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VOLUME II - DAY TWO

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P R O C E E D I N G S

8:32 a.m.

DR. MODLIN: Good morning. The first item on the agenda for this morning will be an update from the general recommendations work group. And Chinh, will you be leading the charge?

DR. LE: Thanks, John, and good morning. Actually, this is going to be my last meeting at ACIP and if you would allow me, John and Dixie, I'd like to say a couple of things first.

Well, I know it's water under the bridge, but I'd like to share with you some of my last thought about the pneumococcal conjugate vaccine, which I really believe there is some lesson to be learned about what we do.

At times, I may sound very negative about the vaccine.

Actually, I'm not negative about the vaccine at all.

Otherwise, I would never have been a clinical investigator for the vaccine at Kaiser. And I know it's a wonderful vaccine and we should use it according to the result of sound medical research, which is to prevent invasive disease and expect some reduction of otitis media and bacterial pneumonia in infants.

You know, the cost analysis that Tracy gave us pointed to some potential society saving for children given

catch-up immunization, meaning those in day care centers and to reduce otitis media. The cost-effective -- cost-effectiveness model is a great one, it is a very thoughtful one, but the assumptions that go into the calculation is what I have a problem with, and I pointed out the weakness of the data of the risk of increased risk of disease in day care center and the lack of data in otitis media in older children from the vaccine.

And I hope that those of you who are looked upon as experts in this vaccine, as you give talks across the country and talk to your peers, remember that when we talk to parents who show us the vaccine ads and great expectation from the vaccine, it is a great vaccine, but we should use it in evidence-based recommendation before spending millions of dollars on yet unproven assumptions. We can always go back and expand the use of the vaccine when more data is available in older children. Until then, in an era of limited health care resources and competing priorities, we cannot afford millions of dollars robbing Paul to pay Peter or robbing Peter to pay Paul. CDC still carries a lot of respect, but with an increasingly critical public and health care payors who are reviving the old political

question, where is the beef, we have to keep our credibility up when we make recommendations.

So I think that's a lesson I learned from pneumococcal vaccine. And then a couple of personal notes, I'd like to say thank you to all the mentors and colleagues who have guided me over the years over here. Mentors like Karen Hall, Sam Katz, Pierce Gardner, Stan Plotkin, Bill Rennel, and so on, and many others, and colleagues who are out there as well as colleagues who have never attended this vaccine, but giving me some inspiration. Sitting at the center table, I feel very humbled at times, because I know all the wisdom is actually out there, around us, not with us. So I really thank you for sharing the wisdom and knowledge.

And then secondly, greater than 33 years ago, I came to this country from Vietnam, barely speaking English, and this country has given me tremendous educational and professional opportunities, one of which is to have the honor to serve on this committee. It's a great feeling as an immigrant to be able to say thanks and give back some of the services the great land -- to this great land and its people. And for that, Tracy and John, I thank you very much for giving me the opportunity.

DR. SNIDER: Thank you, Chinh, for your -- for your

service. We really appreciate it.

(APPLAUSE)

DR. LE: Thank you. I'm not running for political office. Don't clap.

Anyway, back to what I was given the microphone for. Actually, after all that nice talk, I'm kind of disappointed to share with you that at the last meeting we promised to bring to you the draft of the revision of the general recommendation and Bill Atkinson has been so busy with his lecture series over this winter and this spring that actually the work on the revision actually just stalled. And we'll have another time line and Bill certainly promised that we'll have a draft by October for the whole document.

For this hour, we have basically two items. One is the issue of how to handle the foreign adoptees from certain orphanages, as you know. And we also have here Dr. John Clements, who will give us the WHO perspective, at least his personal comments. And then a little bit unannounced to the working group as well as to the general ACIP Committee here, we have a new item that fits well with the general recommendation. That's why we have given the time to Diane Peterson, Dr. Peterson, from Department of Health in Wisconsin to

really present and make some suggestions about how to revise the harmonized schedule that we publish in October every year to make it a lot more user-friendly. And obviously, this is the very first step, because it has to be negotiated with the AAP and AAFP to see whether they will harmonize with that as well as some of the recommendations, but I think it's going to be very exciting to make it very user-friendly. So I turn the microphone to Bill.

DR. ATKINSON: Sorry, I don't have a page-turner. This is the third of what's, in my opinion, a contentious issue.

No, I'll take care of it. It's not a problem. You're too senior to be a page-turner. I could be the page-turner, really.

This is the third -- the third of three contentious issues that although pale in comparison to pneumococcal conjugate vaccine are contentious, nonetheless, and do need to be dealt with. And really, the general recommendations, believe it or not, should be fairly simple to finish once we come to closure on this.

If you recall at the February meeting -- And I do apologize for not having a draft for you today, but I guarantee you'll have one by

October -- we dealt with violations of the minimum intervals, the so-called decision rule, and came to closure on that, I believe. We also dealt with the management of people who receive two or more live vaccines, and your recommendation was to repeat the vaccine given second, which is a new first recommendation for ACIP.

And this one, we've got tabled and we're going to take it up briefly today, is the issue of acceptability of vaccines administered outside the United States. Why, you ask. What I'm going to do is ask for a decision by ACIP that essentially boils down to this, that in light of admittedly limited data, and if you think the -- you're going to have limited and conflicting data due from groups of adoptees suggesting inadequate protection, from adequately documented dosage, should ACIP modify its recommendation for acceptability of vaccines received outside the United States.

Why should you care about this? You should care because it's estimated that in FY98, there were over 16,000 international adoptions, of which about half were under the age of one and about half came from two countries, Russia and China. This does not even include the large number of immigrants to this country

beyond the adoptees that also -- we oftentimes have to address these issues. And so I have -- I want to present this in three segments.

The first, I want to show you what data exists, of which -- some of which we've only come into -- we've only gotten our hands on within the last couple of days. Second, I would like to show you the -- what exists now as far as recommendations. And third, give you several options about ways that you can go and possibly some suggested wording on how to do that.

Before I start, I would like to let you know what the current wording is. This, in 1994, was the first time that this was dealt with in the ACIP -- in an ACIP statement and it said, in essence, beauty in its simplicity, that the acceptability of vaccinations received outside the United States depends primarily on whether receipt of the vaccine was adequately documented, i.e., written, and whether the immunization schedule, that is the age at vaccination and spacing of vaccine doses, was comparable with that recommended in the United States, and the nuts and bolts are any dose with written documentation administered at the recommended minimum intervals and ages can be counted as valid. That was very

straightforward and has been taken -- exception has been taken to this. This was from 1994, and this is what we still quote to this day. The question is, is that still valid and should we continue to use that recommendation?

I would like to show you three -- Basically, the only -- the data that exists comprises probably less than 150 children that have been evaluated by three different groups, some of which some of you have seen, some of which you have not, because it is currently unpublished.

The first data I would like to show you -- And this has to do with what is the actual immunologic situation, vis-a-vis vaccine-preventable diseases, in children who fit the criteria which ACIP has laid out and also the Red Book that accept a dose of vaccine that, in fact, is supported by written documentation. This is a small study done in 1996 and 1997 by Peggy Hofsteder, at that time in Minnesota, currently at Yale. She evaluated in her clinic 55 children who came from Eastern Europe, China or Russia, as shown on this table.

And this -- By the way, these data are summarized in my handout, which may or may not actually still exist on the back table. It was there yesterday. I assume it's

probably still there. We can get you a copy if you do not have one.

You'll notice that the average age of these 55 children, who of which about two-thirds were from -- about half were from Russia, the other half were divided between Eastern Europe and China. The bottom line is this -- She accepted in this study children who had three or more documented doses written, dated doses of DTP vaccine. And she evaluated their diphtheria and tetanus antitoxin titers, I believe, with neutralization tests. The bottom line is this, that if you take all 55 children, that only 38 percent of those children actually had serologic evidence of protection against diphtheria and tetanus. You'll notice that the percent immune varied from 50 percent in Russia -- in the Russian children to about 12 percent in the Chinese children. So, basically, three or more doses written -- with written documentation did not correlate specifically with evidence, serologic evidence of protection against these diseases.

If you stratify this, which was really the nuts and bolts of this, if you stratify these data by where the doses were given, it turns out

that -- that about 65 percent of children shown on the

right side of children who received at least one dose in the community had evidence of protection against diphtheria and tetanus versus only about 18 percent of children who had received a dose in an orphanage setting.

So her interpretation of these data were that in fact she couldn't totally explain it, but assumed that there was either error, falsification of records, or inadequate vaccine storage and handling. Hence, children that -- in her opinion, at least, children from orphanages is the key issue, more so than children from specific countries.

That was the first set of data that could really look at this and her basic principle these days, and she continues this at Yale, was basically to do D and T antibody testing, if available, on children who had three or more doses of vaccine, of DTP. Anything less than that, she basically recommends they be repeated and basically repeats a lot of the other vaccines that, in fact, have low reactogenicity potential: measles, mumps, rubella, Hib, et cetera. This is the first data. Notice the number of children in the study was a total of 55.

The second piece of information is -- was presented.

This is from Jane Aronsen at Columbia University. This is a study being funded by CDC and Columbia University that is in progress now. It was basically done to -- And this is not in your -- This is -- Actually, this is summarized in your handout. They have been looking at, basically, the prevalence of TB infections in adopted children from other countries. They have, as a result of this, also been looking at hepatitis B serology and they do have evidence -- they have records that they're able to correlate hepatitis B antibody titers to the children's records.

To be included in this, it was necessary to have documented at least two doses appropriately spaced of hepatitis B vaccine. She had 96 children of the 500 in the study. Notice the age here is about one and a half years old. Again, the distribution is about half in China, a third from Russia, and about 20 percent from other places, notably Eastern Europe. Notice that of the children with two documented doses of hepatitis B vaccine, only about half of them actually had hepatitis B surface antibody. About half were surface antibody negative and a couple were actually already antigen positive.

