what we have for 2000 and here's the percent change. So this is just vaccine serotypes. Again, almost a 40 percent reduction in kids less than two, a 20 percent reduction in these other age groups, and if you compare those groups to the 65-year-olds as a referent, the less than two is highly significant. So I think we're seeing this strong effect in the latter half of last year in the vaccine serotype disease. Just a closer look at the vaccine-related and the non-related strains, just showing the less than two to the 65 and older. It's interesting. The numbers are very small, but if you look at the vaccine-related group, there's a 30 reduction that's almost as strong as what we saw with the vaccine-type strains but, again, the numbers are small and I'm not so sure we can draw

specific conclusions from that. If you look at the other -- the serotypes that are in the other groups, again, we only had 18 strains in all of last year and there's really no difference at all with what we saw with the over-65's.

So, in summary, I think we've seen a significant decline in cases in the second half of 2000 in children less than two and the decline is due to a decrease in the vaccine serotype strains. The small number of cases really limit our ability to confirm a reduction in vaccine-related strains, but this may be occurring and we'll have to keep an eye on that. And there's really been no increase in the vaccine serogroup strains that we can see so far.

So, in conclusion, I think that pneumococcal conjugate vaccine had a measurable effect on invasive disease within months of its licensure, within that first year, and I think that as coverage increases, we'll need additional surveillance data to indicate the magnitude of disease-preventable and further examine this potential for a replacement disease.

DR. MODLIN: Thanks, Dr. Whitney. A very encouraging

report. Let's open it up for comments and questions. Paul?

DR. OFFIT: Just one quick question. Do you get any sense that -- whether or not there's a decrease in invasive pneumococcal disease caused by serotypes in the vaccine in children who were not vaccinated? In other words, that there is a herd effect due to decreased colonization.

DR. WHITNEY: I don't have data to examine that yet just because we don't have the vaccine histories on all of these cases that have been reported. We haven't kept track of that over time, so we really don't have a sense of -- we can't measure that right now with the data we have.

DR. MODLIN: Bill Schaffner?

DR. SCHAFFNER: Hi, Cindy.

DR. WHITNEY: Hi, Bill.

DR. SCHAFFNER: I thought you might just want to give them a heads-up about the case-control study that's underway.

DR. WHITNEY: Yeah. We're doing a multi-state case-control study within ABC's right now that's going

to look again at effectiveness and we might be able to get some of the herd data from that, but that study is finishing its first year right now and I think it'll take about three years to complete.

DR. MODLIN: Any other comments, questions? Dr. Paradiso?

DR. PARADISO: That was nice data, Cindy.

DR. WHITNEY: I thought you might like it, Peter.

DR. PARADISO: I'm not at all bias about that. I just think it's the reason we do this job.

Just as a advertisement, at the IDSA meeting on the 17th, which I think was Saturday, Steve Blackwell presented the Kaiser data which is part of the Phase IV studies and I think goes through March of this year and I tends to confirm the patterns that you're seeing here. And to Paul's question, we all speculated a little bit on herd immunity, but I think it's a little early to see that. But obviously, the data in the Kaiser study is showing a similar pattern.

DR. MODLIN: Thank you, Peter. Any questions or comments? Dr. Whitney, thank you very much.

DR. WHITNEY: I would also like to tell you about the

vaccine failure system that we're going to be starting, but I think I left my overheads over here.

So, obviously, Prevnar is a highly effective vaccine, but there are going to be sometimes when the vaccine -- when a child will get disease even though he or she has been vaccinated. And I just want to tell you just quickly about a system that we're designing that will track these instances where the vaccine has failed, as it were.

The objective of this system will just be really hypothesis generation. What we would like to do is explore situations in which Prevnar might be less effective in a certain subgroup of children.

So for this surveillance system, we're defining a case as a child less than five who has pneumococcus isolated from a normally sterile site, such as blood, spinal fluid, and who has received at least one dose of Prevnar. And we will count -- or examine cases where the strain is available for serotyping, obviously.

The methods of this system will be to collect to isolates and determine the strain serotypes and then we have a data collection form that will record host

and vaccine factors that may contribute to Prevnar failure, such things as chronic illnesses, immunosuppressing condition, age at immunization, time since immunization, number of doses, vaccine lots, and concurrent immunizations.

So how do we want people to report to this system? There is a failure case report form that should be sent in along with the isolate and a CDC lab report form through state health departments to our streptococcus laboratory, and then we will take care of the data from there. Forms and instructions are available from the NIP web site and cases may also be reported through VAERS, although that's not required. We will be exchanging information with them.

So that's it. We've been pushing now to make this system widely known so we can start collecting more cases.

DR. MODLIN: Thanks, Dr. Whitney. Ben, are you going to say something about vaccine supply?

DR. SCHWARTZ: Yes.

DR. MODLIN: Okay.

DR. SCHWARTZ: Well, the good news is that

pneumococcal conjugate vaccine works very well and prevents invasive disease. The bad news is we don't have enough of it. So what I would like to do is I would like to update this group on the supply situation for the conjugate vaccine. I'll then ask Kevin Reilly from Wyeth to add a couple of comments from the manufacturer's prospective, and then I'll conclude this presentation by talking about how ACIP can work with us to come up with the best approach to dealing with the situation.

The background is that there's been a high demand for pneumococcal conjugate vaccine. I think at a previous meeting Walt presented data on the number of doses administered in the public sector and that number is now similar to that for hemophilus influenza type B conjugate vaccine, indicating that the acceptance -- the update of this pneumococcal vaccine has been very good. Overall, the demand in both the public and private sector is estimated to be about one and a half to 1.6 million doses per month.

With this rapid increase in demand, the need for vaccine has, I think, perhaps exceeded the expectations and the

basis for production and, therefore, back orders by health departments have existed for much of this year. In August, for the first three weeks of the month, the deliveries of this vaccine had not been made because of some lot release issues with the company. And therefore, some very serious back orders existed at the beginning of the fall and the end of the summer. Therefore, on September 14th, a Morbidity and Mortality Weekly Report Notice to Readers was published making recommendations for vaccination in a setting of shortage.

I would like to share some of the numbers that have come from Dean Mason's group in our Immunization Services Division.

These are the numbers for inventory of conjugate vaccine at health department depots. And basically, projects that have 15 days or less of inventory are situations where a serious shortage would be experienced by providers in those areas and, as you can see, that situation exists for 28 out of the 56 grantees that provided information for this summary. In an additional 11 projects, there is between a 16- and

29-day supply which likely results in shortage for some physicians and the amount of vaccine is acceptable in only of 17 of those areas. And when I say acceptable, it's not optimal but probably not significant shortages in the public sector in those areas.

In addition, at the beginning of this year, the turnaround time for filling orders was only three days. At present, the longest date for a pending order goes back into mid-June. The average number of doses shipped per month in January through August was over 700,000 doses although many of those were delayed in August. However, if you look at the bottom of the figure, in September only 383,000 doses had been shipped. That's in the public sector. To get the total distribution, it's about double the public sector distribution.

I would like to very briefly review the vaccination recommendations that were published in that MMWR. Those recommendations were to continue vaccinating infants at two, four, and six months of age, to continue vaccinating those who were between one and five years and were at high risk based on the ACIP definitions,

but to defer vaccination of children who were between two and five years old and not at high risk, and then in situations where shortages were even more severe, to defer vaccination in the 12- to 23-month age group including vaccination of those who had not previously received any doses, as well as deferral of the fourth dose that's generally given at 12 to 15 months of age, and then to maintain records so that those who were deferred can be vaccinated later.

The rationale for these particular recommendations is that this approach would cause minimal disruption of infant vaccination. And the experience we had with hepatitis B vaccine and thimerosal suggests that when you disrupt vaccination of infants, sometimes it's very difficult to get back on track once the problem has been resolved. Secondly, these recommendations were made because they would provide the greatest protection of infants before the high-risk period which begins at about six months and extends through until about two years of age.

Pre-licensure studies have shown good efficacy of vaccine after three infant doses, so we felt that

deferral of the 12- to 15-month fourth dose may not be that detrimental. And then finally, the manufacturer indicated that increased vaccine delivery would begin in the fall and that we would catch up to some extent in the latter part of this year.

Since these recommendations have been issued, we have received comments from a number of people and a number of different groups and I will share those comments and critiques with this group. One of the comments was that we should have been more definitive rather than giving providers some leeway to adjust their own practices based on their own supply situation but rather should have created a level playing field for all providers whether or not they were short on vaccine. A second comment was that we should have recommended vaccination for unvaccinated kids between 12 and 23 months of age because these children are at higher risk for pneumococcal disease than some other children would be.

Other recommendations have centered around cutting one of the first three infant doses in situations where shortages are particularly

problematic, either vaccinating at two and four only or at two and six months. And then finally, some have suggested that we should begin vaccinating only at greater than six months of age when the entire vaccination series would be three doses instead of four doses so that a schedule might be six months, nine months when kids come back for a routine visit, and then at 12 to 15 months when they would be coming in and getting their additional dose of vaccine.

So these are some of the alternative strategies that have been proposed. What I would like to do is ask Kevin to offer some comments from the manufacturer and then I'll come back and present some more.

DR. REILLY: Thank you, Ben. A reply on behalf of Wyeth just to be clear there's no problem.

I think Ben has set the scenario that the demand of the vaccine has been exceptional and I think the acceptance of Prevnar has been very fast and very strong so that the -- what we would normally expect as the ramp-up period to high levels of compliance with the recommendations has been much shorter than we anticipated so that the demand for the vaccine has been

quite high.

We have distributed, in total, 11.4 million doses to the market through the end of September and that's covering the private and the public sector. And for clarify, as Ben mentioned, the public sector and the private sector are roughly equal, approximately 50/50 at this stage. I think in our tracking, the immunization rate for the primary series has already moved to above 90 percent compliance, which is really for a new vaccine fairly exceptional.

We are experiencing back orders and, you know, the shipments are tied into batch releases, large batch releases, which you saw yesterday with the discussion of the DPT vaccine also. The back order is rolling over. We are releasing product and shipping product, but back order has built up to be quite considerable at the moment and we are trying to work to get that down. We are also trying to work with the CDC, individual physicians, group practices to try to get the best use of the product and we will continue to do that to try to make sure that the product availability goes to the most -- the most important needs at this time.

I would also clarify, because there has been some questions about it, we are releasing product to both the public sector and the private sector and our release -- in fact, everything is roughly in balance. The total demand is roughly 50/50 public and private. The back order situation is approximately 50/50 between public and private. And we are shipping and releasing product approximately 50/50 on a monthly basis to public and private requirements. We are trying to run our system where first-in orders get filled first and try to rotate the orders in that way. We have been working with the CDC to try to fill orders to see CDC centers that are lowest in inventory. So I think the reference to the June census could be that they inventory on hand, but we have been working closely with the CDC operation side to try to put inventory in the places where it's most needed.

I think in overall in -- to be completely honest, two factors have contributed to the situation we're in now. Firstly, the demand was higher than we expected, but we're also actually releasing lower levels of product than we originally planned. We are working on

manufacturing issues in our facilities. The standards for vaccine manufacture are quite high and quite complicated. We meet all government regulations. All of the product released is up to the highest standards of current GNP, but some of the changes we're having to make in our manufacturing process, particularly our post-manufacturing processes, which is the processes involved in terms of preparing a release and getting release of batches, is extremely complicated and have created a bottleneck. We do have manufacturing capacity because we're also scaled up to introduce this product internationally. Our total manufacturing capacity is in excess of 30 million doses. So we do feel that we are going to be able to get out of this situation in supply. Whatever amounts of vaccine are needed in the U.S., 30 million is well in excess of any feasible level in the U.S., but we are experiencing bottlenecks in terms of getting release of product at this time. We're working on that and putting in extra resources to resolve that as fast as we can. It is not an easy situation. It's not a simple situation of just turning the tap on higher.

At the beginning of September, we thought the we would be out of it by the end of this year. Our assessment now is we look like we'll probably be having rolling back orders into 2002. We feel that we'll get out of the back order situation by about the end of the second quarter of 2002.

Thanks, Ben.

DR. SCHWARTZ: When we spoke with the company representatives before publishing the MMWR, projections were made that the amount of vaccine distributed in September, October, November, and December would vary between about one and a half to two and a half million doses a month. Given that the September distribution has fallen far short of this projection and given what Kevin has told us, we have concerns that the recommendations that had been published previously will not be sufficient to provide guidance to clinicians in the public sector as well as in the private sector regarding optimal use of supplies of this vaccine. Therefore, I would propose the following strategy.

We would ask that ACIP reconstitute the pneumococcal

conjugate vaccine working group -- and it's good to see that Dave Johnson is here today -- and that that working group then include representatives from ACIP, from AAP and AAFP, from FDA, as well as from CDC. We would propose that the working group evaluate data that are available from the manufacturer and from other sources on production issues, on vaccine demand, and doses used for infants versus used for catch-up, as well as on the immunogenicity of more parsimonious vaccination strategies for infants.