This -- The interpretation of this was, yes, it's

possible that some children do not develop antibodies until a third dose and about -- I think about half of these kids had only received two. But this also was -- they thought evidence of perhaps the records did not adequately represent what their presumed antibody titers -- or what their protection actually was. This study is ongoing and they do intend to do some serologic testing for measles and other antigens as the study progresses.

The third and last piece of information I'd like to give you before I move on to other recommendations is unpublished data that Ben managed to get from Mary Allen Staat in Cincinnati, who runs an international dock. And this is not in your handout, because literally we received these data only a couple of days ago. She started her study because of Margaret Hofsteder's results showing inadequate protection in these vaccinated children. They have been doing it in a very similar way.

Notice that they've had 30 children. So we're up to now a robust -- about 175 in for the entire population that we have data on. About 17 months average age, a third from Russia, about a quarter from China, and a quarter from Eastern Europe. All of the children to be

included in the study had at least two doses, written documentation of two doses of DTP vaccine. Eighteen of them had at least two doses of hepatitis B vaccine.

Now, this is what -- I thought this was going to be a lot easier than it actually is going to be, because she is using an ELISA for tetanus and diphtheria antibody and found 100 percent of the children who had received at least two doses of DTP to have ELISA-protective antibody based on the interpretation by the laboratory doing the -- doing the thing. For diphtheria, 75 -- 72 percent have protective antibody against tetanus. And again, about two-thirds were surface antibody positive. Again, that is similar to what Jane Aronsen found in her study. She did not -- Dr. Staat did not find a difference in whether the vaccines had been administered in an orphanage or in the community. So while the data that existed prior to three days ago that we had seemed to imply that there was perhaps countries and locations that we could target for skepticism on records, this data seems to not support that. So the small amount of data that we had seems to conflict. Why it conflicts is not clear.

The studies were done at slightly different times. This is an ongoing study that was done in 90 children

adopted in '98-99, I believe. Dr. Hofsteder's was a couple of years earlier, in '96-97. So perhaps that has something do with it. Otherwise, it's not totally clear why this difference in results.

That is, in essence, the data available for which you have to make some kind of decision on how to recommend management of these kids.

DR. MODLIN: Bill, I wonder if we could ask you a couple of questions about these data. Would this be the appropriate time?

DR. ATKINSON: Of course.

DR. MODLIN: Bill Egan? I've got some -- a couple of my own, but go ahead --

DR. EGAN: Yeah.

DR. MODLIN: -- now.

DR. EGAN: I guess one difference, if I saw it correctly, was the age at which the children are tested, 17 months versus 37 months. I mean, antibody levels will go down with time. And

were -- In both of these studies, were they using the same definition of "protective"? Because even for D and T, what's considered a protective level, there is some discussion about that. Were they using .01 or --

DR. ATKINSON: No, they weren't even using the same

test. I believe --

DR. EGAN: No --

DR. ATKINSON: Yeah.

DR. EGAN: Yeah.

DR. ATKINSON: It was -- I got the levels that were defined by -- that was included with the data that Dr. Staat sent us, and it basically varies. They've actually used two different laboratories that actually themselves use two different definitions. One laboratory had .1 as being "protective," quote, unquote. The other one had three levels of non-existent, marginal and protective.

DR. EGAN: Yeah, I mean, some people may use .01 as protective.

DR. MODLIN: Yeah. Bill, the other thing is, with a mean age of 17 months, I'm sure there's a distribution. It probably means that many infants are under 12 months, as well. It would be nice to see what the actual age is, because many of them are likely -- they still have passive-acquired maternal antibody as well, at least for tetanus and perhaps diphtheria. So that would be another potential confounder with the -- with the second data set that would be important to take a look at?

DR. ATKINSON: I don't believe she sent us those data. We -- Again, we just got it a couple of days ago, so --

DR. MODLIN: All right.

DR. ATKINSON: -- we don't know that.

DR. MODLIN: Which could do it exact, I assume --

DR. ATKINSON: Yes.

DR. MODLIN: -- have the same effect. Kristin?

DR. NICHOL: I'm just wondering if there are any confidence intervals or P values available. In trying to look at these numbers with such small ends, I would guess in some of them, the confidence intervals are so wide that it may be difficult to have much confidence in the precision, the specific estimates.

DR. ATKINSON: I think that's true. The only one that I think had a lot of significance was in Dr. Hofsteder's data showing the difference between orphanage-acquired -- orphan vac- -- orphanage vaccination and community vaccination.

DR. NICHOL: So that was a significant --

DR. ATKINSON: Other than these -- Some of these are ongoing studies and some of them did not provide P values, but, obviously, the numbers are quite small and the confidence intervals are going to be very wide.

DR. NICHOL: The other question I have -- And forgive

me, I'm not a pediatrician --

DR. ATKINSON: Nor am I.

DR. NICHOL: -- what proportion of children would we expect to have protective antibody titers if they were immunized in the United States? I'm just, again, thinking about a comparison group
and --

DR. SNIDER: Yeah, I would just add to that, if they came from another provider and it was in a field setting, not a clinical trial setting. Do we have any data?

DR. ATKINSON: Walt?

DR. ORENSTEIN: I think our -- we have seroprevalance data. I think with tetanus antitoxin levels that -- I can't think, Dixie, off the top of my head for just seroprevalance studies, but certainly the trials, virtually everybody achieves protective levels of diphtheria and tetanus antitoxins after a primary series.

DR. SNIDER: I just think it's an issue -- it's a broader issue about people bringing records from another -- having received immunization from another source. And for legitimate reasons, people are focusing in on these other countries, but I think we

want to be careful about the stigmatization associated with this and make sure we have a complete understanding of the situation as it applies in our own health care settings in the United States as well and the relative inadequacies of records of both in-country and externally.

DR. MODLIN: I think that's a fair statement, Dixie, but I'd also like to point out that this Committee, its primarily responsibility is for the health of the children who are being immunized and we have to -- number one, have to assure that they're adequately immunized, protected against the diseases to which we want to protect them against. And I think we have to focus on that issue and then certainly be aware in the way in which we address it that we are sensitive to the other issues, as well.

But we don't have a whole lot of time, unfortunately, on this, probably not as much as we should, but it is a -- it is an important -- very important topic. Why don't we go around here. Larry, do you want to mention what the 2000 Red Book is --

DR. PICKERING: Yeah. I'd like to ask Bill one question first.

In Dr. Aronsen's data, are there any hepatitis B core

antibody levels to determine whether or not the surface antibodies due to the vaccine are natural exposure?

DR. ATKINSON: Yes. They did check for core antibody and those kids were excluded. They only included in this -- There were some -- obviously some children who had been infected prior. Those were excluded and her group of 96 only included those who were core antibody negative.

DR. MODLIN: Rick?

DR. ZIMMERMAN: It seems that this -- that these data sets as they conflict are, due to the small numbers, really inadequate to make a decision. Is there any chance that in another three, six months, we would have additional data?

DR. MODLIN: It sounds like the Cincinnati study is still underway and you're just presenting preliminary data. Isn't that the case, Bill?

DR. ATKINSON: I think it is still underway and I believe that Dr. Aronsen's study and collaboration with the Tb group and the Division of Quarantine is actually still in progress as well. But whether or not the amount of data will come out to really be sufficient to influence or convince anyone of anything is anybody's guess, frankly.

DR. MODLIN: Walt? Ben?

DR. SCHWARTZ: The Cincinnati study still is ongoing and they hope to get 100, 150 kids over the next year or so, perhaps.

But my question is, as we think about what kind of policy might be developed, one of the potential recommendations is to do serology. And you've raised the issue of the accuracy of serologic results of the comparability between ELISA of the neutralization assay. Do you have any idea what types of serology are generally available so if a clinician was seeing a child? And would they, first of all, have access to doing diphtheria-tetanus serologies and if so, the reliability of the lab results they might get?

DR. ATKINSON: It's my impression that ELISAs are generally available from reference laboratories. The reason that Dr. Hofsteder is no longer doing titers is because she was not satisfied with the quality of -- They were actually doing ELISAs at Yale and she wasn't happy with them since she was doing, I believe, newts (sic) in -- when she was in Minnesota, or what she believed was a more precise test and was not confident that the ELISAs were very representative, which is why, in fact, she has not tested any additional children,

because she was having problems getting the antibody titers actually at Yale.

So she wasn't satisfied with her reference lab. So they're probably available. How they could be interpreted and what -- the variability between labs, I can't really speak to that exactly.

DR. MODLIN: Stan Gall.

DR. GALL: John, I don't know if this is the appropriate time, but whatever you were saying about small children really applies also to pregnant women. The pregnant women that we're seeing really are under-immunized and I don't know if ACIP, in any of their statements, has any type of a recommendation for immigrants or adolescents. I think these are really groups that are not well immunized and the last cases of neonatal tetanus deaths was in Tennessee.

DR. MODLIN: Chinh?

DR. LE: Yeah, I think Stan's point is very well taken, especially when we consider the general recommendation document as hopefully an overall document for children and adults as well. So I think we should give some thought about including something on the adults.

To answer Ben's question, I think in clinical practice, it's very easy to get reliable testing for hepatitis B,

measles, mumps, rubella, and we obviously know the sero correlates of protection. Diphtheria and tetanus, it's all over the place because of the commercial lab and that's a difficult point. But we can guide practitioners into which is available, which is feasible, and so on. And again, most of the discussion and recommendation will be a little bit of a broad guideline and give the parents and the clinician some opportunity for their own judgment of how much blood they want to draw on the child and that kind of stuff, too.

DR. MODLIN: Jon?

DR. ABRAMSON: Yeah. I'll simply say that the Red Book recommendation is up there. And we had a discussion on this matter and the bottom line from our standpoint is the data are inadequate to make the kind of very firm decisions about the options one, two, and three that are there. So we extended, basically, our option one to give a physician a little more guidance and some more flexibility. But I, personally, and the Committee did not feel like we had enough data to make a decision on option two or three.

DR. MODLIN: Chinh, maybe you and Bill can help me out with the -- sort of the need to move on this in terms

of giving the overall general recommendations --

DR. LE: Sure. I think --

DR. MODLIN: -- published.

DR. LE: I think Bill has three options to just go over very quickly, and I think it probably will come down to a relatively easy choice, although we do like to have Dr. Clements from the WHO give his perspective, because it's a little bit different than --

DR. MODLIN: Okay. In the interest of time, Bill, why don't you go ahead and present those?

DR. ATKINSON: Okay. We have basically three options for you to consider, none of which are entirely satisfying.

Option number one, basically, is do nothing and change nothing. This basically means accept doses that are supported by written documentation and are appropriate for U.S. intervals. The advantage of this, obviously it's consistent with what we said before. The disadvantage is that, as you've seen, in some circumstances it may overestimate the vaccination status of these children since some of the -- at least there's some question about the validity of some of them.

I'm going to go to the -- The third option is the --

almost the mirror image of that, which is accept no records. This was the impression -- I don't mean to speak for Dr. Clements, but the general impressions from the World Health Organization, at least as far as Dr. Clements, and I think he can comment on that, was that basically they would recommend to repeat everything, to accept no records. The advantage of this is you're certain the child is protected. The disadvantage is -- And also the advantage is you're not picking on certain countries. You're not seeming discriminatory or arbitrary about records from certain countries versus those from other countries since obviously no one can ever know which record is correct and which is not. This is the other end of the spectrum, which is basically repeat everything.

The second, intermediate one is probably I suspect the one that will actually go, which means that to accept some records, but for certain subgroups of children, country-specific, perhaps source-specific, say those who spent time in orphanages or those who come from certain countries, to either repeat all of those or to repeat some of them based on serologic testing. Both Dr. Staat and Dr. Hofsteder, and actually Dr. Aronsen, I believe, also, the international communities, are

basically using an algorithm similar to the second part of this, the alternative to basically look at children who had two or three doses of DTP, checking their diphtheria and tetanus antitoxin titers and using that as an indicator of whether additional doses should be given.

So, basically, it boils down to accept some and exclude some. The key question, of course, is are you going to make the skeptical -- you know, who are you going to test? Are you going to make it country-specific like was sort of suggested indirectly in the Red Book or are you going to make is source-specific like some -- at least some of the data suggests, kids who may have been -- gotten some of their doses in orphanages.

So that seems to be sort of the crux of the question. My guess is -- My guess was the Committee would probably go with an intermediate and try to select certain children to do additional testing or be additional -- have additional skepticism about their records.

DR. MODLIN: Okay. I wish we had more time on this, unfortunately, because I think it's a topic that really deserves much more attention, but let's do what we can with the time we do have. Paul?

DR. OFFIT: Is -- Bill, is there an interest in doing a study which would be larger, better powered, and appropriately controlled that it would allow us to have the data that would make for a more informed decision on this?

DR. ATKINSON: I haven't spoken to the people in the Division of Quarantine or Tb, whether they would be willing to expand this. The question is, it may not be possible, because obviously, you've got -- you would have to basically have representation for every country and -- or at least, unless you wanted to specifically pick on China, Russia, and Eastern Europe, you know, what about Korea, what about Colombia, what about every other country that immigrant children are coming from? Second, you would have to have enough children from various locations to probably -- to be able to assess whether orphanage really is a predictive issue or not. My guess would be that that would be a really big study that would probably be tough to do and it would take a lot of money to do it, and I, being just a junior staff person and cannot speak to funding issues.

DR. MODLIN: Bill, I'm sorry. I'm going to take exception with you. I'm not sure it would be a difficult study to do. You've already pointed out that

at least half of the children who are adopted into this country come from a relatively small number of countries.

DR. ATKINSON: True.

DR. MODLIN: So that it shouldn't be too difficult to find a representative sample. The question is where you do it. There are a growing number of pediatricians who are interested in the health of foreign adoptees and they're setting up clinics at a number of different educational institutions, tertiary care medical centers around the country, and I'm certain that just this group could help come up with a short list that -- just for starters. And I would -- I would agree with Paul, in that I think this is an important enough topic that some reliable data would be very, very helpful. And the question to Chinh and to you is, can we do it in time for the next edition of the general recommendations?

DR. LE: That's right. I'm not sure that we can really hold this document longer for more study and more criticism, because really, it's still taking snapshot pictures of a moving target. Those orphanages changes, health in Russia changes. You know, we had the big diphtheria thing, now the western countries are putting

new vaccines in. Things have turned around. We'll be dealing with a -- dealing with a moving target.

I think we just need some broad medical guidelines. Let the parents and the clinicians have a little bit of say in what they choose to do. I think that certain disease that we try

and -- that we can hit, but I don't think we can try to really get more and more data and slow this vote down.

DR. MODLIN: Fernando?

DR. GUERRA: Yes. One thought is that perhaps the Academy of Pediatrics and the Academy of Family Physicians who probably follow many of these children shortly after their arrival in this country could perhaps, by survey, try to get some idea of numbers. We have no idea right now, that I know of, of how many of these children or any particular community where it might be possible by having access to that population and working with a local health department that we could begin to better define what their level of protective immunity might be. I know that in just a small project that we have been doing over the last six months or so we have picked up about 200 refugees, and that's just within our own facilities and I suspect in the broader community there must be many more.

DR. MODLIN: Georges?

DR. PETER: Two points. One is I think -- I think that we can't simply say flexibility and expect that to be sufficient, because these children will increasingly be entering school the next four or five years and guidance will be needed as to what records will be accepted. Secondly is, if you allow the parents to have choice, which is an important consideration, the question is going to be asked and physicians asked, what's the danger, for example, if you repeat the tetanus. And we've always had guidelines on how many doses are excessive and -- but we've never really discussed what the toxicity is. Say a child was well immunized but did get the full series, what kind of data exists to suggest that the child would be at greater risk of severe reactions? We all know we shouldn't give more than six doses of tetanus, but the data has never really been discussed.

DR. MODLIN: It's a good point. Other comments? Yes, Chuck?

DR. HELMS: Just following up on what Chinh and Georges just said, it seems to me that there's such individual variation, probably, around each child coming in that it becomes far more of an individual decision than a

large prescribed decision for a population and that the idea of broad guidelines rather than specific data is going to be far more helpful to people.

DR. MODLIN: I think the problem may be one of predictability around the individual case, though, Chuck. I know Peggy Hofsteder quite well. I know that she is a thoughtful, experienced, very careful scientist and investigator, and even though her numbers are small, I think the magnitude is pretty impressive in terms of the degree of under-immunization. I've also had the opportunity to talk to several physicians who've worked in China and in Eastern Europe, and they say indeed, particularly in the orphanages, they're very -- that by far, the most important thing is to get these kids adopted and out of the orphanage and the -- the compelling thing for the staff is just to fill out the paperwork and get it done. And they -- People have had firsthand experience and firsthand knowledge to indicate that, indeed, we have very good reason not to rely on any records, not just immunization records, but all other records that come from these -- that accompany these kids.

So I think it's a very real phenomenon and I think that the Committee is going to have to acknowledge that,

somehow deal with that. And then I do think that we need to encourage much better data that we can act on more precisely even though we may not have it in time for this -- for this edition.

Ben?

DR. SCHWARTZ: Just looking at the options you've set out, the second and the third options recommend repeating doses if documentation doesn't exist or if the children come from certain areas. I think it's reasonable to repeat or to give vaccination if documentation doesn't exist, but where it does, I'm wondering about the benefits of serology rather than repeating vaccination, particularly given the concern regarding extra immunization with tetanus and perhaps also with pertussis, given some of the recent data that we've heard about, large reactions in people associated with the fourth and particularly the fifth dose of pertussis vaccine. So I don't know the basis for Peggy's concern about the accuracy of serology, but I think that would probably provide good guidance to clinicians as to whether to accept records or whether to repeat the vaccination series.

DR. MODLIN: Dr. Severyn?

DR. SEVERYN: Thank you. Dr. Christine Severyn from

Vaccine Policy Institute, Dayton, Ohio.

I was -- Earlier in the discussion, you talked about -- asked if there was some sort of a comparison group, a control group, per se, of appropriately vaccinated U.S. children, where you follow them up at the same time period that

you're -- post-vaccination that you're assessing these children. And as Dr. Egan said, the antibody levels fall with time. It's well known that disease can occur despite adequate antibody levels of selected vaccines. I, myself, had received measles vaccine several years ago, followed it up with antibody levels and they were flat. And I know with hepatitis B vaccine, the public health community tells us that suboptimal antibody levels does not necessarily indicate lack of immunity based on anomalistic response.

I question Dr. Orenstein's assertion that perhaps the seroprevalance data obtained from the licensing studies provides a valid comparison. The follow-up during vaccination development is short-term, and the studies that Dr. Atkinson was citing, I believe, were testing these children vaccinated months longer or before. Please correct me if this is incorrect.

So unless you have a valid comparison, you know, were

you testing antibody levels of appropriately vaccinated U.S. children alongside these foreign adoptees, this data means nothing.

Do you have any response at all, anybody? I know Dr. Nichol alluded to that. Dr. Egan alluded to that. So I think perhaps you're talking about long-term studies, Dr. Modlin, running alongside the testing of the foreign adoptees. It would much improve the validity of the study if you were testing appropriately vaccinated U.S. children, following them up at the same time frame that you are the foreign adoptees.

DR. MODLIN: Fair enough. Larry?

DR. PICKERING: I think that's a very good point. One of the problems that I see with the studies that have been done is the laboratory validity and I think they're -- if these studies are done in different locations, there needs to be a standardized laboratory, particularly for some of the -- where some of the commercial assays may give somewhat misleading results. And the point that was just raised, to have an appropriate control group, which may include children immunized in this country with their known periods of immunization would, I think, be one of the appropriate controls to validate whether the laboratory assays that

are performed are indeed accurate.