We would then look to this group to come up with a possible revision of the September 14th guidelines and then I would ask the Committee whether those guidelines should be published as an ACIP or CDC recommendation before we have our next scheduled meeting in February or whether you would propose some other order of events so that we can get the guidance that's needed out there as soon as possible, yet make sure that all the comments and concerns of this Committee and of the liaison organizations are taken into account.

DR. MODLIN: Ben, your request is obviously an important one. I would just point out that the

guidelines that were published earlier in September were not ACIP guidelines. We did not build in contingencies for vaccine shortages into our statement but were necessary considering the information that had become available to the program.

I think the best way -- Let me personally offer I think the suggestion to get the working group together as quickly as possible to deliberate this issue is probably the most appropriate step, and if necessary, this is something that since we have a conference call coming up anyway, we might be able to deal with at that time as well if there's something that requires the action of the Full Committee.

Dave?

DR. JOHNSON: You almost took the words right out of my mouth, John. I don't think that it would be prudent for us to wait until February to take this issue up and have a vote on it at that time. So if we can do it in conjunction with our telephone conference call around thimerosal and vaccines, that timing might be good. I would -- but otherwise, I would think that if we can't do that for some reason, I think we should do

our best to make recommendations to CDC and have a CDC statement revised.

DR. MODLIN: Okay, fine. Jon, how do you guys feel about this process?

DR. ABRAMSON: Yeah, I think it needs to be speeded up. There are other concerns that we have about how the vaccine is being distributed and we're going to be discussing those at the COID meeting. I think those also have to be taken into account.

DR. MODLIN: So this will be an opportunity to introduce that into these discussions.

DR. ABRAMSON: Yeah.

DR. MODLIN: Natalie?

DR. SMITH: Yeah, I agree that there's -- the field needs a lot more clarity on what the recommendations are. I'm particularly concerned about suppliers that may have zero doses and I also hope that there is an equitable distribution. There are some kids that are being missed entirely.

DR. MODLIN: That's a good point. It does need our attention. Peggy?

DR. RENNELS: I just had a question that I need

an answer to. You mentioned the efficacy was good after the three primary doses. Could you give us a figure?

DR. SCHWARTZ: The study that was done pre-licensure at Northern California Kaiser showed greater than 90 percent efficacy in the interval following the third dose before the fourth dose given at one year. The data that we don't have is how many people may have missed that fourth dose and what the efficacy is among those who were only vaccinated with three doses for a longer period. We're thinking that maybe as we get the group together, as we get information from the company that may not be published, and that as we include the folks as consultants to the group -- for example, Steve Black from Northern California Kaiser -- that we may be able to get more information that would supplement what's already available to address that issue.

The other issue clearly that I think we should consider is the possibility of using a dose of the polysaccharide vaccine and we would look forward to any information that the manufacturers might that would help us look at that question.

DR. MODLIN: Well, we do have post-licensure studies going on, presumably. So, yes, Dennis?

DR. BROOKS: Yeah, I have a question that maybe Walt can answer. We get two supplies for Prevnar. One if for private patients and one is for VFC. We've been able to get the private supply but have been able to get the VFC supply for many weeks actually.

DR. ORENSTEIN: As Kevin mentioned, we're receiving overall at CDC 50 percent of the overall production, but it's clearly not adequate. We have been working with the states and we have preferentially tried to give it to states with zero inventory. I don't know what the Maryland situation is and how they're prioritizing vaccine, but we are trying to prioritize what we get to states who are reporting that they have zero inventories in their state depots.

DR. MODLIN: Yes, Eric France?

DR. FRANCE: Eric France. You mentioned, Ben, that it may not have been clear to all providers that if you did not have a shortage in your own clinic you should be following these recommendations. And certainly, again, thinking personally at KP Colorado, we have made

much effort to change our providers' practices and that's probably true in other places and maybe a short-term or almost immediate notification might help to free up some supply for those physicians that are in need for just the minimum, and something rather quickly in terms of communication might help with that.

DR. SCHWARTZ: I think that would be an excellent first step. One of the things that Wyeth has proposed is sending a letter to groups that order this vaccine along with the MMWR recommendations and perhaps that can be included in the communication, and we can work with the company on that document.

DR. MODLIN: Okay. Further questions?

(NO RESPONSE)

DR. MODLIN: Ben, thank you very much.

The -- I just want to note that the session this afternoon on the OSHA requirement for engineered needles we will not be able to -- Ms. Hogan will not be able to make it. So we will not have that session. Since we are running a little bit ahead, my suggestion will be to make an attempt just to work right through whatever our lunch hour may be and finish up quite a

bit earlier so that people can possibly make earlier flights, if necessary. Is there any problem with that?

DR. OFFIT: Is there going to be -- There was a Yellow Fever working group at lunch? Is that still the case, or not? I guess --

DR. MODLIN: Well, that's a good point.

DR. CLOVER: Yes, it is. It is still scheduled --

DR. MODLIN: Which is an important meeting. So maybe it would be best to go ahead and have our lunch break or at least plan on that so that the working group can --

DR. CLOVER: The other option is just -- let's continue as is, and the Yellow Fever working group will just stay after and that doesn't keep everybody else from --

DR. MODLIN: I think we will have the time to do that. We certainly made up the time in the schedule. Would that be okay?

DR. CLOVER: That will be fine with me.

DR. MODLIN: Okay. We could achieve two goals. And that being, we'll start with the next item on the agenda which is an update on varicella disease and

varicella vaccine. Dr. Jane Seward, Karen Galil, Dr. Jumaan, and Dr. Vessey are listed on the agenda as presenters. Jane, you're leading off, I assume?

DR. SEWARD: I am now. Good morning. It's been six years since varicella vaccine was licensed. So we thought it was high time to show you some of the excellent data that we have now in coverage safety, effectiveness, and disease impact.

This work is the work of CDC, state and local health departments, special studies, FDA with VAERS, multiple parties, and many of them will be obvious today as I present.

Just to remind you about the burden of disease due to varicella in the five years preceding vaccine licensure, there were, on average, four million cases a year resulting in about 11,000 hospital admissions, 100 deaths, and the majority of deaths and hospitalizations occurred among children and adults.

Time line of policy decisions, just to refresh people who may not have been on the Committee at the time, the vaccine was licensed -- it's a live-attenuated vaccine, licensed in March of 1995. VARIVAX and Merck

is the manufacturer. In May '95, the AAP published their recommendations. A month later the ACIP approved theirs. There was a full year of delay until the federal contract was signed, so vaccine was not available in the public sector until the end of '96. In July of '96, the ACIP recommendations were published and then the years later the updated ACIP and AAP publications were published.

Just to remind you again, the ACIP and the AAP recommend one dose of vaccine for children less than 13 years, with routine vaccination at 12 to 18 months and any older child should also be vaccinated before their 13th birthday. For people over 13, it's a two-dose schedule four to eight weeks apart. The original ACIP recommendations recommended the vaccine for the first group listed there, which were health care workers and family contacts of immunocompromised patients. The updated recommendations also recommended the vaccine for susceptible persons at high risk for exposure or transmission. That includes day care center employees, teachers, et cetera, people in institutions, and the ACIP still says the vaccine is

desirable for all other susceptible adults and adolescents. The ACIP in the updated recommendations recommended the vaccine for post-exposure use, for outbreak control, for HIV-positive children with adequate CD4 percentage counts, and suggested that states put in place school and child care requirements.

To monitor the varicella vaccination program in the United States, we have varicella -- we have surveillance for vaccine. We monitor very carefully vaccine coverage through the National Immunization Survey, Vaccine Safety, through VAERS, and through special post-licensure studies. Vaccine effectiveness through a multiple -- lots of ways, outbreak investigations and special studies. And then we have surveillance for varicella and also now for herpes zoster.

Our vaccine distribution, as you can see here, there was rapid uptake in the private sector and delayed uptake in the public sector because the vaccine wasn't available. But since it's become available, the public sector uptake has been faster than the private sector uptake. 2001 is just half a year. In 2000,

there were 6.2 million doses of vaccine distributed and the birth cohort is four million. So I expect there's a fair amount of catch-up vaccination occurring.

The coverage, as you heard this morning, in 2000, vaccine coverage nationally was 68 percent, but that had risen by the first quarter of 2001 to 75 percent nationally. So we're very happy that the vaccine coverage is increasing and still continuing to increase. We're aiming for greater than 90 percent which we hope we'll reach well before 2010.

This shows where states rank for their coverage. There are three states with coverage over 80 percent now in red -- shown in red here. A number of state with vaccine coverage in the 70 percent range shown in orange, 60 percent, and then down to 30 to 40, two states here. So there's a considerable variation in coverage rates throughout the country.

Requirements for school entry, by September 2001, which was this school year, 27 states had implemented child care or school requirements. Nineteen states had both child care and school requirements in place. Seven states had child care only and one state had

school only, and another five states had past requirements that will be implemented over the next several years. There will be a number -- A number of other states are in process and this can change very rapidly. So another recommendation could pass anytime. And this just shows where the requirements are in place, red being child care and school, yellow child care only, and green school only.

This is a busy slide and I apologize for that, but it does show state rankings from the highest coverage in the District of Columbia, the lowest coverage in Idaho. The national average of 67.8 percent in the year 2000. What the slide shows is the red states here were states that had child care requirements implemented prior to 2000. So there's obviously an association between having a child care requirement in place and high coverage. I don't know which comes first. I think sometimes states that have a lot of interest put in a requirement, but clearly, once the requirement is in place, it's also going to increase coverage.

Surveillance for vaccine safety, we are not going to present this to the Committee because you saw some

of it at the time of the updated recommendations and we've shared three very complete peer review articles by Bob Wise and the FDA, with CDC as co-authors, Bob Sherrar with Merck, and these cover VAERS data, and then Steve Glack's post-licensure safety study. So all of you have seen those articles. I will just show one slide on results from the Merck/CDC VARIVAX in Pregnancy Registry.

The article that has been published on registry data which went through 3/16/00, you have copies of it now. These are updated data on 412 pregnancy outcomes from the time of licensure through six-year period post-licensure. The pregnancy registry monitors exposures three months prior to and all the way through pregnancy. Through this time period, of the 412 pregnancy outcomes, 97 women were sero-negative. There have been no cases of congenital varicella syndrome identified. So the rate is zero due to the small -- relatively small numbers. Still the 95 confidence interval goes up to ten. And women are continuing to be enrolled in this registry.

In addition, the registry and VAERS reports in

general have alerted us to the fact that there have been cases of product confusion with varicella vaccine administered to pregnant women where VZ was indicated. And this was -- There was a MMWR alert put out several years ago and this situation is continuing to be monitored closely.

The next section of the presentation on post-licensure vaccine effectiveness and breakthrough disease will be by Dr. Galil who works in the varicella activity with me and Dr. Jumaan.

DR. GALIL: I'm going to present data from the ten post-licensure investigations that we're aware of CDC. Some are published and some are going to be presented shortly.

What you know is that in the pre-licensure trials that were done, the vaccine showed 70 to 90 percent effectiveness against all disease and more than 95 protection against severe disease. Since licensure we've seen post -- vaccine effectiveness estimates that range from 42 percent to 100 percent and protection against all disease from 75 to 100 percent.

To remind you, we define breakthrough disease as

a compatible rash illness that occurs more than 42 days after vaccination, and that's so that we don't confuse some of the replication of the vaccine strain virus with breakthrough disease. The diagnosis has mostly been clinical certainly in the outbreak investigations because by the time the investigation is started, most of the cases have occurred. So we've been forced to rely on that. There's one study in which PCR positivity was used, and it's important to remember that if we're using a clinical diagnosis, we might underestimate VE. If you use PCR positivity, you might overestimate the VE.

In addition, there are differences in how severity has been defined in the pre-licensure trials. Most of them use the definition of less than 300 lesions and greater than or equal to 300 to be severe. In the more recent outbreak investigations, we have actually looked at disease as being mild if there are less than 50 lesions in total and no complications; severe if there are more than 500 lesions or any severe complications. So this slide actually shows the ten investigations that have been done since licensure and

they're shown in order of when they were investigated. And as you can see, the highest estimate overall is from Izurieta. That was an outbreak done here in Atlanta in '97. The effectiveness was 86 percent. And the lowest estimate to date is three up from the bottom, by Lee, et al., and that was an investigation in New Hampshire approximately a year ago. The vaccine effectiveness estimate was 42 percent. And as you can see the vaccine -- the confidence limits don't reach the lower limit of what we would expect for those vaccine. Another recent investigation by Berrios, et al., which will be presented shortly at IDSA, had the next lowest estimate of 59 percent. If you now look at moderate to severe disease, most of the estimates have been very high with the exception again of Berrios where it was 75 percent.