DR. MODLIN: Right.

DR. PICKERING: Two other points, John, that I'd like to make. One is that if you look at adoptees, 90 percent of the adoptees in this country come from Asia, Eastern Europe. and Central and South America. I know a little bit about some of the immunization programs in Central/South America, and we have Dr. Santos here, who may want to comment. I think it is completely wrong for us to condemn the immunization policies of all countries, many of which are very good. And I think the wording that we have in the Red Book that was based on Dr. Hofsteder's data to look at certain areas, particularly orphanages, is still, I think, the best data that we have. These data are still a work in progress and may yield appropriate results, but we can't really, I think at this time, interpret them. Maybe Dr. Santos would want to comment and validate the immunization programs in other countries.

DR. MODLIN: That's a good point. Maybe it's a segue for Dr. Clements, who's been standing at the microphone. Why don't -- Dr. Clements, why don't you go ahead and then if Jose wants to --

DR. CLEMENTS: Thank you.

DR. MODLIN: -- add on, we'll invite him to do so.

DR. CLEMENTS: Thank you. The first point I want to make is that I made comments that are quoted in the paper based on the general latitude that WHO has in immunization, that it's more practical to go ahead and give an immunization than it is to screen to find out if an individual is susceptible or not, because of the cost and because of the availability of testing. I recognize this model may not be valid in the United States, so I wanted to explain where I was coming from. The second point I want to make is that if I was approaching this problem, I would see it primarily as a sociological issue, with some hard science to -- and the epidemiology to back it up. But the first study that we heard indicated that there was a mismatch between the records and the sero status of the individuals. And I think the Chairman has already laid out that the social dynamics which result in adoption and the helping of that child to leave the country of origin into the United States is surrounded by very dramatic emotions and activities.

And I think that's the way that I would approach it, that the paper that is received with the child about the vaccination status is subject to all these issues,

and therefore, you're going to have a hard time to determine which of them is valid and which of them is not. So I think it's a behavioral issue, not a seroepidemiological one.

DR. MODLIN: Dr. Santos, did you want to follow on Larry's comments?

DR. SANTOS: Thank you. I certainly cannot speak for every country, but I think that, in general, in Latin America the efforts by -- headed by Latin American Health Organization have certainly allowed most countries to have very adequate immunization coverage, with most of the traditional epi vaccines, and recently, with the inclusion of Hib and hepatitis B, I think that the questions have to do with the quality of the vaccine, where the vaccine comes from, rather than with the process itself. And to that end, I think that the efforts of the Latin American Health Organization, with consolidated purchases of vaccines, we've been able to regionally ensure the quality of vaccines being delivered to most countries and just based on recent surveys of most Latin American countries, coverages are quite up to standard. Without gloating about it, I think that recent efforts regionally have been very good and I think that, echoing Dr. Clements' comments,

the issue surrounding adoption policies and practices are tainted somewhat and I would say that in general the immunization policies in Latin America pretty much guarantee that children that have an immunization record are immunized appropriately.

DR. MODLIN: Thanks, Dr. Santos. One more comment and then we need to wrap this up. Yes?

DR. DUART: Roz Duart, Division of Quarantine.

A point of information, albeit incomplete, but -- And I wish Dr. Susan Cookson was here, because she works closely with the panel physicians for every immigrant child and adoptees included, I believe. They must be seen by panel physicians, and they're working on revising the technical instructions. These panel physicians are abroad in all the countries, and maybe that would be a way that we could do some assessments, because I know she's very interested in health assessments for all things, including vaccinations. So like tuberculosis assessments that they're doing to see the quality of TB screening abroad, this might be added. So I wish she was here to speak to this issue. Thank you.

DR. MODLIN: Thank you.

It seems to me like we've got two options here. One is

to go ahead and make a decision on one of the options that Dr. Atkinson is presenting to us. The other would be to -- since the General Recs. will not be complete until the next meeting any way, spend a little bit more time on this. I hate -- You know, I hate to put it off, but on the other hand, I think it's an important enough topic that if we could bring in one or two of the outside investigators and focus on this and consider it much more carefully, that we might not be forced into making a decision that would be a short-term decision.

How does the Committee feel about this? A lot of nod -- nodding about what?

DR. OFFIT: I agree.

DR. MODLIN: Okay.

DR. OFFIT: I mean, I feel uncomfortable making a decision in -- you know --

DR. MODLIN: Okay.

DR. OFFIT: -- with this limited data.

DR. MODLIN: Okay. Bill and Chinh -- Yes, Chinh?

DR. LE: I guess the question is, the summer's coming and do we have enough time to bring you any new data or even if we were to bring all the experts back in, is there enough uncertainty left in October that we'll be

procrastinating another year?

DR. MODLIN: I think perhaps just a little bit more time to think about it, to consider what the options may be and to spend a little bit more time at the committee meeting with a resolve to make a decision at that time, I think, would make sense. I think the other members of the Committee are sensing the same thing I am, just some discomfort at moving on this at this time. Is that fair? I think it is. So if that's okay --

DR. ATKINSON: Can I -- Can I offer one possible --

DR. MODLIN: Sure.

DR. ATKINSON: -- corollary suggestion, is that I agree that I seriously doubt there's going to be any more data available, perhaps a few more dozen kids from Cincinnati, but I'm not sure that's going to help anything. I have prepared -- The last page of the handout is some prototype wording for the new document. I'm not going to go up here and go through it all, but this is what it is, is a combination of Red Book wording and current ACIP wording that talks about orphanages, that talks about being skeptical and checking things. Maybe I could encourage the members of the Committee to look at the wording of this

statement, which is harmonious with that which is in the Red Book.

It also gives a little bit more direction as far as what is a valid record and children in which testing might be considered based on, actually, the recommendations that Dr. Hofsteder and Dr. Staat are currently making. So it's a combination of all three things, of ACIP, of the current Red Book wording, and with some additional clarification about exactly -- The Red Book just says do serologic testing. This is a little bit more specific, although not greatly.

So perhaps you could just contemplate this and if anyone has any comment, I will incorporate something like this into the draft of the General Recommendations. If anyone has any strong feelings about it, would prefer to word it differently or want me to scrap it entirely, I can do that. If you could give me some feedback on this, this at least is a starting point that at least is consistent with the -- with the recommendations that are currently out there and being practiced now.

DR. MODLIN: That's a good idea. We will ask the members of the Committee and everyone else to take a close look at this and to get suggestions back to Dr.

Atkinson within the next three weeks, I think would be a reasonable time frame. It's not very -- not very long.

And again, I think we'll think about a little bit more of a focused and careful approach to this, spend a bit more time on it at the October meeting.

Bill, thanks.

DR. ATKINSON: We have one other very brief presentation, which is by Diane Peterson --

DR. MODLIN: Okay.

DR. ATKINSON: -- to just comment on some issues in the schedule, which is coming around again.

DR. MODLIN: Okay.

DR. ATKINSON: As much as we don't want to think about it, they've done quite a bit of work on trying to make the schedule more user-friendly, and with that, Diane, if you would make some comments about the actions that have been done in Minnesota.

MS. PETERSON: Good morning. First of all, I'd like to make just a few comments before I get to my slides, and I'd like to clear up that I am not a doctor. I'm here this morning representing AIM, or the Association of Immunization Program Managers, where I sit on the Executive Committee, together with Dr. Natalie Smith,

who's here with us this morning also. What I'm going to be presenting is an issue and a concern that we've had in AIM and I will be talking about how we've addressed this at the Minnesota Department of Health. It has been my task over the years to put together a childhood immunization schedule for distribution to providers in Minnesota. We base that schedule, of course, on the national recommendations and in the last six years on what you know as the Harmonized Childhood Immunization Schedule. You have a packet of materials that has the colored clip on it and that is what I'm going to be referring to as we go along.

At the Minnesota Department of Health, I take my turn on our hot line, which is a service we provide to the public and the provider community and for which we received more than 13,000 calls last year. About one-fourth of those calls were triaged with a technical staff person like myself and two-thirds of those were from private or public clinic personnel. Those calls have provided valuable feedback to help us understand the need to keep the schedule of immunizations simple and user-friendly.

I show you this because I want to first show you where Minnesota is located, if you don't know, and also to

make the point that we, too, like most of the nation have many providers with many different shots to give on a schedule to newborns each year. They are extremely busy and if anything is difficult to understand or is misinterpreted, it will be and that may result in a missed opportunity to vaccinate a child on schedule. You all recognize the most current edition of the Harmonized Schedule, that for the year 2000. And it's the second piece in your packet. What I will attempt to walk you through is how we've taken extremely accurate and technical information and reformatted it to improve its usefulness in the provider community.

The first change we've made is to expand the age range for the schedule itself through 18 years, the normal pediatric age range. The second enhancement is to eliminate the ovals and extend the age range for catch-up vaccination to begin on the day following a child's failure to receive their vaccines at the appropriate ages and to extend that through 18 years for hepatitis B, for the second dose of MMR, and for varicella.

The next enhancement was to introduce color into the bars: orange meaning the acceptable age range; green -- and it doesn't show up very green on the screen here,

but it is on your handout -- meaning catch-up vaccination; and purple, which indicates the age range at which all pediatric patients should have their vaccination history assessed with action needed to give vaccines to those who are not up-to-date. Now, this may seem to you like an unusual choice of colors and I would agree, but let me explain.

We launched a multi-media campaign in 1996 which utilized the theme of "Got your shots?" and three main colors are, in fact, green, orange and purple. By consistently using this overall look on our immunization schedules, we hope to tie them in with the campaign's other print materials, such as posters, magnets, band-aids, the patient educational materials, our newsletters, and a TV spot that we have. And we're trying to build a whole climate of immunization around this campaign.

Now, you may say this is all well and good if you have the capability to print in color, but if you don't, you can consider other techniques, such as using shades of gray or others, as you see in the Disease Control newsletter, which is the third piece in your packet. And that's a newsletter that we send to all providers and others in the state on a bi-monthly basis. And as

you can see, in the spring edition is when we highlight the new childhood immunization schedule and have it printed there in black and white.

When we decided -- When we decided how to best communicate and quickly these key color indicators, we decided to strike the 59-word text of instructions entirely and instead replace it with very concise, color-coded phrases that accomplish the same thing. That is, of course, orange for the acceptable ages, green for the catch-up, and purple for the assessment. As you know, the year 2000 schedule includes yet one more vaccine, and that's for hepatitis A. It's the first vaccine on the Harmonized Schedule that is not recommended universally for all children but what, as we see, this Norwegian doc is pondering. For selected states and regions, after consulting with the local health authority, I'm not sure that our providers would know what that means in our state. Well, we have, in fact, included hepatitis A vaccination on our schedule since 1996, and we've also include -- included vaccination with the pneumococcal polysaccharide vaccine and the influenza vaccine. And we have separated these from the more routine vaccinations by a dotted line that indicates these vaccines are for

selected populations and included the groups as stated in the ACIP recommendations in the footnotes. And in this way, we hope to have fewer missed opportunities to vaccinate these more vulnerable populations.

Now a brief note about the footnotes. We've added new footnotes for all of the additional vaccines on our Minnesota schedule. We've simplified them wherever possible. We've changed as much as possible from passive to active voice and we've put them in columns to improve the readability. You'll find this at the bottom of the front page. And the overall schedule, therefore, fits on one 8 1/2 by 11 inch page, looks like this, and of course, you have it in your handouts. Well, even though we like to think we do things a bit better in Minnesota, we have found that our rates are not unlike those of many other parts of this country, and the Harmonized Schedule, as you know, deals primarily with children who start and stay on schedule. The last retrospective survey that we did, and we did it on all 65,000 kindergarten children in the State in 1996 and 1997, found that nearly 30 percent had not finished even a basic series of four DTP, three polio, and one MMR. And again, if you read the 59-word text of the Harmonized Schedule, it says that -- and I quote

-- "Any dose not given at the recommended age should be given as a catch-up immunization at any subsequent visit when indicated and feasible." And again, our doc here is trying to determine what, in fact, is going to be indicated and feasible. Well, our solution has been to include catch-up charts on the back side of the schedule. If you turn it over, you'll see one for children under the age of seven and the other for those who are seven and older.

And you may want to take a few moments to read over the charts, especially for the schedule on how to catch up a child for Hib vaccine, which you know is truly a challenge, but it does work and I would contend that we'll probably be able to do the same for the pneumococcal conjugate vaccine. And to be quite truthful, the back side of the schedule often becomes the side that is posted in physician's offices, because it is closer to the reality of many children seen in their practice.

With careful planning and concise, clear writing, we've even ended up with room for a few well-chosen special notes that address major issues and needs in the State. The schedule, then, is reviewed and adopted each year by our State's own advisory committee. And I would

point out that both Dr. Norton and Dr. Nichols sit on that committee. We then print it on card stock and mail it to all of our clinics in the State in the spring of each year, publish it in the newsletter, and the like.

We also have put the schedule up on our web site. If you go to our web site and you hit "Schedules and Recommendations," you'll see the listing of the childhood schedule. We also have an adult immunization schedule, which builds on many of these same concepts and is in your packet and looks like this. It's up on the web site. We have a schedule for international travelers, which is the last item in your packet.

Well, I thank you for giving me this opportunity to talk about how we've been able to work with annual childhood immunization schedules, and I offer you these ideas that you may want to consider in developing the 2001 schedule. Of course, everything we do is copyright-free. So please feel free to adopt whatever works for you.

DR. MODLIN: Thank you, Ms. Peterson. We're running very behind, but --

(APPLAUSE)

DR. MODLIN: -- opportunity for a comment or two. Rick

Zimmerman?

DR. ZIMMERMAN: Speaking on behalf of AAFP, we would suggest, and I concur with Diane, that the catch-up schedule for children I think should become part of the recommended schedule. I mean, we ought to push -- put -- and we may take an extra page or extra half page, but I think we ought to include the catch-up schedule.

DR. MODLIN: Thanks. Yes, Dr. Nordin?

DR. NORDIN: Speaking as a pediatrician practicing in Minnesota, I can tell you which side of that is posted in the nursing stations in our clinics and it's not the front side. The front side's pretty easy, although it's less simple than it was ten years ago, but the back side is the crucial part.

DR. MODLIN: Thanks. At this time, I'd like to welcome Dr. David Fleming to -- back to the table. Dave, have you started your -- started your new job yet?

DR. FLEMING: I'm a one-week old infant in my new job --

DR. MODLIN: Okay.

DR. FLEMING: -- at this point, yes.

DR. MODLIN: Terrific. Well, welcome. Dixie?

DR. SNIDER: Well, I think Dave wanted to make a couple of comments, but I wanted to take this opportunity to -

- and perhaps it's a little bit anticlimactic for Chinh Le, but I wanted to recognize our three departing members at this time and express our deep appreciation for what Chinh and Fernando and Dave have contributed to this Committee. They have been tremendous in terms of the amount of work they've put in over the past few years, at a time when vaccine issues, vaccines, vaccine safety issues have just skyrocketed in terms of the number of them, the complexity of them, and the visibility of them. And I think everybody has really kept their cool and attempted to maintain the endpoint in mind, that is the protection of the public's health. And I just think we should take this opportunity to do the same for all three as we did for Chinh and give them a round of applause.

(APPLAUSE)

DR. SNIDER: And I do have the usual tokens of our appreciation for them.

DR. MODLIN: David?

DR. FLEMING: And I can't miss this opportunity to take about 30 seconds of your time.

The good news that I learned this morning is that, you know, it doesn't look all that different sitting at this table when I'm at the CDC end of it. But I was

driving up here this morning and I realized that this really is the first meeting, ACIP meeting, that I'm missing in seven years, because I was here as a liaison for the Hospital Infections Program before being fortunate enough to be a committee member. I'm sure I don't hold the record in that regard, but nonetheless, it was very difficult to watch that streak personally for me come to an end.

I'd like to believe that that's an aberrancy, but I'm realistic enough to realize that it isn't, primarily I think because of the expertise and dedication of the folks that sit around this table and the competence of the CDC staff that support your work that make you able to deal expertly, really, with all the issues that come your way. So if you could screw up a little bit in the future so that I could get involved, I would be very --

Seriously, though, please let me know if there is anything that CDC can do or that I personally can do to support the work of this Committee, because my heart is always in ACIP.

Thank you.

DR. MODLIN: Thanks, Dave.

DR. GUERRA: John, if I --

DR. MODLIN: Fernando?

DR. GUERRA: If I could, as a matter of personal privilege, I would first like to certainly congratulate David Fleming on his recent appointment, and we certainly look forward to our continued association with him.

I'd like to join Chinh, also, in expressing my sentiments of what for me has been truly an important part of my public health and pediatric experience of serving on the Advisory Committee for Immunization Practices for the past six years. It has been one of those important life experiences that I have learned an incredible amount from, the experience, and certainly from being in the midst of some people that know a lot and that -- Every time I come to these meetings, I leave re-energized and certainly recommitted to taking on some of those formidable challenges that we continue to face on the front lines.

I hope that the Committee continues to take on those important areas of concern that are unrelenting and that continue to affect a lot of people that perhaps we don't always give attention to with some of our broad policies and that we continue to hopefully serve in a way as a conscience for public health as it is distributed equitably to groups across the country and

certainly the world, recognizing that a committee like this has a profound influence on many of the vaccine efforts and programs and services, initiatives and research that goes on. It's a wonderful time, certainly, for the Committee to be involved in a lot of these issues.

I hope as, again, a matter of personal privilege, that there will be an opportunity for other professionals who are out in the field that are from my ethnic background to have a similar opportunity and privileges I have had and have enjoyed, because I think there is a real need to have that voice in a group like this, given the fact that the Hispanic community in this country is one of the most rapidly growing. It is one that certainly is finding itself in many parts of the country that we had not even thought about and certainly deserves to have the same kind of attention and commitment and opportunities. I thank you very much.

DR. MODLIN: Thanks, Fernando. I think as many of you know, Fernando is one of the real veterans of the Committee, having -- now, well into your second term, having been convinced to stay on at the end of his original term. Fernando has also served a major role

in chairing the working group on influenza, which has been one of the most active and important working groups throughout the term of the Committee and one of those working groups that has a continuous life span, unlike many of the other working groups that we have. And speaking of influenza, this is an opportunity to go on to the next agenda item, which will be an update on the influenza vaccine supply. Kaji, will you be leading the discussion?

DR. FUKUDA: Thanks, John. Actually, just one housekeeping detail. The influenza long-lived working group is going to be meeting at the lunchtime break and the room that we'll be meeting in is Azalea C, so just for your information. I don't think we knew that until this morning.

In the next several minutes, we're going to discuss some -- a situation about the influenza vaccine supply. During the summer, there are some serious concerns which had arisen about the availability of influenza vaccine in the fall time, and as a result of those concerns, there's been a great deal of discussion among the various federal agencies and also with the influenza working group. And what we wanted to do was

both apprise the Committee of what the situation is as we understand it right now and then I think it also raises some difficult issues for the Committee to grapple with today.

So the -- What we're going to do is I think Dr. Roland Levandowski from the FDA is first going to apprise us of the -- of the vaccine supply situation as we understand it. He'll be followed by Dr. Jim Singleton from NIP, who is going to go over how vaccine -- influenza vaccine has been used in the United States over the last several years. And then we don't have it on the agenda, but Dr. Carole Heilman has graciously agreed to bring us up-to-date on some activities that NIH has initiated because of these concerns about vaccine supply. And then what I'll do is I'll sort of summarize the situation at the end and present what I think the Committee needs to address today.