If we now look at some of the risk factors that have been identified for vaccine failure since licensure, the main ones are asthma and reactive airways disease which was found in an outbreak in Georgia, as well as a Boston school outbreak. And you can see the relative risk and confidence limits there. In addition,

systemic steroids at the time or shortly before breakthrough disease but not at the time of vaccination has been associated with a more than two-fold increase in risk. Eczema was identified in the Maryland school outbreak with a three times increase in risk and receiving MMR vaccine not on the same day but within 30 days before varicella vaccine increased the risk of breakthrough. And I should mention that that is contraindicated in the ACIP recommendations.

In Pennsylvania, Boston, and Maryland, age at vaccination appeared to be associated or was associated with an increased risk of breakthrough, and you can see the effect there. We were looking at children who were vaccinated at 12, 13, and 14 months of age in two of these investigations. And in Boston you can see, when it's broken down into these fine gradations, there may be an increase in effective age. These are pretty small numbers. And finally, time since vaccination may be a risk factor as well. In New Hampshire it was associated with a three times increased risk if it had been three or more years since you were vaccinated, and in Maryland, close to the same

for children vaccinated at least five years in the past. I should mention that some of these estimates are uni-variate, and certainly the Maryland, Boston, and New Hampshire outbreak analyses are continuing. So we hope to have multi-variate analyses before long.

The question arises, how significant is breakthrough disease? And I think we feel that that would depend on how infectious this is, what its mode of transmission is, and what the severity is. And I'll show you some data on all of those.

In the New Hampshire outbreak, the index case was a healthy four-and-a-half-year-old boy who was vaccinated at 18 months of age. He developed moderate breakthrough infection with approximately 150 vesicular lesions and was described by his parents as being moderately ill and was in bed for one day. He was in class for two days before rash onset, developed rash on a Friday morning and was taken home immediately. And that exposure was enough to infect 47 percent of the classmates who had not had prior disease -- so 47 percent of both vaccinated and unvaccinated children. Five were unvaccinated; 12 were vaccinated. And this

suggests strongly that there was airborne spread. This is the epicurve from that outbreak and you can see the vaccinated cases in yellow and the unvaccinated cases in red. You can see the large second generation that resulted from this one child. These are two photographs that were taken during that outbreak investigation. On the left you can see the boy who was actually the last case of disease in the outbreak and he was a vaccinee who developed a total of two lesions, one on the buttock and the second one you can see on his chin. He was actually PCR-positive for wild-type disease. So it can show you how very subtle breakthrough disease can be.

On the right is a photograph of the mother of two children in the outbreak. Both her children were vaccinated and developed breakthrough disease, and two weeks after they developed breakthrough disease, she had wild-type disease. She was unvaccinated, so she had a very dramatic case. So she may have been a case that was spread from breakthrough to a susceptible person, although she certainly was exposed to other children in the day care center as well.

Further data on severity comes from the Varicella Active Surveillance Project. I'll show you data from 1995 when the project was started to 2000. It was conducted in Antelope Valley, California, West Philadelphia, and Traverse County, Texas.

These are the number of confirmed cases in each year. In red, you see the number of cases that were unvaccinated and in yellow, the breakthrough cases. As you can see, there's a dramatic decline in overall case counts but a rising proportion of breakthrough cases. And in the year 2000, 27 percent of the cases were breakthrough.

If we now look at the severity of these cases, you can see that 81 percent of children who were vaccinated but got breakthrough disease had mild disease, i.e., less than 50 lesions and no complications; whereas, only 36 percent of unvaccinated children had mild disease. Complications tend to occur less commonly in vaccinees. The numbers are small. So some of these are not statistically significant yet, but there were more cases of supra-infection amongst unvaccinated children and no cases of ataxia, cerebellitis, or

pneumonia amongst the vaccinees. No breakthrough cases were hospitalized. Breakthrough cases missed less school or work on average than unvaccinated cases. So the preliminary conclusions are that the vaccine effectiveness we found since licensure appears similar to the pre-licensure estimates, although there have been some recent and low estimates. Some risk factors have been identified for breakthrough disease including early vaccination 12 to 14 months of age, a longer time since vaccination, vaccination given within 30 days of MMR, steroid use or reactive airways disease, eczema. We've also concluded that breakthrough disease can, in certain cases, be highly infectious and that the mode of transmission may be by the airborne route.

I didn't show data, but there are cases of breakthrough to breakthrough and breakthrough to natural varicella as well. And in terms of severity, the majority of breakthrough cases are mild, though approximately 20 percent are not.

So the next steps will be to continue to determine the public health significance of the breakthrough

infections and then to do further studies and investigations to either identify more or confirm the risk factors that I've mentioned so far.

Next, I'll ask Dr. Rupert Vessey to present data on the immunogenicity of VARIVAX and breakthrough disease.

DR. SNIDER: Could I ask you quickly to say how you separated asthma or reactive airways disease as a risk factor from steroid use since many --

DR. GALIL: Yeah. I didn't show all that. There are -- This was data from the Vaccine Safety Datalink that Thomas Verstraaten did, and he used an algorithm of -- for asthma. There was an algorithm of how many asthma medications they had to be on, for what period of time. So they did a multi-variate analysis to look at it and feel that steroid use itself might be more associated. We also have data that I didn't show on just asthma and it is somewhat confounded by indications.

DR. SEWARD: Just to summarize, the VSD study that attempted to separate out those two things found that asthma was not a risk factor. It was the treatment.

DR. VESSEY: Okay. Well, I would like to thank you for letting me present some of our data from our

clinical trial database on VARIVAX. And what I'm going to do is present some data that relates to the possible effective age on vaccination on the human immune response to the vaccine and also show you some data we have from a post-licensure study looking at breakthrough rates over time.

So as you all are very well aware, the primary assay that we have used in the clinical studies of VARIVAX is the gpELISA which measure varicella antibodies against partially purified varicella glycoproteins. And this slide shows you the relationship between the varicella antibody titer determined by this method six weeks post-vaccination, shown along the horizontal axis, and the cumulative varicella breakthrough rate over seven years of follow-up in a cohort of children. And this is depicted by the solid bars.

In addition on this slide, there is the median number of lesions in breakthrough cases depicted by the hatched bars. And what this slide shows you is that there's an inverse relationship between the risk of getting a breakthrough event and also -- and the six-week post-vaccination varicella antibody titer.

And also, it shows you that children with high titers tend. to have a milder breakthrough. I think the importance of this slide is that although we recognize that what we measure by gpELISA is not the sole effective mechanism for control of varicella, it does show that we're measuring something that's relevant to protection against the disease. I would also like to point out that even in this small group of children who did not seroconvert consistent with what post-licensure studies have shown, the breakthrough disease is actually quite mild, with a median number of lesions of 50.

Now, although there is this inverse relationship, you can also clearly see that there's no absolute correlate of protection. So what we have typically done is used a varicella antibody titer greater than or equal to five gpELISA units as an approximate correlate of protection in clinical studies.

So this next slide shows data from the database that was submitted in support of the original filing, and what we've done here to try and look at some of the issues that Karen identified in her breakthrough

report is to break down the antibody responses according to the age at which the children received vaccination. These are varicella history negative children. So it's consistent with standard immunization practice. And what you can see is that varicella antibody geometric mean titer and the percentage of subjects achieving response greater than or equal to the approximate correlates of protection are very similar in all these groups. So this suggests that there's no gross effect of age at vaccination on the humeral immune response to the vaccine.

We were interested in whether these young children, the very younger children -- there might actually be kids in there who have residual maternal antibody and whether this group -- within this group there might actually be a subgroup of subjects who might respond less well because of that.

So we have looked at seropositivity prior to vaccination in clinical trial participants, and what you can see here is that between 20 and 40 percent of children age between 12 and 14 months do have a detectable antibody by our test prior to vaccination.

By the time they reach 15, 16 months, it's settled down to sort of background level of seropositivity.

So we've look in children 12 to 14 months to see if we can identify any effect of these pre-existing antibodies on the post-vaccination immune response.

So these are children 12 to 14 months of age, again taken from the original database, and we've broken them down into seronegative, children with very low titers, less than 1.25, children with, let's say, a modest titer between 1.25 and five gpELISA units, and then children with titers more than gpELISA units. And the first thing that I would draw your attention to is the fact that in this age group, the majority, the overwhelming majority of children who are seropositive have very low titers, below five gpELISA units. There's a small proportion who have higher titers at the time of vaccination.

If we look at the seronegative children and the children with titers less than five gpELISA units, the post-vaccination immune responses, both with respect to the geometric mean titer and children achieving a response equal to or above the approximate correlates

of protection, the responses are actually very similar, again suggesting that these low levels of antibodies that are present in most of these children are not interfering dramatically with the humeral immune response this vaccine.

The data in these children are a little bit harder to interpret. We only have a very small number in this data set. And in fact, there were three of these 17 children who started with titers very close to gpELISA units and ended with titers just under five gpELISA units, and probably that's variation within the -- within the assay which has a 1.67 fold variation. So with this sort of number, it's difficult to be sure whether there are any children in there who do have any kind of impairment of their humeral immune response. We've also tried to look at this in another way. We have some older studies where children received two doses of vaccine three months apart, and what we've done is take these children who were 12 to 23 months of age and we've broken then down again into the same pre-vaccination titer categories. And what you're looking at here is firstly their primary antibody

responses and then the antibody responses they achieved after a second dose. So in this respect, you could regard the second dose as an antigen challenge, what happens when they see antigen. And all these categories of children appear to make good anamnestic responses to repeat challenged antigens, suggesting that the first dose did induce immunologic memory. Obviously, there are shortcomings with this data. I mean, the numbers in these groups, in particular, are very small and the numbers shown in black are the children between 12 and 14 months and those are very small numbers, too, although they do show the same patent if you look at them independently.

So, finally, I would just like to show you some data on varicella breakthrough rates. These data are taken from the post-licensure study which Merck is conducting with Dr. Steven Black and Dr. Henry Shinefeld in California. And in this study, about 17,500 children 12 to 23 months of age were given VARIVAX in 1995 and they're followed by telephone survey every six months to see if we can capture information on varicella breakthrough cases. And in this column

here, you can see the breakthrough incidence rate in terms of rate per 100 person years. And what I think this shows is that there's a peak here and when the children are between about three and a half and six years of age, and that probably corresponds to time of maximum exposure in this population. It's consistent to some surveys, although not consistent with every survey, but I think that's probably what's going on here. After that peak, the breakthrough rate declines and there's no evidence of a sustained increase in breakthrough that would indicate a waning protection with time, at least from these data. Of course, these data were generated in a climate where vaccination coverage rates have been changing over time.

So just to summarize what we've been able to look at in the last week or so and present here for you, first of all, we've shown you some data that varicella antibody titers six weeks after vaccination is inversely related to risk of breakthrough which provides some validation for this measure as a measure of vaccine immunity. The primary immune response to the vaccine doesn't appear at the gross level to be

affected by age at vaccination in infants. There are quite a few of the younger children, up to 40 percent of children 12 months of age, who have antibodies prior to vaccination by our test. And in general, it appears that these low titers of pre-vaccination antibody don't impair the primary response to the vaccine. We've also tried to look in a limited data set at whether the first dose establishes immunologic memory, and on these small numbers, it appears that it does. And from the point of view of varicella breakthrough rates, these appear to be peaking at an age when maximum exposure may occur that doesn't seem to be a sustained increase in breakthrough over time that would suggest waning of protection.

Thanks.

DR. SEWARD: On with the show. I'll now show you information on varicella disease surveillance and some herpes zoster disease surveillance. As many of you, but perhaps not everyone, varicella is not nationally notifiable. It was not at the time of vaccine licensure. It still is not. So there was no national passive surveillance system in 1995. CDC therefore,

in collaboration with state and local health departments, instituted an active surveillance system in three sites in 1995. There is some passive reporting via the National Notifiable Disease Surveillance System from states that have continued to voluntarily report and that was 19 states and territories in 2001. And then we have some other methods set up for surveillance. We are collaborating with the state of Massachusetts measuring statewide varicella and herpes zoster incidence in a BRFS survey, and in the VSD project, looking at incidence for varicella and herpes zoster with the Group Health Cooperative in Seattle.

So, firstly, active surveillance, this is a busy slide, but I wanted to show the three sites together because I think the pattern of disease is rather dramatic, with a decline in disease in 1999 and attenuation of seasonality in all three sites. You see monthly disease rates in the blue bars and the red line shows cases, reported cases per 1,000 population from the beginning from January and now into 2001.

If we look at this data by site, we see the effective

we see vaccine coverage here as well. This is measured from the National Immunization Survey, so we don't have it for the first two years, but there was some vaccine used in Antelope Valley but not much in 1995. Perhaps about 20 percent coverage in 1996 and then coverage picked up dramatically, reaching 80 percent or so in 2000.