So, Roland, if you can get the ball started, we'll go.

DR. LEVANDOWSKI: Thanks, Kaji. Good morning, everybody.

I'd like to just start by telling you that there are currently four licensed manufacturers of an activated influenza vaccine. I think you know who they are, but I'll name them. They're Aventis Pasteur, Incorporated,

in Swiftwater, Pennsylvania; Medeva Farma, Limited, located in Liverpool, England; Parkedale Pharmaceuticals, located in Rochester, Michigan; and Wyeth-Ayerst Laboratories, located in Marietta, Pennsylvania.

For the past few influenza seasons, these four manufacturers have produced combined total -- totals annually of approximately 80 to 90 million doses of vaccine. And as you know, recommendations for influenza vaccine use were extended to include persons 50 to 64 years of age as a new risk category during the last year. That recommendation was made with the expectation that vaccine production would continue at the current levels and possibly increase in future years. However, based on current information for the 2000-2001 influenza season, vaccine production is expected to be delayed and it could be substantially less during that period -- during the period of time that most vaccination is normally going on, during October and November.

The protective efficacy, I'd just like to remind you of, in activated influenza vaccines is related predominantly to the induction of antibodies against the hemagglutinins of influenza viruses. And activated

vaccines are most effective when the hemagglutinins in the vaccine strain is closely related to hemagglutinins of the circulating influenza viruses. Therefore, every year extensive surveillance is done to detect new variance of influenza virus in people and studies are done to determine whether the current vaccines induce antibody responses that can inhibit the newly-emerging influenza virus variance. This information is used to recommend new strains for inclusion in the vaccines. When new influenza viruses are chosen for vaccine production, there's always a need to optimize the new strain to manufacturing conditions. Current production of influenza virus vaccines depends on the availability of viruses that replicate well embryonated eggs. The so-called high-growth reassortant viruses help to increase vaccine yield, but I'd like to remind you that not all high-growth reassortants replicate equally well; and even if they do, they may not go through all the processing steps equally well. In addition, there are differences in the actual manufacturing processes that may cause yield to vary from manufacturer to manufacturer for these new strains.

For the 2000-2001 inactivated vaccines, two new influenza viruses have been recommended for inclusion.

And those are the A New Calendonia 2099 strain, which is an H1N1 influence A virus. And A Panama 2007-99, which is an H3N2 influence A subtype.

For this A Panama 2007-99 strain, several new high-growth reassortants were prepared and they were sent to manufacturers to determine which one had the best replication and processing characteristics. Based on information from manufacturers in both the United States and Europe, the reassortant with the best overall characteristics was chosen for manufacturing. However, as information has been collected during full-scale manufacturing conditions, the yield of the A Panama 2007-99 high-growth reassortant has been lower compared to the high-growth reassortant that was used for last year's vaccines. And I'll just remind you that was the A Sydney strain.

It should be noted that the high-growth reassortant used in the previous year was unusually robust in terms of its yield. In other years, the yield of new strains has sometimes increased as the extent of manufacturing experiences increased so that it remains possible that yields for the A Panama 2077-99 high-growth reassortant could improve as times goes on.

Since the vaccines are formulated to be trivalent,

however, the component with the lowest yield restricts the amount of vaccine that can be prepared at a given time period. And this has an impact on how much vaccine can be available during October and November because time, then, becomes the limiting factor in preparation and distribution of the vaccine. However, the time factor can be addressed partly by extending production time.

There's a second factor that could result in delays or reduction in the amount of vaccine during the coming October and November. Earlier this year, FDA inspectors identified and documented manufacturing problems at two of the four manufacturers of inactivated influenza vaccine. Both manufacturers are working closely with the FDA and have indicated that they intend to make corrections and supply vaccine for the 2000-2001 season, but the implementation of corrective actions requires time for completion. As a result, it's possible that there could be a delay in production and distribution of vaccines by these companies.

If the affected manufacturers are unable to complete corrective actions in a timely manner, than vaccine may not be available from them for use in the 2000-2001

season. In that event, it's unlikely that the other licensed manufacturers will be able to produce sufficient additional vaccine to eliminate that shortfall. According to information from manufacturers, most of the vaccine is distributed by October and used by November. Therefore, manufacturers generally have completed most influenza vaccine manufacturing and distribution by October. However, manufacturers questioned have indicated that if there were a definite markup for their vaccines this year, they would consider continuing to make the vaccine available beyond the time that they normally conclude their operations. The extension of manufacturing time could help to offset the reductions expected from the lower yield of the newer -- of the new H3N2 influenza virus. However, the availability of vaccine at a very late time will not prevent difficulties in conducting vaccine programs or in administering vaccine.

It's less likely that there will be more vaccine available than previous years and it's more likely that there will be less vaccine, although it's a very fluid situation, so the overall impact remains very uncertain at this time. But what is certain is that FDA, CDC and the manufacturers are giving this the highest priority

and will continue to work together closely to find strategies to ensure that influenza vaccines are available and used wisely.

I'll stop there. Thank you.

DR. FUKUDA: John, I don't know how you want to do -- We could have questions to the individual speakers and then we'll need to have a longer discussion at the end, but --

DR. MODLIN: Maybe it would be best just to go ahead, Kaji, with the other speakers, and -- Are we again focusing on the supply --

DR. LEVANDOWSKI: Right. And it might be best to hear everything, then I think --

DR. FUKUDA: And then open it up. I agree.

DR. LEVANDOWSKI: -- have a longer discussion. Okay.

DR. SINGLETON: Okay. I'll go ahead and get started. Dr. Levandowski told us something about the supply. I'm going to try to give some information about the possible demand based on past usage of influenza vaccine. I'm going to talk about the main sources of data to do this, trends in influenza doses distributed that are estimated, trends in influenza vaccine coverage, and expected doses needed for the 2000-2001 influenza vaccination season, and then I'll summarize.

The main sources of data that we use were the U.S. Census Bureau estimates of the year 2000 population. We used the National Health Interview Survey, the Behavioral Risk Factor Surveillance System, National Nursing Home Survey, and manufacturer reports of influenza doses distributed, gross and net distributed. The first main data source, the National Health Interview Survey, it's conducted by CDC. It's an annual national household health survey of the civilian and non-institutionalized population of the U.S. We use this to monitor progress toward Healthy People 2000 and 2010 objectives. The 2010 objectives for influenza are 90 percent vaccination among people 65 and over and among institutionalized populations and 60 percent for adults under age 65 at high risk.

They ask detailed questions about one randomly sampled adult per household, including "During the past 12 months, have you had a flu shot?" There's questions about selected medical conditions and occupation that we've used to create high-risk groups.

The Behavioral Risk Factor Surveillance System is conducted by CDC. It's a state-based survey where the states actually conduct the telephone interviews. It represents the civilian and non-institutionalized U.S.

population living households with telephones. It included questions on chronic conditions, just for diabetes and in selected states, asthma and heart disease. They ask a similar question about receiving a flu shot. In 1999, they added a question for people who said they got a flu shot, what kind of place did they get it at, and I'll have some data for you on that at the very end of the presentation.

I want to talk a little about what we know about the -- you know, the supply and how that trickles down to actual usage. Dr. Levandowski has produced estimates of how many potential vaccine doses are available, that actually -- lots they actually released for -- for the mark- -- that could be released for the market. Not all those end up being packaged and sold and of those that are actually distributed, some are returned or discarded by the end user, where the majority are probably used. We don't know the actual amount of vaccine that's wasted out in the field.

This next slide, it shows the upward trend in vaccine -- production available, the top line, from Dr. Levandowski that he's estimated total amount of doses that could be released in the market, and the red line, gross distributed doses -- We left out the 1997 data

because we're reviewing the accuracy of that end point -- And to find the net doses distributed, which represents an upward bound on what might actually have been used.

And if Dr. Levandowski wants to comment on these numbers further, he can do that.

The next slide shows trends in vaccine coverage based on the National Interview Survey and the Behavioral Risk Factors Surveillance System Survey. And this shows a similar upward trend in self-reported flu vaccination use from 1989 through 1999. In the -- The upper trend mirrors that seen in the net doses distributed. The highest coverage is among persons age 65 and over, and those are the red lines -- the red line there on the top, followed by persons age 50 to 64, the blue lines, and then, finally, persons 18 to 49 in green on the bottom.

We put data from both the NHIS and the BRFSS to show how similar they are, and we have the more recent data from the BRFSS, which is as preliminary at this point but tracks very well with the past data. And then the actual coverage estimated from -- in 1999 among persons 65 and over was 67 percent; among persons 50 to 64, it was 36 percent; and among persons 18 to 49, it was 19

percent.

Actually, could you put that on top of the other slides, just superimpose it?

The slide previously included all people in each of the age groups. And in the BRFSS, we looked at the data from persons with diabetes and you can see that blue line in between the red and the other blue line is persons with diabetes age 18 to 49 -- pardon me, 50 to 64. And the persons with diabetes 18 to 49 is actually right on top of the overall rate for persons 50 to 64. And you can't see it there, but generally what this means is that persons with diabetes have much higher vaccination rates within each age group.

Now, these next couple of slides have got a lot of data in it and I'll try to walk you through it. The first column -- What I tried to do here is estimate how many doses we might expect there to be demand for in this upcoming flu season. And this is for the different groups at increased risks for complications from influenza. The first column has estimated number of people at risk in millions. So, you know, the bottom line on that is 67 to 76 million persons at increased risk. Close to half of those would be persons 65 and over.

Now, we looked at -- The second column shows a range of vaccination rates expected this coming season. We used 1999 survey data, which actually reflects coverage that would have occurred in the 1996-97 season because of the 12-month recall period. We used that for lower bounds in all the groups. So in the second column, the lower numbers are -- for most of that is from the 1997 survey data representing what probably happened in '96. So it's a very low bound on what probably is going to happen this coming year. And the estimates for children were based on one study of children in asthma and in one HMO, at ten percent.