In West Philadelphia, most of the population in this area are served by public sector vaccine. So, essentially, there was little, if any, vaccine available in 1996. Therefore, in all three sites, we viewed the declining cases in '96 as year-to-year variation in disease and not evidence of disease impact. The same in Texas, year-to-year variation in disease through 1998, but then very dramatic decline in disease as in the other two sites visible in 1999 with increasing vaccine coverage.

Reduction in cases in the three sites from 1995 through 2000, you can see that overall, if we compare 2000 to 1995, it's been a 70 to 80 percent decline in cases overall. That decline has been greatest, as you might expect, in children one to four who are probably

receiving more of the vaccine, but significantly, there's also a decline in children under one who are not vaccinated and adult and older children who are probably not receiving a lot of vaccine, indicating reduced disease transmission and exposure in these communities now.

Severe disease outcome in these three sites, these are hospitalizations for three sites combined from 1995 through 1998. There were, on average, 30 to 50 hospitalizations a year. This dropped to eight hospitalizations in '99 and increased to 13 in 2000, but it's eight so far this year and the varicella season is completed although there may still be a few cases. So quite a dramatic decline also in hospitalizations evident from 1999 onwards in the active surveillance sites.

Passive disease surveillance, Michigan has been a consistently high reporting state for varicella, going back to the '70's. I'm showing you data here from 1992 on. The vaccine, as you know, came in in 1995. They had a big varicella year preceding that and the patent of disease decline in these passively-collected data

is very similar to the active data with disease decline noted. About a 50 percent disease decline in 1999 and then continuing to decline in 2000 and a further decline through the varicella season in 2001.

This is West Virginia. Very similar pattern. And these are four states that report to NNDSS, more than five percent of their birth cohort number of cases in the pre-vaccine era, and I show here reduction in cases in 2000. I compare to average cases from 1995 -- from 1993 through 1995, showing these kinds of reduction in cases at these levels of vaccine coverage, and we're tracking week by week cases reported in 2001 and comparing them through, say, week 40, which ended last week, with the same time period in 1995 -- 1993 through 1995, and these are the kind of reductions we're seeing for this year to date. So extremely dramatic evidence of vaccine impact in states with passive surveillance data as well.

I'll just show you some slides in varicella and herpes zoster surveillance that we've been doing in Massachusetts, collaborating with the Massachusetts Department of Health. As I said, statewide

surveillance using survey methods, optional module for the Behavioral Risk Factor Surveillance Survey. They've been measuring annual varicella incidence by age in five-year and annual herpes zoster incidence by age. And then also in Seattle, with Group Health Cooperative, collaborators there are Lisa Jackson and Cary Belke, and they have been looking at varicella and herpes zoster incidence from 1992 onwards.

This is varicella incidence per 100. So a proportion of children in the population are getting varicella in Massachusetts in 1999, '99, and 2000. As you can see here, in 1998, eight percent of children or 80 per 1,000 population was similar to the pre-vaccine era, with the highest incidence in one- to four-year-olds. A dramatic decline in incidence in all age groups. A little increase here in under one, so that's probably year-to-year variation, but, again, a dramatic decline in incidence in most all age groups.

In herpes zoster, this is herpes zoster in the last five years, so we can't detect in this slide year-to-year changes, but we show this slide because the numbers are more stable due to looking at a five-year period. We

do have data from '99 and 2000, but these two lines overlap. I think that we are confident, though, that with this data I'm about to show you that there's no increase in herpes zoster that we're seeing as varicella is declining.

Here we have incident rates of varicella by year and Group Health Cooperative in Seattle. As you can see, varicella incidence varies from year to year. There are big years followed by smaller years. And we have data through May 2000, but we chose not to show that because the data wasn't complete for the year. So this is incidence of varicella per 100,000 person years. This is the same for herpes zoster. You don't see any seasonality, very consistent rates of disease from year to year, and finally, incidence rates of herpes zoster by age and time period showing three times periods, pre-vaccine, very early vaccine, which you could also consider pre-vaccine, and then perhaps vaccine years. Because vaccine uptake was fairly delayed in Washington state with very stable incidence rate for herpes zoster in these three time periods for all age groups.

So, in conclusion, I think for varicella we see a dramatic decline in disease and complications. There's a consistency of decline in cases and all surveillance systems. For herpes zoster, we see no change in age-specific incidence. For the vaccine, coverage is 68 percent or now 75 percent and increasing. Our states are rapidly implementing child care and school requirements. I think the vaccine has a good safety profile. It has robust protection against severe disease. That's been very consistent in all studies and outbreaks, and we're continuing to define the range of protection against all disease and possible risk factors for vaccination failure.

Thank you. We'll now take questions for any of the presentations. In addition, Phil Krauss is here from the FDA and may want to comment.

DR. MODLIN: Jane, thanks very much. Obviously, very encouraging information on the surveillance front. I think some of the vaccine efficacy information is new to the Committee. Maybe I could ask the first obvious question and that is, are we beginning to, at some point, think about talking about a second dose of

vaccine for children? I don't know if, Jane, you want to respond to that or somebody -- Tom, or anyone else from the company, or Dr. Vessey. What's the current level of thinking about that at the moment.

DR. SEWARD: We're certainly planning to sit down with Merck and look at data from a two-dose schedule and continue to look at the public health significance of breakthrough. I think it may well be that a breakthrough -- or a failure rate of 15 percent in some cases can start outbreaks or have 150 lesions and may not be acceptable in the long run. So that is planned over the next three to six months and also doing some costing, cost-effectiveness analyses.

DR. MODLIN: Jon?

DR. ABRAMSON: Yeah. Five years ago when we came out with the recommendation, we were -- and we made the recommendation of HIV, which may have not been at the same time -- I don't remember --

DR. MODLIN: It was later.

DR. ABRAMSON: Right. But we were concerned about as the incidence went down, we needed to revisit the issue of whether to inject HIV-infected children with a live

varicella vaccine, which then stays in your body for the rest of your life. In looking at your data -- We're about to have that discussion at the COID meeting this weekend. In looking at your data, do you have a point where you think there's a trigger for rethinking that specific issue?

DR. SEWARD: I would have to defer that to people like Ann Jumaan who are conducting the trials with children with HIV. I don't know if anyone -- Ann was hoping to come down to this meeting, but due to events in New York, she was not able to do that. I know that they're continuing -- they're extending the trials in children with HIV with lower -- you know, who are somewhat compromised, immunocompromised. So far the vaccine is just recommended, as you know, for the children who have adequate cellular immunity.

DR. MODLIN: Myron, you may have some information.

DR. LEVIN: Actually, it's my study that she's talking about. And I'm not sure I understand the question.

DR. ABRAMSON: Well, Rich Whitley brought up the point, which I thought was a good one, and that is there comes a point where, yes, everybody agrees you would

rather have the attenuated virus rather than the wild-type virus. But there comes a point where the risk of having wild-type virus is so low that you would rather have no virus in the child. You would rather have neither the wild-type nor the attenuated, because as these children down the road become more and more immunosuppressed, you worry about even the attenuated virus. So the rationale for rethinking the issue is there comes a point where the incidence of the disease is low enough that you have to rethink the issue.

DR. LEVIN: I agree with that. I thought you were asking some safety-related question or lack of boosting. There may come a time when we don't need to worry about that disease in that population.

DR. SEWARD: We've still got exposures from herpes zoster that you'll have to consider, though.

DR. MODLIN: You'll have exposure from herpes zoster, hon. Not to carry this farther than it should be, but I just would point to the successes that we're having in treating HIV-infected children now. And if the mortality rate in the pediatric population has dropped from five to eight percent a year now down to one percent

a year, it's suggesting -- there's been some maintenance of t-cell immunity in this population. So that would also mitigate perhaps against special concerns about this extremely immunocompromised population as a group.

Natalie?

DR. SMITH: Yeah. There's a striking difference in state coverage rates, and obviously, it's of particular concern for cohorts of kids that have not been vaccinated or possibly naturally exposed. Can you describe some of the factors that go into those disparities of --

DR. SEWARD: Well, [inaudible] state perspective. I think some of the issues related to delivering the vaccine, for example, in Alaska, but those, with the help of Merck, are being rapidly overcome. I think some of the reflected practices in those states in not promoting the vaccine perhaps as rapidly as others or logistic difficulties in getting them to far-reaching corners of rural states. I think those are changing now, though, and I think as states put in child care and school requirements that those disparities will

more rapidly be overcome.

DR. MODLIN: Yes, Dr. Neuzil?

DR. NEUZIL: Yes. Just a comment on Dr. Vessey's data. I think there might be an alternative explanation why we don't see sustained breakthrough with duration of time from vaccination, and that is that if the disease incidence peaks at age three, we may also have subclinical infection that's boosting immunity and then you have that decline post that three-year period. And the reason I think this is important to consider is because as wild-type virus circulation does start to wane, you may see more breakthrough, if that makes sense, because that duration effect may be more profound.

DR. VESSEY: Actually, I did try to allude to that point when I finished that slide by saying that we're currently in a situation where those data have been generated where there's not full vaccination coverage. So there will be wild-type virus circulating which could influence that -- the data that we see there. So we absolutely recognize that. And the question that you're asking really can't be answered in an

environment where wild-type virus is still circulating and children may get subclinical boosts.

DR. MODLIN: Paul?

DR. OFFIT: Thanks for what were very clear presentations. I guess the word I struggle with is the use of the word "breakthrough" here. The term -- I guess I'm trying to challenge us to come up with a different term because the term suggests that the disease has broken through, whereas, in fact, at least according to Dr. Galil's presentation, about 80 percent of what we call breakthrough illness is, in fact, very mild, which one would consider to be a success. I mean, the purpose -- a successful varicella vaccine is one in which children don't have moderate illness, aren't hospitalized, and aren't killed. So to think of it sort of as breaking through or failing is in some ways incorrect. I don't think it's trivial because I think parents -- you know, often they'll come back with a child that has ten or 15 lesions and they feel that they somehow got cheated by their vaccine. Whereas, in fact, that's a success, I think. I don't know, the term "breakthrough" just sounds like

there's no modification; whereas, in fact, there usually is tremendous modification of illness.

DR. SEWARD: I think we struggle with the term as well. We have discussed with Merck changing the name. I think that it's generally defined as a modified disease. However, even with five lesions, we've seen transmission to unvaccinated people. So it's not insignificant in its public health impact even with few lesions. That's what we're trying to look at in more detail.

DR. OFFIT: Yeah. What I think -- For example, for the mucosal infections, like influenza or rotavirus even, you know, what we do is we modify disease but we don't call that mild disease that occurs, breakthrough illness, even though there probably is at some level transmission even with those mild diseases.

DR. MODLIN: Good point. Myron?

DR. LEVIN: Two questions. First for Karen. The two cases -- the two studies you showed us that where the breakthrough rate was significantly higher than the others, is there any clear explanation of that other than you teased out a few factors? Was there something

different about those situations?

DR. GALIL: No. One I worked in New Hampshire and Dr. Jumaan worked on the other in Maryland, and what was striking is that there wasn't a good explanation of why the rate would be so slow. And even with the risk factors we found, it certainly wouldn't explain the majority of vaccine failures.

DR. LEVIN: Could they have been immunized by different sources?

DR. GALIL: They had been -- In New Hampshire, there were 26 different providers who vaccinated these children over five years. Only, I think -- I think the same lot was only used in three children maximum. Most children received a lot that was unique. Some siblings received a lot that was the same. So there was no clustering by provider, by lot number, by anything else. And it also incurred in the middle of winter in New Hampshire, which is not a time that there are a lot of insect bites or other things that are usually confused for breakthrough. So, you know, we had extremely complete -- we had 100 percent of parents responding. So all the things that we usually are able

to blame on why we might have gotten an odd result right there --

DR. LEVIN: And the second question is that maybe you and Rupert can comment on. You show -- You suggested that one of the risk factors was early immunization. And Rupert actually looked at that with respect to maternal antibody and there was a difference. But there was no difference when he looked at the response of those children, at least in the short time period. How are you --

DR. GALIL: That's a great question. I think one of the things we worry about is that antibody -- mean titer is measuring antibody, and we suspect that some [inaudible] immunity might be the more important factor for protection. So we're measuring something that we think is a correlative protection, and it might be a very good correlative if you're age four. Maybe it isn't a correlate at 13 months of age. We don't know. But the measles history -- and I certainly wasn't around for it and other people know it better was similar in that the decision to vaccinate at nine months of age was made on good data showing that

children should respond. And then there were actually vaccine failures which led to the age at vaccination being raised sequentially up to 15 months of age, and it was only lowered once most mothers in the U.S. had vaccine-derived immunity.

So we looked at it because we should look at everything we find and then we went back to other outbreaks and asked them to look at the same thing and have now found, you know, a small but consistent pattern. I think it certainly merits more investigation, possibly some mediated immune studies of young children to see whether they really are adequately protected when vaccinated at 12 or 13 months of age.

DR. VESSEY: As I said when I was presenting, we acknowledge that a gpELISA test does not measure the full range of effective mechanisms that the immune response can deploy against a virus. It's a marker called an immune response. And it could be that underlying differences in cell mediated immunity could be responsible, although we have to have a robust and consistent assay that we can run on cells that we can collect from little children in order to prove that,

which will be difficult.

DR. MODLIN: Yes, Forian?

DR. TRUDEAU: Forian Trudeau from Merck. I just want to comment on the measles situation because I think it is important to see the difference.

When we immunized with measles vaccine or we have pre-existing antibodies and we come back and immunize either again or for the first time in the face of antibodies, we don't see a good take. In fact, there's not much of a boost the second time around and the increased effectiveness of measles by giving it two times is mostly catch-up or converting people who haven't yet converted. It's not so much boosting the antibody titers. This is dramatically different have varicella as Rupert has shown. You have about a ten-fold higher antibody titer when you give varicella a second time. So it really behaves different whether or not the antibodies are reflective of the mechanism.

DR. MODLIN: Good point. Dr. France?

DR. FRANCE: Dr. Vessey, I was wondering if you had looked at your data regarding atopic children and children with eczema and asthma and whether they may

respond differently.

DR. VESSEY: Yeah, that's a really interesting question. And when I was talking to Jane and Karen last week and looked at some of the risk factors they had identified, I wondered whether -- what was underlying. This was a qualitative difference in immune response and that's why they have a couple of risk factors that appear to be unpinned by [inaudible]. And maybe the type of immune response that those children generate is different, and we wouldn't be able to detect that with the type of -- with the way that we measure the antibody response, but that's a possibility. I mean, maybe they are listing more of a Th-helper two immune response and maybe that's less effective, but we don't have the tools to dissect that out and see whether that's the correlate of those atopic respecters.

DR. MODLIN: Walt?

DR. ORENSTEIN: I was just interested in the epicurve you showed. I think for the New Hampshire outbreak and the illusion you made to the very large dissemination and how well the virus circulated and whether some of

these oddball or different estimates might be due to intense exposure rather than perhaps waning immunity. I'm wondering if you've looked at the other outbreaks, as to whether they've had this kind of explosive second generation that would suggest the same degree of intensity of exposure.

DR. GALIL: I looked at overall attack rates amongst unvaccinated susceptible children in all the other published outbreaks or abstracts where we could get that information, and most of them have a fairly high cumulative attack rate in the unvaccinated. The exceptions are that it was slightly lower in the Maryland outbreak, but a lot of them do have attack rates in the 70's and 80's, and in our case it was an 86 percent attack rate. So it was very high but not so much higher than other outbreaks. So it's hard to think that that is the only explanation.

I should also mention that in order to look at some of the risk factors, we're actually going to work with Steve Black and Merck to look at trial data. We've just agreed to do that. They have about 700 or 800 breakthrough cases, and we can look at some of these

in that data set, I'm hopeful.

DR. MODLIN: One final question. Yes?

MR. KRAUSE: I'm Phil Krause at FDA. Just to emphasize what you said, Walt, the pre-licensure database indicated that people who had more severe or greater exposures to wild-type virus were more likely to come down with breakthrough discussions. So in household exposure studies, for instance, the vaccine efficacy was really never much higher than about 70 percent. Whereas, if you look at the population at large, including non-household type exposures or perhaps less severe types of exposures, the general vaccine estimate was 70 to 90 percent. So it's very reasonable to assume that in an outbreak setting that the amount of virus which is circulating is much greater.

The other related point, of course, that there is the potential for there to be some reporting bias here as well because only the most severe outbreaks and those which end up causing the largest number of secondary cases, et cetera, those, of course, are the ones which are going to come to attention the most rapidly.

Overall, though, it appears as though the vaccine is behaving very much the way we expected it to when it was approved, which I think overall is quite good news.

DR. MODLIN: Tom?

MR. VERNON: John, thank you. I want to take the privilege of further comment on Dr. Natalie Smith's question about the diversity among the states.

It seems to us -- to all of us that the low immunization rates in some focal areas of the country are going to result in a group of children who are not only not immunized but not being exposed to the wild virus, and we may be looking five to ten years from now at more serious disease in adolescents and young adults and pregnant women. It's hard to say that there's any -- certainly not any single factor that causes the difference among the states, but there are two I'd like to highlight.

One is very consistent with our own market research is what you say matters, you as professionals, if you will, whether it's in the doctor's office or thought leaders in a given state. And in some states it is very clear that there has been lack of enthusiasm from the very

beginning about the vaccine and about recommending school attendance requirements to the political leaders in that state. And I would -- I would mention Washington state is an example of that.

A second factor is, indeed, the shrill nature of some voices in some states against government mandates, in general, against -- not just against this vaccine but in generally -- in generally adoption of school attendance requirements. There are two very large middle western states, Ohio and Illinois, to this day which have not formally adopted school attendance requirements, much less had them in place. In both of those states there are very vocal voices opposed to immunization and especially to school requirements for immunization, both have small citizen groups, but also among key legislators. So in Ohio, for example, there is a single health committee chairman who adamantly refuses to allow a bill to be heard, recommended by the state health department, by the state chapter and the Academy of Pediatrics and all else, even though there is apparently a vote in his committee which would pass it. But he is listening to groups within the state.

So these are reasons for differences among the states. And to the extent that any of us have an opportunity to speak to these issues, I will take a political moment to lobby that you do so.

DR. MODLIN: Thanks, Tom. Jane, Karen, thank you very much for a terrific presentation.

I misunderstood a little bit earlier regarding the OSHA presentation. We will have the presentation on the OSHA requirement for using safety engineered needless and the implication for childhood immunization delivery. Ms. Hogan is not able to join us from OSHA, but the presentation will be led by Ms. Linda Chiarello from NCID.

Are we set to go? We're not. I understood that she would be here and is not here yet.

If that's the case --

UNIDENTIFIED SPEAKER: We are ready to go.

DR. MODLIN: You are ready to go. Dr. Yusuf?

MS. CHIARELLO: Well, good morning. I would like to take this opportunity to thank the National Immunization Program for inviting the Division of Health Care Quality Promotion to be part of this

discussion on the use of safer technology in the immunization setting. And I learned about 15 minutes ago that I'm also giving the OSHA presentation and I have -- I'm certainly not an OSHA expert. I will read through the slides that Amber has sent, but I have to tell you in advance that I have not seen them. So that will be a very interesting presentation.

I've basically been asked to address the -- in ten minutes, the epidemiology and prevention of needle stick injuries during immunization. Obviously, my remarks are going to be fairly brief and they really are designed to be more of a springboard for discussion than a treatise on this particular subject area.

There are a few key points that I hope will be the message that I deliver and that you take from this presentation. The first is that we really have very limited information on needle stick injuries during immunization. We do know that the risk of transmission of transmission, of blood-borne virus transmission, associated with injection-related injuries overall is low. Nevertheless, needle sticks are very costly and should be prevented, costly in terms

of the treatment, particularly with post-exposure prophylaxis that is offered, and there's also tremendous emotional costs that are associated with these events and to health care workers that believe or know that they have been exposed to HIV or hepatitis C, in particular.

The majority of needle sticks associated with injection procedures are preventable, but we believe very strongly that prevention requires a multi-faceted approach, which I think is part of r reason we were invited to participate in this discussion because much of the focus today is on the implementation of safer technology and we would like to put that in appropriate perspective.

As I mentioned, there's very little information on needle stick injuries during immunization. There's only one published study and that is from Canada looking at rates of injury during these events. And in that study, there were 13 needle stick injuries during 112,000, almost 113,000 childhood vaccinations. This was a rate of one per almost 9,000 vaccinations. However, when you look at these, seven of those injuries

were clean and therefore should not be considered as contaminated events. So in terms of the need for post-exposure care, in this one study, it would be one in every 19,000 immunizations, childhood immunizations.

The best information that we have on -- descriptive information on needle stick injuries comes from the National Surveillance System for Health Care Workers, or NSSH, which our division created in 1995 and we now have 50 participating hospitals that have contributed information on almost 16,000 blood exposures. 80 percent of these are needle stick or other sharps-related injuries. As a point of information for this presentation, there are 239 exposures that occurred in an outpatient office or clinic, therefore in a setting that may be comparable or where immunization is provided. These were all injection-related procedures, and 37 percent of those injections were given by intramuscular route and two-thirds by the subcutaneous or intradermal route. We have no information on the original purpose for that particular injection.

When we look at the mechanisms of injury, which are very important for prevention planning, we see that of these injections, 44 percent actually occurred during use in the patient as the needle was being inserted or actually more commonly withdrawn, or during the procedure the patient moved and jarred the device. These are required exposed needles and, as I'll show in a moment, these are largely not preventable with current technology. 56 percent occurred after use during a variety of circumstances when people were handling or transferring the device during clean-up, recapping, in transit to disposal, or during disposal, which reminds us that in the continuum of having an exposed needle from the point of original use to the point of disposal, there are many opportunities for injury.

We assess the preventability of needle sticks in our division by looking at it from an hierarchial perspective. Our first question is, was the needle necessary in the first place? Obviously, with injections it is. Our second question is, is there a current technology that would have prevented those injuries? And we look at -- with injection

procedures, there's no current technology that will prevent the injury during use in the patient. The only point at which that prevention becomes effective is immediately after use of the device, after it's withdrawn from the patient.

So you see here -- I guess this isn't very bright. But you see here that we find that 44 percent of those injuries could have been prevented with safer technology, and 44 percent are not currently preventable with the safer technology or a recommended work practice.

What are the infection risks from injection-related procedures? We cannot speak to immunization. There are many factors that really influence this. Each event has its own independent risk and it needs to consider the route of exposure, the severity of exposure, the particular virus involved, the health care worker's susceptibility, and the use of post-exposure prophylaxis or treatment.

Prospective studies of exposed health care workers have shown us that the risk of -- from a percutaneous injury exposure to hepatitis B virus carries a risk of

six to 30 percent. And that variation is largely dependent on whether the individual was exposed to hepatitis B E antigen or not.

The risk for hepatitis C transmission is several magnitudes less, 1.8 percent on average, and the risk after a HIV percutaneous exposure is about 0.3 percent. So, obviously, there are virus-specific differences that influence the risk of transmission.

The good news is that the highest risk virus has been mediated in large part to what you have done and in large part to what OSHA has done. ACIP recommendations for hepatitis B immunization have resulted in a dramatic decline in the annual incidence of hepatitis B transmission to health care workers. And now as more workers are being immunized as they enter the health professions, we should continue to see this decline go even further.

The risk for hepatitis C virus based on a specific event is not fully understood but is believed to be similar to HIV. And it is for HIV that we have the most descriptive information on occupational transmission. And through June 2000, there have been -- there were

49 health care workers who acquired HIV through a
percutaneous exposure and what's of interest here is
that the majority, 38 percent, involved a hollow-bore
needle. And when we look at that device more -- those
devices more specifically, they were usually needles
that we used in a vein or artery so we considered them
blood-filled.
So, really, if we think in terms of prevention,
preventing these exposures is really the direction we
would like to be going, what prevention strategies can
be used? I'm actually going to start from the bottom
and work up.
Because safety awareness is critically important,
having a culture of safety in the institution, training
health care workers in safe work practices when they
are using a device could cause injury, is important from
the time a person enters the health professions.
Safer work practices have been recommended for
probably 15 or 20 years now, and those include
point-of-use sharps disposal containers and
encouraging avoiding recapping of devices or using a
scoop technique. But with these in mind, the emphasis

today is on the utilization of safer technology. And one of the problems that we face in looking at safer technology is that there is no clear definition of what a safe syringe for injection should be. And as these slides show you, there are many different engineering controls that have been added onto syringes or needles designed to protect health care workers. For example, we have sliding sheaths that lock after use that's been added to the syringe. More and more what you see are things that are being added to the needle, something that will glide over the needle after use, or in this case, there's one that is hinged and folds over the needle after use. This happens for phlebotomy, but there is one for syringes as well. And now there is a syringe with a retractable needle feature that also has been designed. So there is no -- there is no specific design that defines what these are for injection purposes and the designs are not necessarily intuitive. People do not necessarily know exactly how they should be used.

There are several considerations that I think are relevant to this discussion and that is the

consideration of these products for selection in immunization programs. One would be the clinical considerations for these devices and in many places where immunizations are provided, syringes alone of syringes with needles are used for multiple purposes and some of the safer technology limits the purpose for which that device can be used. There are some who believe it's necessary to change a needle after medication withdrawal and some of the devices limit the ability to do that.

There are workers -- worker concerns: how each is it to use; is there a need for technique change; how long does it take to become familiar with using the device.