Pregnant women is based on all women currently pregnant, so it does not represent the actual coverage in women who would be past first trimester during the flu season, but that is our best approximation at this point.

The upper bounds for coverage were based on extrapolating from the 1995 NHIS and the 1999 BRFSS. For most groups, there was about a 2.2 percent absolute increase per year for people 65 and over and for people 50 to 64 and about a three percent increase for persons 18 to 49. Coverage was assumed to reach the Healthy People 2010 objective of 90 percent for the

institutionalized population.

And coverage for high-risk children and pregnant women was assumed to reach the level extrapolated for high-risk adults age 18 to 49. So those are probably upper bounds on what would actually be expected. And the final column shows the estimated number of doses that would be needed given the different vaccination rates. And the total of 30 to 42 million doses would be projected for persons at increased risk, and the majority of these would be among older adults.

This shows the same type of data for other groups for which vaccination might be recommended or given. For high vaccine coverage for health care workers here, we estimated 70 million, of which about 20 percent would be 65 and over or have another high-risk condition, it would be -- have another vaccine indication besides being a health care worker. We extrapolated the trend in coverage for health care workers, which is about a three percent per year increase from 1989 through 1997. So that would bring that up to about 46 percent.

Now, we estimated that there were 40 to 60 million household contacts and this would exclude health care workers and persons at increased risk. So this would

be otherwise healthy people who wouldn't be in a target group. And that was based on looking at family composition and estimating the average number of contacts in different age groups among -- and then multiplying that times the total number of high-risk people and accounting for the overlap between multiple high-risk people living in the same household.

So we have a pretty wide range on it. It's not a thing we can directly estimate. We have no idea what the coverage is in this group. So what I put in there for coverage was the overall rate for persons 18 to 49 back in 1996 and then the projected rate among high-risk people 18 to 49. And that gives a wide range of number of doses that might be needed in that group.

The upper vaccination levels for healthy adults were extrapolated from the -- the BRFSS and NHIS data through 1999 by age group. For healthy people age 50 to 64, I assumed there was an additional 20 percent of people who would be otherwise unvaccinated would get vaccinated this year because of the new ACIP recommendation, and that would bring the rate up in that group to almost 50 percent.

Just to summarize those two tables, I estimate a total of 56 to 82 million doses might be needed in 2001. The

actual number is probably closer to the higher end of that, because I was using old data to estimate the 56 million. Thirty to 42 million of those doses would be for persons at increased risk. A majority of those doses would go to older persons, with less than two million to nursing home residents. Two to four million would go to health care workers, though some of these doses would be included in those going to high-risk persons. A total of 26 to 40 million doses would go to healthy persons under age 65. That would include healthy health care workers and persons living with others at increased risk.

The low estimate of 56 million doses, as I said, is based on vaccination rates reported for 1996, primarily. And if you go back to that very first slide -- You don't have to show it, Kaji, but we -- there was an estimate of 58 million net doses distributed in 1996. So that corresponds very well with the estimates I'm coming up with.

Some limitations. There's uncertainty in estimating the size of target groups particularly for household contacts. There's a lot of uncertainty in estimating vaccine coverage for some groups, including children, and we don't have direct data on contacts, although we

will be getting some data on vaccination of healthy adults who live with older people. We just haven't got that number today.

And self-reported -- Vaccination and medical usage are self-reported, so there's uncertainty in some of that. From a couple of studies, the sensitivity of self-report of a flu vaccination ranges from 92 to 100 percent and specificity from 71 to 98 percent. There's also a lot of uncertainty in projecting vaccine coverage. I imagine if three different analysts did the same exercise, they would get three slightly different answers.

And another question is, "Will demand change if vaccine supply is limited?" Now, if we assume that the 82 million doses is how much demand there will be this coming season, and if we also assume that less than 82 million doses would be available, then the expected demand among persons at increased risk and health care workers could be met if at least 45 million doses were available and there would have to be some shift in vaccine to these groups.

Now, if we added in household members of persons at increased risk, all those groups could be vaccinated if at least 51 to 67 million doses were available and,

there again, there was some shift in vaccine to those groups. And the closer the vaccine availability is to the expected demand, the less shift of vaccine to doses, should that be what we want to do would be necessary.

I just want to show one more slide. It's data that we've just analyzed on where people got their flu shots and it's -- might be informative in the subsequent discussion. This shows for 18 to 49-year-olds, 50- to 64-year-olds and 65 -- persons 65 and over where they said they got their flu shot in the 1999 BRFSS. And you can see that a doctor's office was the most common. That increased with age, so when you look at people 65 and over, over 60 percent said they got their vaccine in a doctor's office or HMO. The question, actually, it said in a doctor's office or HMO.

And if you look at the younger group, 18 to 49, almost a third of those people said they got the vaccine in the work place, and then that decreased with age. If we assume that 82 million doses were used, 72 of those million would go to non-institutionalized adults, and of those, based on these numbers, 33 million would be given in doctor's offices, 14 million in a work place, and three to seven million in each of the other

different places, including health departments and stores, senior centers, et cetera.

So that's the end of my presentation.

DR. MODLIN: Kaji, you're going to present some policy options or discussion in a few minutes. I wonder if -- I wonder if before that it would be wise to just open this up to some questions regarding the presentations, the data that Dr. Levandowski presented. Would that be reasonable?

DR. FUKUDA: Yeah, I think maybe before people forget numbers. And then that'll be -- Actually, Carole is going to just go over one -- what NIH is doing in response to this, but it might be better to go over some questions on numbers --

DR. MODLIN: Let's do that, and then we'll move on to the NIH and to the policy issues.

Paul?

DR. OFFIT: Maybe this is a question for Roland, but what is the likelihood that we will have available 45 million doses this year?

DR. FUKUDA: Roland, you want to come up and --

DR. MODLIN: He can use the microphone --

DR. LEVANDOWSKI: Is this okay --

DR. MODLIN: That's fine.

DR. LEVANDOWSKI: -- if I stand back here?

DR. MODLIN: We'll get your microphone on, but -- Okay.

DR. LEVANDOWSKI: Okay. I'm not sure that I can really estimate what the likelihood is. I think that we are working very diligently to make sure that that doesn't happen, that the total number of doses will be higher than that. But at this point, I don't think we have enough information to know exactly where the supply side is headed. That will probably become a lot clearer over the next few weeks, but I think that's probably the best answer I can give on that.

DR. MODLIN: Questions over here. John?

DR. ABRAMSON: Does the severity of the disease in any year affect the number of doses that are given? Because -- The question really relates, then, to severity, publicity. What's the effect of that? I don't see any information about that.

DR. FUKUDA: John, maybe I'll take a stab --

DR. MODLIN: Sure.

DR. FUKUDA: -- at answering that.

My guess would be that probably not very much. I mean, I think that in talking with the manufacturers, it's pretty clear that vaccine sales decrease very substantially once you get into the beginning of

November and disease activity really usually doesn't pick up until late December, January, so on. So by the time most of the vaccine is given, it's way before we know what the season's going to look like.

DR. ABRAMSON: The real question is not how much is distributed, but how much is given back? And that would be the way to tell whether severity alters the amount of usage of the vaccine.

DR. FUKUDA: Yeah, I couldn't answer that. I think that would have to be answered by the manufacturers.

DR. MODLIN: Chinh?

DR. LE: Yeah, I -- You know, the data on the vaccine used reflects very much our HMO utilization as well. Every year, we waste about some 50,000 to 75,000 doses at the end of the season, because as a large group, we are able to buy a whole bunch a little bit cheaper and kind of just stock our pharmacies, and then at the end of the season, we find that we waste a lot. And last year was the first time we used the same utilization pattern according to our computers to look at what is the utilization in each group. I can tell you no matter how much science and educational material we send out, basically, patients getting flu shot is very much a behavioral issue, not so much a science issue

any more. And so we have very good target of the percentage that you have and last year we didn't waste as much.

But I think in a age of perhaps some supply limitation here, I think that behavior issues certainly becomes more apparent in a sense that if the public knows there is a vaccine shortage, there may be a stampede of people trying to get very early so they that don't miss out on the boat. And no matter what recommendation we put out, you know, kind of step-wise, high risk first and young people later, I think it's going to be difficult to implement.

DR. MODLIN: Rick Zimmerman?

DR. ZIMMERMAN: I think that's a possibility with it, but I think particularly among the -- those vaccinated in work places and in senior centers, et cetera, where there's an organized campaign, if the vaccine isn't there when the organized campaign is expected in October, then I think we're going to see less vaccine usage, because this -- whether those campaigns can be successfully delayed or not, it's an open question given the expectations. So I don't know what's going to happen. I think there is the potential for less demand in those situations where there's organized

programs. I don't know what the sum total will be.

DR. MODLIN: Dave Fetson?

DR. FETSON: David Fetson, Aventis Pasteur. Do the American vaccine manufacturers export influenza vaccine to other countries? And if so, in this year with an anticipated possibility of a diminished supply, will they be allowed to continue to export or will there be some curbs as there were back in 1976, when American manufacturers were not allowed to export the swine influenza vaccine?

DR. FUKUDA: Roland, I think you're going to have to address that.

DR. LEVANDOWSKI: There are exports of vaccine from manufacturers in the United States, both to Canada and Europe predominantly, but also to South America. And we do not have any regulations in place that would prevent manufacturers from sending the vaccine to the location they would like it to go. So the answer is no, we don't have any curbs in place on how a vaccine is distributed in that sense.

DR. FETSON: Brazil wants to use 19 million doses of influenza vaccine this year. That's just one indication of the international demand for this vaccine.

DR. MODLIN: Thanks.

Could I ask what the cost implications might be for the price of influenza vaccine if there is a shortage?

DR. FUKUDA: Again, I don't think we can answer that, unless one of the manufacturers wants to get up and address that question.