There are some safety feature considerations. If you look at the literature, you'll hear many "self" terms self-blunting, self-retracting -- and when you start to look at the devices, there are no selfs. Every one of these requires the worker to actually engage the safety feature for it to be safe after use. The ability to activate with one hand, the timing of activation relative to completion of the procedure, and the ability to provide permanent protection are all

things that need to be considered. Very often overlooked are the patient considerations. And when one is looking at injection equipment, one needs to be concerned about the completeness of medication delivery, is there dead space in that device after use, is that going to alter the delivery of the medication or vaccine, and is there any unusual pain or discomfort to the patient.

What may be most exciting for this group is to think about future strategies for preventing needle sticks during immunization, and the concept of needle elimination has not even been brought into the discussion. Are there alternate routes of vaccine administration that can be developed or promoted? Intranasal, skin patches, for example. The use of jet injection equipment, that technology continues to grow and be refined. Are there ways to reduce needle use such as combination vaccines and are there opportunities for unit-dose vaccine administration with devices with safety features that would come from the manufacturer that way.

So, in conclusion, really the majority of needle sticks

related to injection are preventable, but I think I've tried to communicate that a very comprehensive approach that considers all relevant prevention strategies is needed to maximize the prevention potential and the use of safer technology has an important role in preventing needle stick injuries during immunization.

Thank you very much.

DR. MODLIN: Ms. Chiarello, did you want go ahead and give Ms. Hogan's presentation?

MS. CHIARELLO: Well, I will try.

DR. MODLIN: I think it would probably be a good idea and then --

MS. CHIARELLO: I think so, and then --

DR. MODLIN: -- we'll open it up. Thanks.

MS. CHIARELLO: I expect that by now everyone in this room is quite familiar with the OSHA Blood-Borne Pathogen Standard. It has been in place for almost ten years now and everyone has had to look through the requirements and apply them -- or see if they're applicable to their own health care -- their own health care setting. I think the important point that Amber

was hoping -- was intending to make today is that this particular standard applies to all employers with employees who have reasonable anticipated exposure to blood or other potentially infectious materials. And it does apply not just in health care settings, but it applies in other -- in general industry such as in first-aiders. Now, the only place it doesn't apply is to construction, agriculture, and maritime, and I don't see anyone in the room here who is probably particularly concerned with that.

Given the fact that the blood-borne pathogen standard has been in place for almost ten years now, there are really only three areas where there have been significant changes in the last year. One is in the exposure control plan, which is listed as C here; in the area of engineering and work practice controls and personal protective equipment; and then in the recordkeeping requirements. And there are really two separate recordkeeping requirements that are part of OSHA at this point.

OSHA's web site is a very important source of information, not only for information but also

resources for educating health care workers and employers on the relevant applications of the blood-borne pathogen standard.

Since 1991, there have been considerable advances -- advancements in medical technology, particularly in the area of sharps injury prevention. And in September of 1998, OSHA issued a request for information on the use of safer technology in health care settings, how well it had been adopted, implemented, to what extent it had been implemented, the experience of health care facilities with devices, the acceptability, and what impact it had had on prevention. There were -- And the findings of that RFI really are what led to OSHA being convinced that the safer technology could have an impact on preventing needle stick injuries, especially in health care settings. There has been considerable union and congressional involvement in this particular issue and many health care unions have made it as a major priority for their membership. We now have, I believe, 23 individual state laws that are requiring the implementation of safer technology. Some of these may

overlap with OSHA laws and so it becomes the issue of which law supersedes which. It usually is federal. But each of these laws is somewhat different in terms of what their requirements are. And then in November of 1999, OSHA actually updated their compliance directive. Now, the compliance directive -- I'm assuming most of you are familiar with what that is -- is a document that basically instructs the OSHA compliance officers on how to interpret and enforce this OSHA blood-borne pathogen standard in health care settings. So it really is directed to the compliance officer, but for an employer, it can be a very important resource for understanding the implications for that particular setting.

The most recent activity was in November 2000 when President Clinton implemented or passed -- signed the Needle Stick Safety and Prevention Act. So considerable activity in terms of needle stick prevention coming from a variety of places in the country.

What the Needle Stick Safety and Prevention Act did was to mandate that OSHA clarify and revise the 1991

blood-borne pathogen standard. So in the course of doing this, what OSHA has done in that revision is to add definitions of what constitutes an engineering control. They have implemented new requirements in the exposure control plan, and I'm anticipating that some of that description will be here. One of the things that is different is that there is a requirement that non-managerial employees, basically front-line workers, be involved in and have input on the selection of safer technology. And there is a new requirement for a sharps injury log which is different from the OSHA 200 and what will now become the OSHA 300 log.

So for an immunization program, what is required? OSHA says that the selection of engineering and work practice controls is dependent on the employer's exposure determination. So what this means is really this is a performance-oriented standard. So when a compliance officer goes into a facility, they're looking at how the standard has been implemented. The employer must identify worker exposures to blood or a potentially infectious material. The employer must review all processes and procedures with exposure

potential. And in this case, I would expect that to mean looking at how immunizations are provided in a health care setting; what processes are in place to reduce the opportunity for a needle stick injury to the workers -- things like point-of-view sharps disposal containers which themselves are an engineering control; and then on an annual basis, to re-evaluate when new processes or procedures are used, and that would very much depend on the success or lack thereof of interventions that have been put in place by the employer or new evidence of risk from needle stick injuries.

Now, this I think -- this requirement on engineering and work practice controls I think is the one that is most confusing. I know it's confusing to me and I think it's very confusing to employers. Where it says that employers must select and implement appropriate engineering controls to reduce or eliminate employer exposures, what are appropriate engineering controls? And the definition of an engineering control is really it can be a sharps disposal container, self-sheathing needles, or safer medical devices -- I

believe they're one in the same -- that isolate or remove the blood-borne pathogens hazard from the workplace.

Let me just back up for a minute. I think that the question that is unanswered here is whether -- what is an appropriate engineering control in this situation and how is that defined by the employer. And if there are no needle stick injuries, does that mean that there's no need for implementing safer technology? If you have point-of-use sharps disposal containers and no injuries are occurring, does this mean that you would be absolved from any risk if your particular organization was reviewed? And I think because it's a performance standard, that's determined on a case-by-case basis. So I don't have a good answer to that for you.

They've also defined what needleless systems are, and in this particular case, that would apply to any needleless injection equipment that is currently available. And we're all familiar with the fact that jet injection equipment is still developing. And I guess my question would be, should immunization

programs be evaluating this type of equipment for use in its respective state programs?

They have a new acronym, a SESIP, which is a non-needle sharp or a needle with a built-in safety feature mechanism that effectively reduces the risk of an exposure incident. And basically, those devices that I showed you in my presentation would be classified as a engineered safety device, or a SESIP. This has -- This particular slide shows you information about the safety devices that are available and you can get the in Virginia, the EPINET system, Dr. Janine Jaeger's program, has a list of devices that are considered to be safety devices, that have a safety feature. There's very little information on the effectiveness of this technology in preventing needle stick injuries, very few studies, prospective studies that have been done really documenting the extent of reduction. That doesn't mean these aren't important, but in terms of having evidence-based information, there's actually very little that is available.

So what must the employer do? One is to evaluate available engineering controls that would be

applicable in this case to an immunization setting and implement those that are appropriate for the setting and train employees on the safe use and disposal of these devices. That's really what the requirement is. The employer must document the evaluation, how the devices were actually evaluated prior to implementation, and the implementation must be documented in the exposure control plan. And this must be updated on at least an annual basis at which time any new devices or technologies would be expected to be reviewed again. And then anything that is new and determined to be appropriate is expected to be implemented as well.

Now, what does it mean to solicit non-managerial employee input on selection of technology? Well, when one is considering the various devices that are available, it would require that there be some small group of employees who are front-line workers and would be using this technology to assist in identifying and selecting what would be the most appropriate for that particular health care setting, and they do look for representative samples of employees who would be

participating. So in a large health care facility, one would expect if they're going to bring in a new injection technology, they would involve laboratory personnel, would involve front-line workers who are on -- in the inpatient units, it might involve pharmacy, the operating room, outpatient settings, but wherever that -- the conventional device is being used, there would be an expectation that that would -- that those employees would participate in the selection of the new technology.

The employer must -- I'm sorry, I've said that. I've tried to communicate in my presentation that there are a number of considerations that should be looked at when evaluating safer technology, not only employee safety but also patient safety, and considering the efficacy of the procedure as well as the commercial availability of the device, and this too must be documented.

Now, the new recordkeeping requirement is a source of considerable confusion. There are two requirements as I mentioned. One is the sharps injury log, and the goal of this log is to actually identify devices which do not protect employees. So this log must contain,

at a minimum, if there is an injury, the type and brand of device that is involved, the department or area where the incident occurred, the description of the incident, and it must be free of any personal identifiers. So it's trying to look at the circumstances of injuries and not the individual. This is a place where you can contact OSHA for more information and, as I mentioned early on, OSHA does have a number of resources that are available in the area and regional offices as well as OSHA in Washington and through their web site that can be extremely helpful in answering many of the questions individuals may have.

Is that it? I apologize. I'm sure Amber would have given you much more detail, but I've tried to at least

DR. MODLIN: You did a beautiful job of giving someone else's presentation, sight unseen. Dr. Yusuf, are you going to wrap up?

DR. YUSUF: Good afternoon. The objectives of this brief presentation is to provide some information related to [inaudible] and implementation of the OSHA

standards at immunization grantee level and also provide some preliminary estimates of cost related to using SESIPs for childhood immunizations at the national level.

We surveyed immunization program managers in August of this year by e-mail and inquired about their awareness of the revised OSHA standards, the use of SESIPs for immunization in their programs, training of staff related to SESIPs, and perceived barriers for implementing SESIPs in immunizations.

Of the 59 program managers e-mailed, 52, or 88 percent, responded to our survey. 90 percent of the respondents indicated that they were aware of the revised OSHA standards; however, 40 percent indicated that the immunization program had disseminated SESIP-related information to their public sector clinics and 25 percent indicated that the program had conducted SESIP-related training in public clinics. Very few programs had disseminated information or conducted training in private sector clinics.

20 percent of the respondents indicated that SESIPs were currently being used in most or all of their public

sector clinics to vaccinate children and about the same proportion said that such devices were being used in all or most public sector clinics to vaccinate adolescents and adults.

The most commonly reported difficulty or barrier to using SESIPs widely to immunize children was the need for additional cost for SESIPs. This was followed by identification of suitable SESIPs, securing new contracts for manufacturers of SESIPs, need for additional space on availability of pre-filled syringes with SESIPs, disposing current pre-filled stocks that do not have SESIPs, and staff resistance to change.

We also tried to derive some preliminary estimates of the cost at the national level for using SESIPs to vaccinate children. Our estimates were based on estimated number of vaccine injections administered to the zero to three-year-old children in the U.S. annually, the distribution of private versus public sector of vaccines, the percent of vaccines used or delivered using pre-filled preparations, and we assumed cost of standard syringes to be about five cents

per syringe, whereas, SESIP syringes to be about 43 cents per syringe. And I should note that the cost for these devices varied depending on the device. So our estimates here are basically intended to give you a ballpark estimate of what the cost may be at the national level.

As you can see in this second row of the second column, approximately 31 million vaccine injections are administered to zero to three-year-old children using public purchase vaccines every year. And the bottom line of that column, the cost for SESIPs for delivering these vaccines would be about $11.6 million. In the second row of the last column, about 28 million vaccine injections are administered to zero to three-year-old children using private purchase vaccines, and in the bottom row of that column, the additional cost for SESIPs related to delivering these vaccines would be about $10.6 million.

As some public sector vaccines or public purchase vaccines are administered in the private sector due to mechanisms such as VFC, the syringes for these vaccines are purchased usually by the private sector. When

this is accounted for, ballpark estimates for cost of SESIP implementation at the national level, the burden for the public sector is about $5.4 million. For a private sector, it's about $16.8 million.

In conclusion, program managers are aware of the revised OSHA standards. However, few immunization programs have disseminated information or conducted training. Perceived difficulties for implementation of SESIPs include additional costs, identification of appropriate devices, securing new contracts, and need for additional storage space.

In this context, options to consider include working with our partners to disseminate information to immunization providers. These include partnering with AAP, ASTHO, and others, as well as with OSHA. OSHA materials such as fact sheets can help in this purpose and direction to OSHA web sites, as well as web sites of other organizations that provide information on the revised standards as well on available devices can be helpful. NIP can work with OSHA to develop tools to help immunization providers meet the requirements. Such tools can describe the criteria

for evaluating SESIPs, for evaluating or documenting the evaluation, and for documenting needle stick episodes.

This information was gathered as part of a team effort in NIP, and that's all I have. Thank you.

DR. MODLIN: Thanks, Dr. Yusuf and Ms. Chiarello. We have a few moments for questions. I might lead off by suggesting, I wonder with the pretty phenomenal increase in costs with these new devices if anyone has ever considered doing a cost utility analysis of any kind. In other words, I would be interested in know how much it costs to prevent a case of hepatitis B infection in a health care worker or a case of HIV infection or a death. Has anyone --

MS. CHIARELLO: The Government Accounting Office has actually written -- has attempted to do that looking nationally primarily at hospital settings. It would be difficult to extrapolate to all health care settings and it really -- it depended on the -- it was a combination of the cost of the device and the -- and the cost of post-exposure treatment and severity of exposures and frequency of exposures and

seroconversion. So it was a very -- it was a fairly complemented -- complex -- relatively crude, but a great effort on their part to develop that, and it really depended on the most cost -- it would be most cost-effective where there was severe injuries and the cost of post-exposure care and frequency of seroconversion was high and the cost of the devices was fairly low. So in nine of the cells where they -- three of them were cost-effective. Denise, is that correct?

UNIDENTIFIED SPEAKER: Yes.

MS. CHIARELLO: Yeah, thank you.

DR. MODLIN: It would be interesting to perhaps see that information sometime.

Stan?

DR. GALL: John, this seems like this is another federal mandate. I don't seen any reimbursement increase, and one of the complaints continuously is physicians really have such poor remuneration for participating in a vaccine program. If they're pushed against the wall, they'll just drop it. This -- I mean, somebody didn't think it through.

DR. MODLIN: Jon, and then Dr. Foster?

DR. ABRAMSON: I would just --

DR. MODLIN: Jon, you're not wired yet.

DR. ABRAMSON: Okay. I guess I will simply state that the President of the American Academy of Pediatrics has written a letter stating his concerns for the Academy, from the Academy's viewpoint, on how this can be implemented.

DR. MODLIN: Dr. Foster?

DR. FOSTER: I actually have been actively involved in attempting to implement some of these things in our clinics and in our setting, too, and had to do this from scratch because basically we initially got the OSHA law without a lot of guidance that went along with that. And there's a lot of mandates in there. For example, the recordkeeping mandate requires that you keep record for 30 years after employment is passed. But I do have some concern about a couple of the devices. First of all, from my experience in an educational program alone, I probably would have decreased some of these needle sticks without the addition of these devices that we have to put on. Most of the devices require an extra step before you get ready of the

syringe. Of course, most of the training we've gotten has been to immediately to get rid of the syringe in a proper container in a proper manner. But the concern is that some of these devices that have come out -- I'm not sure if there's any type of approval as far as what they are, but one of such device which is the needle shield, which is an add-on for the syringe, actually does have a significant dead space. I measured it last week in one of the devices and it was a 0.1 ml dead space that was in there which meant one of two things. If you were to draw up a syringe from a multi-dose vial, you would actually be wasting 0.1 cc's of the product. However, the problem was that if you drew up a single-use syringe full, you're actually going to give 0.1 cc less of the vaccine to the patient. So you're actually losing a significant amount of vaccine. I'm not sure -- Actually, I shouldn't say that. I don't know what the significance of the loss of .1 cc -- most of them are .5, but it seems like that would be significant.

So, in addition, also that volume of loss in a 10 cc vial would come out to be approximately a loss of two

doses. So in a shortage of vaccine, that's pretty significant, too.

DR. MODLIN: Right. Further questions or comments? Dr. Yusuf?

DR. YUSUF: To try to also provide some information related to the dead space issue, it is a question that several -- both individuals from the field have inquired with NIP about. They were also facing some concerns that some of the devices may have increased dead space. In response, we had talked with some individuals in FDA regarding -- to try to find out what is the licensing procedures. And anecdotally, what they informed us was that in the licensing procedure for the safety devices or syringes with safety devices, those things are taken into consideration as to what proportion of dead space there is. However -- and companies when putting in for a license may state that they meet certain standards or provide test results for these standards. And they also noted that it may be possible that manufacturing processes change, but what they encouraged was that if there was such a concern for certain devices to bring it to the attention of the

FDA's compliance division as well as the manufacturer to get more clarification.

DR. MODLIN: Natalie, California is almost certainly ahead of the crew on this issue, I would guess. Do you have any comments in terms of what your experience --

DR. SMITH: We actually had legislation ahead of the OSHA laws that's actually been implemented. And we initiated had a sharps group that was very helpful in helping us make the transition. We, too, had varying experiences with the different devices and found some more useful than others. We, as a state, don't provide syringes, so it wasn't -- it didn't hit us, I guess, hard as it might some other states.

DR. MODLIN: Further comments or questions? Bob?

DR. CHEN: This is just kind of general comment. A couple of years ago, I had a -- my sabbatical at the WHO started the Safe Injection Global Network, and just to kind of -- for the group's knowledge, what's happened is that this issue of injection safety was probably the single largest iatrogenic disaster of the 20th century on a global level and probably continues to be a major iatrogenic problem obviously in developing countries

where the assurance of sterility is not possible. And the problem is that immunizations has by and large been in the forefront, at least in the developing world arena, in terms of the expanded program of immunization in terms of this focus on injection safety. However, they failed to make any real progress in the long-term because immunizations constitute a very tiny part of all injectables. It's probably less than five percent. And the same issue -- the same is probably true in the U.S. so that, by and large, these OSHA rules and all the things are driven by non-immunization-related injection safety concerns. And I guess part of the problem is that it's very hard in the health care system to kind of isolate the immunization program as a purely vertical process with its own set of injectables and its own set of trainings because those same nurses, by and large, inject for other medical products, et cetera.

So, by and large, I know the numbers may not totally suit the immunization arena in the developed world but, by and large, it's hard for us as the tail to wag the dog.

DR. MODLIN: Thanks, Bob. Deb Wexler?

MS. WEXLER: Hi. I just have a question for clarification.

Now, I understand that OSHA requires by July 21st that clinics and medical settings have a plan in place, is that correct, or is it that we have to be using safety devices? I mean, do they have to be being used or do you just have to have your process in place to evaluate?

MS. CHIARELLO: Well, the new requirements actually took effect in April, on April 1st, I believe, was the date. So there is usually several months that allow for the implementation before the enforcement phase will begin, but I really shouldn't speak for OSHA on that. It has already taken effect. So the expectation is that if -- if there is -- someone does go into a facility, there would be an expectation that the exposure control plan would have taken into consideration the safer technology and implemented that that has been determined to be appropriate. That's that catch-all phrase where, how do you define what is appropriate, and it becomes very subjective even within health care organizations. I think what's

creating a lot of problems.

I didn't completely answer your question. I think it's better to check with OSHA for interpretation on the date if there's been any change.

MS. WEXLER: I know the date is three months after that April date.

MS. CHIARELLO: Right.

MS. WEXLER: That's when you have to be in compliance.

MS. CHIARELLO: Yes.

MS. WEXLER: I guess my question was more about, what do you have -- what exactly -- I guess that's an OSHA question and must --

MS. CHIARELLO: It really is. But from my discussions with OSHA, they would have expected that there had been some determination of the exposure risks in the health care setting, some review of sharps injuries, for example, what devices are involved. We're just talking about injection devices here. And in health care settings, there are a myriad of devices that cause sharps injuries. And to have a strategy in place to consider the new technology, to evaluate it, to involve the front-line workers in that decision-making process

and to implement what in the facility has been determined to be appropriate. And I think Bob's point about the fact that a lot of immunizations occur in the context of a lot of other health care is very important to be aware of and that may not be the immediate priority for some of those health care settings -- injections.

DR. MODLIN: Yes?

MR. ROSENBERG: Zeal Rosenberg, Beckton Dickinson, Worldwide Director there for immunization.

Just a point of clarification. There was a handout that was distributed as part of the packet for OSHA questions and answers, and it indicated -- one of the questions was -- very relevant to this group -- about whether federal clinics and state -- federal and state health workers are, in fact, covered by this, and the answer was that they're not. And I want to give a clarification for the future, that there is, in fact, a House bill that's gone through several committees and is expected to be on the floor. And for information purposes, that's 2768 that extends all of these regulations to, in fact, the state and federal health workers. So just as a clarification.

MS. CHIARELLO: Some states have stated OSHA plans. So, in some cases, public workers are not covered and in other cases they are.

DR. MODLIN: Larry Pickering?

DR. PICKERING: Thank you. Two points, John. One is that this may indeed be a self-correcting problem. I know the two of the hepatitis preparations already have these devices on them and it would be interesting to hear from the manufacturers if they have any plans about putting these on the immunizations as they're delivered to physicians. That's number one. And secondly is, is not the point of this to really have you and the AAFP and the AAP and other organizations develop some educational material that will guide physicians through this very confusing maze?

DR. YUSUF: Yes, Larry. And I think that's been one of the very good outcomes our information gathering and talking with the various parties. As I mentioned in my presentation, one of the things we would like to do is work with our partners and OSHA to develop a tool to let immunization providers know or describe to them exactly what they need to do in terms of evaluating

SESIPs and documenting the evaluation or implementation and how to keep an injury log and those kind of issues. So that we think is very much needed, and so far anecdotally OSHA and NIOSH, as well as other partners, have expressed an interest in working with us in that.

DR. MODLIN: I'm going to ask if there are any of the manufacturers that would like to respond to Dr. Pickering, and then we'll move on.

Dr. Zink?

DR. ZINK: I'm Tom Zink from Glaxo SmithKline, and we currently provide an option for those who want to purchase a safety needle device with our pediatric hepatitis vaccines, both Havrix and Andrax B. It's the first step. We're watching to see how well it's, I guess, taken up and assimilated into the practice of immunization, but we have plans to bring it on for Infanrix as well and eventually for the adult vaccines, too.

Pardon me?

UNIDENTIFIED SPEAKER: [Inaudible]

DR. ZINK: I'm not entirely sure exactly sure how much

the additional cost is. I believe it's something like 30 or 40 cents more. And that's one question I had for Dr. Yusuf was, the data that you have up there in regards to the cost, what was the cost of the device that you were using to come up with the extra additional millions that would be incurred if this was implemented for each of the doses?

DR. YUSUF: We used a cost for a SESIP at 43 cents per SESIP, which we have seen used in other estimates also, also from getting information from the manufacturers. But I did want to note, as I did in the presentation, that the costs do vary by device.

DR. ZINK: Yes, indeed, yes. We've chosen to go with the Beckton Dickinson safety -- I think it's called the safety tip lock and ours is -- the safety glide and we call it our safety tip lock, and it works with our Luralock [phonetic] prefilled syringes perfectly. And it's actually -- in a lot of these situations, I believe it's important that you have a Luralock [phonetic] tip on the end of the prefilled for these to work if you choose that device.

We wanted to give the vaccinators an opportunity to

choose. We still have the other products that are vials and prefilled without the safety tip lock as well.

DR. MODLIN: Thank you, Dr. Zink. Let's move on. Thank you, Dr. Yusuf and Ms. Chiarello. We certainly appreciate a very thorough discussion and one that we needed to undertake at this point.

An ultimate item on the agenda is the adaptation of vaccine formulary selection algorithm to web-accessible tool. I assume that Bruce Weniger will be leading the discussion.

DR. WENIGER: All right. Let me provide a brief introduction to the presentation of this -- of a live web site that we have. It's not actually connected to Ohio, but the server has been duplicated here in this lap top.

A few years ago when hib, hep B, and DTP hib vaccines appeared as combinations, for the first time it presented some necessary choices that providers had to make among what's been called combination chaos. You wouldn't necessarily need to use the same group of vaccines in a refrigerator to satisfactorily immunize children. So we developed a vaccine selection

algorithm tool whose objection was to make it possible for users to pick among these competing monovalent or combination vaccines that which they could use in their program. And the principles were to achieve the lowest overall cost to drive it by economics using rational objective economic criteria; and transparent formulae and methods so that even manufacturers themselves could sort of reverse-engineer the process to help them make pricing decisions when they come up with a new vaccine.

And one of its fundamental principles is to recognize the difference between vaccine products and to avoid treating them like commodity like poor bellies or barrels of light crude oil where we assume products from different sources are identical, and vaccines should not be treated that way.

And the goal that we're going to demonstrate today is to adapt this technique of an industrial engineering laboratory to the web so that anyone could actually run this algorithm for themselves to solve their own problem. Let's see to move forward, I guess I press that button.

And a few years ago, we published this in Vaccine with the philosophical approach behind it and how it works in general. And essentially, there are a number of potential economic criteria about vaccines. Currently, we only take into account the price of vaccine, and for this model we've only gone down to number four, the number of doses required, which certainly has economic consequences, the preparation time, and the route of administration. And some day when there's an intranasal vaccine, we'll have to figure out how much does that save society in terms of various costs so it gives us an idea of how much more we would be willing to pay, for example, to an intranasal vaccine than to an injectable one.

And the other ones here are not in the model because we don't yet have good data that can calculate the value of vaccines that don't have cold storage requirements; or that have longer shelf lives and don't get wasted from expiration; or have earlier age of full immunity; or have a better safety profile; or a better efficacy profile.

And last year we gave a contract to Austral Engineering

and Software to take this model developed by industrial engineers at the University of Illinois and Southern Illinois University and adapt it to the web. And I'm going to now turn it over to Dr. Sheldon Jacobson who will give a little more background before introducing our web specialist.

Thank you.

DR. JACOBSON: Thank you, Dr. Weniger.

My name is Sheldon Jacobson. I'm in the College of Engineering at the University of Illinois at Urbana-Champaign. We're going to tell you about the adaption of a vaccine formulary selection algorithm to web-accessible tool. I'm going to give you a little bit of background and very briefly go through some of the technical content and then we'll have a web demonstration of the tool.

This has been a collaborative effort across government, industry, and academia. Dr. Weniger has provided the government expertise, a lot of domain knowledge. The industry has been Austral Engineering and Software who has provided the web development and capability. And academia has been Dr. Edward Sewell

from the Department of Mathematics and Statistics at Southern Illinois University at Edwardsville, and myself.

To give you some motivation and the objectives for the original development of the vaccine selection algorithm, its purpose was to assist health care professionals in making some vaccine formulary choices, ultimately to automate this procedure so that they can determine what we refer to as a best value formulary, and the transition to the web tool enables one to actually have a very user-friendly environment by which they can use this automated procedure.

The technical content which is embodied in the web tool, like I said, it's been a CDC-academia collaboration which dates back actually for over five years now. The technical content has been included in a number of manuscripts of which Dr. Weniger referred to the first one, but there's been other ones. This covers not only medical journals but also engineering journals, some of which are just coming out I guess next month as well as early in the year 2002. And the web site, if you access it, you can actually get the abstracts of all

of these manuscripts and in some cases actually get the full manuscript.

The principles that we're using are from the field called operations research. Operations research is a mathematical modeling approach which enables one to basically find optimal ways to allocate scarce resources. The particular operations research model, which Dr. Sewell and myself have developed, captures not only the recommended childhood immunization schedule as put forward by this Committee, but in addition, it also deals with certain cost components which Dr. Weniger alluded to, as well as vaccine constraints, for example, brand matching of DTPa and a variety of other factors. And as more constraints and more cost components are, in fact, identified, we can, of course, update the model to include all of these. So, basically, whatever the status quo is at any given time, we can model it and we can embellish it as necessary.

Also, the cost components are very flexible as we'll see in the web tool so that you'll be able to change them based on the particular needs of your health care

environment.

The particulars of the vaccine selection algorithm, as I said, it uses operations research principles to ultimately very efficiently search through a large possible set of vaccine products to ultimately determine the so-called best value, lowest-cost vaccine formulary. To give you an idea of the scope of the search, there will be anywhere between 100,000 to possibly as many as five million vaccine formularies you would have to search if you did it in a brute force crude way. By using operations research principles, we're actually able to prune that down quite significantly and do it much more efficiently so it may take as little as two seconds or in some cases several seconds. But to try and do this in a brute force way would be very prohibitive in a time perspective. And the factor, of course, is that as you add more vaccines to the schedule, in particular if you start adding also combination vaccines where there are choice issues as Dr. Weniger alluded to, then this number really begins to explode in a very large way and, in fact, it adds more value to the algorithm and model

that we've developed.

The potential users of the web site and ultimately the tool that's been developed include, of course, purchasers of vaccine products at all levels -- the public sector, federal, as well as state and county agencies, physician groups of all sizes, large HMO's or smaller practices of pediatricians and family practitioners. The tool also has the potential ability and capability for health insurance companies to, for example, evaluate a particular product and negotiate with vaccine manufacturers for prices, to bring their prices down. They can also use it to determine what they're going to provide, hence reimburse. And vaccine manufacturers on the other side can use it to assess the value of their product and find out if their price has been set correctly -- should they be raising it or lowering it to be able to get market share. So, as a result, it's a very flexible tool in how they would like to use it.

Right now I'm going to pass the microphone over to Mr. Medina who is going to be able to tell you more about the vaccine selection algorithm and the web site.

DR. MEDINA: Good afternoon. My name is Enrique Medina. I work for Austral Engineering and Software, a small business in Athens, Ohio.

What we have done is transformed a vaccine selection - vaccine formulary selection algorithm into a web site. The address for the web site is shown here. What we have in that web site is a customized operations research algorithm solver. This is work in progress. We have finished the proof of concept. It works for -- You know, there is a large number of vaccines there. There are -- As Dr. Weniger said, there is a number of model elements, economic elements that are in the model. There is still work to do. What we would like to have is people that would be interested in using the site and providing, you know, their ideas on how to improve it and -- ideas in general about the tool. Now, the site is best viewed in Internet Explorer 5 at the moment. It also works in Netscape. But user customization of the vaccine database is possible. For example, if a user -- all users will have different prices available to them so they can actually enter those prices and possibly save them for future use.

The demonstration I'm going to provide today is served by a local server, which means the software that actually answers the requests when you browse the net is on this same computer. When you access this site, the server is actually in Athens, Ohio. Again, we're looking for evaluators of the beta product and we welcome any comments.

So with that, I'm going to go back -- go to the actual browser here and then I'm going to open it again in case it -- in case the operation has timed out. It's been open for an hour now.

So, basically, this is what you would see when you enter this site. This is the same information we had on the previous slides. Then there's a background about the project itself. Then there's some information about our company, how to contact us, and then the link for running the algorithm. In this presentation, that link is active. When you go to the site, what you will get on that link is information on how to get to be one of the people that will test the web site. Basically, you can send us an e-mail and we will give you a password to test the web site, and hopefully, you'll be willing

to provide some background -- some ideas on how to improve it.

The most important thing or the key element is a list of vaccines, correct? That was to be expected. Now, we have a header area here that lets us decide which -- lets the user which vaccines they're going to consider in the -- have the algorithm consider for their solution. So for a particular vaccine, let's consider this first one. You have the vaccine type in the first column. You also have the product name, the brand name, and national drug code. You have the manufacturer and then three possible prices. The first one is a federally-contracted price. The CDC price is in the -- you know, in the list that CDC provides. This price is -- we call it the private price. Depending on the size of the organization, they will get a different price from the manufacturers or the distributors. What we have here is what they call the average wholesale price, and the user can also set a price of their own.

Now, what I'm going to do here is -- for the first demonstration I'm going to set all the prices to be used

from the list -- the federal-contracted list and then I am going also to de-select some vaccines. So in this particular run of the algorithm, I'm not going to be considering the DTPa-hib and I am not going to consider two other combination vaccines -- the hepatitis B and I think there was a second one of those. So I will not be considering them. And the purpose here is to show you what the solution will look like. There are some other steps. We have organized the execution of the use of the site in several steps.

The first step is actually to do what I just did, go through the header section here and you can actually de-select one of the manufacturers. So all the vaccines for a particular manufacturer could be not considered for a particular run of the algorithm, or you could select all the prices to be federal prices, or all the prices to be average wholesale prices, or all the prices to be custom prices, or you could go to each of the vaccines and select the price for the particular vaccine.

You can also set what is called the preparation cost per dose, and that depends on the packaging. It

could be a prefilled syringe; it could be a liquid in a vial; it could be powder. And we have provided some defaults, default values, for the preparation costs, but those can also be adjusted for all vaccines in a particular packaging or for each vaccine individually. Once you have done that -- and here's a long list of vaccines -- you can also add vaccines. And these vaccines you add here could be vaccines that don't really exist. So a manufacturer could actually use this to see where their vaccine would be placed in the formulary or if it would be at a particular price. Then at this moment I'm not going to add a vaccine. We have a cost for a visit to the clinic. You can make this zero or whatever value you want. And then we also have a cost for injections. The cost for injections is -- it could be a direct cost of injection, it could be something indirect such as the willingness of a person to get it -- how much are they willing to pay not to get an extract shot. Then there are other parameters that you can set. For example, whether you are going to match -- provide all the DTPa vaccines from a single manufacturer like it is recommended or whether

you will not do that.

And then there is obviously the decision about the birth dose of hepatitis B vaccine. Then you can also save your current settings for future use.

So I am going to verify if I have set it for all the vaccines. I think I have. Then I'm going to try to obtain a solution. So there's my solution for that particular problem. So we get -- we basically get a schedule of vaccinations for age, the total cost of the vaccines, the total cost of injections for each of the visits, the cost of the visits themselves -- remember that these things are -- you can set the price for each one -- each visit and each injection is -- and then the preparation cost and the total price. Then you get a list of all the vaccines that you had -- that you were considering and then you get a shopping list. This is what the person making the decision of purchasing would take and then order the vaccines from their particular distributor.

What I want to do now is change the settings and try to obtain a solution again. Now I'm going to include the vaccines that I had eliminated before and

try to obtain a solution. And these are combination vaccines and, you know, the more -- I guess I didn't set a price for those. I'm going to try to solve it. The more combination vaccines you have, the longer the algorithm will take for -- to get a solution. This is going to take, I expect, something like 30 seconds. In this time, we could take a question if you have any questions about the algorithm or the web site.

DR. MODLIN: About the site, the algorithm, the process? Rich?

DR. CLOVER: I'm just -- On the combinations you showed, it's the same manufacturers' vaccine that's used for the routine vaccines at the two, four, and six month?

DR. MEDINA: Correct, yes. These are all approved vaccines, the ones that I have listed there. And this is the solution. Basically, it knows that it can use the combination vaccine here. In the other -- in the previous months, it used DTPa, obviously from the same manufacturer because that's what we were asking it to do.

I don't know if I -- Did I answer your question or --

We can also --

DR. WENIGER: If I understood your question, Richard, we took every vaccine available in the United States in all its product formulations for the recommended disease prevented by the schedule, and they are in that table. So if there's a formulation that has ten single-dose vials or five single-dose vials, those are all independently listed on here. So if you decide your practice does not want to buy prefilled syringes, you can uncheck the prefilled syringe box and the formulary with the algorithm will only compete the liquid or powdered vaccine. So there's every vaccine we're aware of that has either a private sector or a federal price is in the table.

DR. CLOVER: I understand that. I guess what I was trying to ask is, did the algorithm prioritize price as to sole outcome or the number of different types of vaccines the provider would have to have in order to get the cheapest price?

DR. WENIGER: You're raising a variable that is not in the algorithm and that is -- any economic value that results from reducing the total number of different

vaccines in your refrigerator, and that is an economic value. It doesn't yet model that. Someday it perhaps can. It only looks at the cost of the vaccine, the preparation costs, and the number of doses required and then optimizes the lowest cost mix.

DR. MODLIN: Other questions or comments?

(NO RESPONSE)

DR. MEDINA: As I said before, the web site address is there. It's vaccineselection.com -- www.vaccineselection.com. There's an opportunity there to -- there's an e-mail address where you can send us e-mail and we'll provide as much information as you need. Hopefully, we'll get your feedback also.

DR. MODLIN: Terrific. Dr. Medina, Dr. Jacobson, Dr. Weniger, thank you very, very much.

Any further comments, questions? Rich, did you have a follow-up?

DR. CLOVER: Yes. Just a follow-up to the Yellow Fever group. Due to some departures, we are not going to meet today. We will schedule a conference phone call in the next three weeks.

DR. MODLIN: Terrific. The last item on the agenda

is public comment. Gloria, as far as I know, I don't have anyone that signed up for additional public comment. So hearing none, I want to thank all of the members of the Committee for sticking with us and just to warn you that we'll inevitably have a conference call that we'll hopefully schedule for around the end of November to take up both the -- finish up with the thimerosal statement and then to discuss pneumococcal vaccine availability.

DR. SNIDER: I would like to thank the Committee for all their hard work and also Gloria and all the staff for all the work they do throughout the year.

DR. MODLIN: I'll second that for the Committee.

(APPLAUSE)

DR. MODLIN: See you in February.

(Whereupon, the meeting was adjourned at 1:14 p.m.)

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C E R T I F I C A T E

STATE OF GEORGIA

COUNTY OF FULTON

I, PAMELA T. LENNARD, BEING A CERTIFIED COURT REPORTER AND NOTARY PUBLIC IN AND FOR THE STATE OF GEORGIA AT LARGE, HEREBY CERTIFY THAT THE FOREGOING IS A TRUE AND COMPLETE TRANSCRIPTION OF SAID PROCEEDINGS; AND THAT I AM NEITHER A RELATIVE, EMPLOYEE, ATTORNEY, OR COUNSEL OF ANY OF THE PARTIES, NOR A RELATIVE OR EMPLOYEE OF SUCH ATTORNEY OR COUNSEL; NOR FINANCIALLY INTERESTED IN THE ACTION.

WITNESS MY HAND AND OFFICIAL SEAL, THIS, THE 13TH DAY OF NOVEMBER, 2001, IN ALPHARETTA, FULTON COUNTY, GEORGIA.

PAMELA T. LENNARD, CCR, CVR

NANCY LEE & ASSOCIATES

CERTIFICATE NUMBER B-1797
(CCR SEAL - NOTARY SEAL)

NANCY LEE & ASSOCIATES