DR. MODLIN: Dr. Rubin?

DR. RUBIN: I'm not a price expert, but I -- Fred Rubin, Aventis Pasteur.

Prices are set prior to the season and contracts are negotiated between the customer and the manufacturer. So I don't think that's an issue.

DR. MODLIN: Okay.

DR. RUBIN: There would be no change in the -- in this scenario, even with what we're talking about.

DR. MODLIN: Thank you.

We probably should move on. Dr. Heilman? Oh, I'm sorry. Dean, go ahead, and then we'll have Dr. Heilman --

MR. MASON: Two things. I've been told by manufacturers that the return rates at the end of the year oftentimes from private doctors approximates 10 to 14 percent, if that's any help. The CDC has two

contracts this year, with Aventis Pasteur and with Wyeth, one million doses each. Both of those contracts have already been maxed out in terms of orders from the state. We educated the states early on to order vaccine order, which they did.

Now it becomes a question of whether they get the vaccine and their logistical problem is, of course, when do you plan your clinics and do you plan your clinics in advance hoping to get the vaccine or do you wait now to get the vaccine to plan your clinics? Our vaccine price per dose is two thirty-six, $2.36 a dose.

DR. MODLIN: Thanks, Dean.

DR. HEILMAN: Good morning. I shouldn't take too long. I just would like to briefly share with you a study that the NIH is planning, but I must say that is being planned as a result of a very well-oiled interagency group. So CDC and FDA are clearly part of this particular study.

Briefly, this particular issue that you've just heard motivated the interagency working group to actually do a protocol which has been on the books for quite a while and this protocol has been on the books because of our concern and in pandemic preparedness and this is sort of we saw as perhaps a forerunner of that kind of

an issue. Briefly, what we were doing is looking -- what we are planning to do is to look at the population 18 to 49 years old. And again, as you saw, that population is an increasing user of influenza vaccine on the order of estimated about 20 million doses.

The information that we have had in the past is that lesser amounts of antigen can indeed mount an appropriate immune response in this particular healthy age group. And so the outline of the study is very simple. It's to give 7.5 micrograms of HA per a strain to each one of these people in the 18 to 49 and to have a comparison group, giving them the full dose. The plan is to do 600 people, 300 in each group. If, indeed, we are very lucky and can, indeed, do everything that we are planning to, the estimated time for information is beginning of October.

And I bring this to your attention because you may have information by which you need to incorporate in terms of how you would like to deal with the influenza vaccine shortage. This is of concern to the manufacturers and to a number of us about how this information will indeed be utilized. So I just wanted to let you know that this information may indeed be in your hands at that time.

Thank you.

DR. MODLIN: Great. Thanks, Dr. Heilman.

Maybe -- Bill Egan, would you like to comment just very briefly on what the implications might be for a reduced dose for one segment of the population?

DR. EGAN: Well, it's data that we have to get in and -- you know, to review and try, you know, for efficacy and I think there was some obvious, you know, complications in utilization out there. I'm not sure how we can handle it, actually.

DR. MODLIN: Okay. Thanks, Bill.

DR. FUKUDA: John, so let me -- let me try to encapsulate what I think is the essence of the situation and the essence of the issues facing ACIP.

So just to briefly summarize basically the situation, right now, we have a worst-case scenario in which we would see significant shortages of vaccine in the fall and significant delivery delays of vaccine to local areas. On the best-case scenario, there could be minimal or no overall shortages of vaccine. Even under the best-case scenario, however, we expect that there will be significant delivery delays of vaccine to various areas. And the dilemma there is that we really don't know where we are in that spectrum, or where

we'll be in the fall time.

Now, I think the primary issue for ACIP to consider is what can ACIP do to ensure the best possible protection against influenza for people at highest risks for serious complications. And that's the big question. Now, in looking at that question, I think there are several short-term and long-term considerations which need to go into the mix. The first thing is that right now our best vaccine estimates range pretty widely and we really don't know where we are in that range of estimates. The second thing is that we're quite aware that the whole publicity around this situation could, in and of itself, create a panic and, in and of itself, create an artificial vaccine crisis when there may not be one. So one of our main concerns is to minimize confusion and this entails several different things, but one of them is to provide clear messages both to the public and health care community and in some timely way. And I think another component of that is really to minimize changes to the usual ACIP recommendations. Now, another consideration, which really makes it very difficult, is that the realistic time window for any effective action is really pretty limited. And that's because planning of flu campaigns is already underway

and the majority of vaccine, not all vaccine, but the majority of vaccine has already been contractually committed to end users. Now, as Roland had mentioned, it is possible that we could have late production of influenza vaccine. However, as the manufacturers have repeatedly told us on an individual basis, vaccination activity and sales normally drop very significantly once we get into early November. And so this is a behavior which has really been there for years and, as others have mentioned, very difficult to change.

Now, another point, which Jon Abramson alluded to, is that we really don't know when the influenza season is going to start this year, as we don't know every year, and we don't know what the intensity of the activity is going to be.

We also have many long-term concerns and considerations. I think in the world of influenza things which have happened decades ago continue to have some affect on decisions and discussions now. And so one of our long-term considerations is to minimize adverse effects to future influenza vaccine efforts. Whatever we do now, we're very concerned that it doesn't derail future efforts to vaccinate people.

Our second -- A second major concern here is that,

you know, the vaccine is actually administered by thousands of providers out there and we really want to support that group in whatever we do. Whatever gets decided upon has to be both meaningful and implementable by that group of people.

And then another, I think, equally important consideration is that the influenza vaccine manufacturing process is really fragile in a lot of different ways. An enormous amount of vaccine is produced every year under very difficult and complex conditions. And I think that the public health side has to be very conscious of that and do whatever it can to ensure that that manufacturing capacity remains robust.

So I think that the first option for the Committee to seriously consider is simply to wait for events to evolve. As you have heard, I think there's considerable uncertainty of where we are in some important areas. And if we wait for events to evolve, I think that what that really means is that there would be some discussion today. There would probably be a decision to defer any changes to the current 2000 ACIP recommendations. And then it would also mean that there would be a decision to delay publication of a

MMWR article. And I think that I want to emphasize that we're thinking of the MMWR article and any discussion about what to do as somewhat separate issues.

Now, in terms of the pros and cons of this option, I think that in terms of the pros, if we wait long enough, clearly more information eventually will become available, and at that time, there will be no need to take any formal action. And this option probably minimizes the risk of precipitating a crisis in and of itself, an artificial crisis.

On the con side, I think that it's quite possible, if not likely, that information about the vaccine supply may remain significantly uncertain for at least several weeks at best. And given that kind of time frame and the other vaccine campaign considerations, the window period for taking any kind of meaningful action may vanish if the decision is deferred too long.

Now, the second option for ACIP to consider is that it could adopt the proposed modified vaccine recommendations or some iteration of that. And if it decided to go down this road, basically what that would mean is that there would be a decision to adopt the modified recommendations and to implement those

recommendations for the coming season, and that decision would be made today. And another iteration of that is that there could be a decision to adopt the recommendations in principle but to defer their implementation until some kind of specific threshold were reached in the future. And if that were done, I think we'd have to have some instruction from the Committee on what such a threshold would be.

I apologize for the confusion. These were literally just done before coming up.

Now, in terms of the pros and cons there, I think pros and cons to consider both about the modified recommendations themselves and then the cons of the recommendations and then the pros and cons of the timing. But first, let me actually go over what the recommendations are.

The heart of the proposal which is covered in the MMWR article, is basically this. The proposed modified recommendations for -- or proposed modified implementation of the ACIP recommendations would be to have the Committee preferentially state that it would -- or it prefers to vaccine high-risk persons and the health care staff that take care of them in October and November. And then the second point would be that the

vaccination of other contacts in addition to the health care workers would then begin in December. The third recommendation would be that anybody else who prefers to get vaccinated defer that until after December. And the vaccination of both the contacts of the high-risk groups and all others in December and later on would be contingent upon vaccine being available.

So again, to summarize, the heart of it is to say that ACIP would recommend that in October and November vaccination efforts focus on high-risk groups and the health care workers, and then if vaccine is available, then vaccination of other groups then begin.

Another part of this, and a question which came up, then would this mean that antiviral drugs should be used in any kind of different way than they normally are. And I think that what we would propose, anyways, in the draft is that influenza antiviral drugs should not be used as a substitute for vaccine to prophylax the general population. I think that we would emphasize that they should be continued to use in specific situations, and examples of these specific situations are physician-approved treatment and prophylaxis of individuals and their use in the control of institutional outbreaks. But I think the Committee

would probably have to be clear that it does not see it even under a vaccine shortage situation that these should be a substitute for vaccine.

Let me emphasize three critical points about these modified recommendations. The first thing is that the implementation of such recommendations would be purely voluntary and, therefore, it would depend really on an extensive education and outreach program, much more extensive than we normally do for influenza vaccine. And I think the outreach program would really have to go into the private sector in a way that we don't normally do.

The second thing is that we have to point out that the ability to steer vaccine under the best of scenarios is limited. Much of the vaccine is already contractually committed to end users and whether you can re-steer that vaccine brings up a whole host of very complex issues.

And the third point I'd like to point out is that if these modified recommendations were adopted, this really means that there would be a deferred implementation of the current recommendation to vaccinate all 50- to 64-year-olds for the 2000-2001 season. In the modified recommendations, what we do is

sort of separate out high-risk people in that age group and then healthy people in that age group.

So if we look at the pros and cons of the modified recommendations, is that the modified recommendations really, in essence, maintain ACIP's focus on protecting high-risk persons. It does not fundamentally change that but, if anything, emphasizes that general philosophy. The second thing is that by basing the triage guidance in terms of time, it provides reasonably clear triage guidance for providers out there. And I have to emphasize the "reasonably," because I think they're still difficult to implement. But I think the third point is that if such a strategy were implemented and if it were successful, it could significantly reduce morbidity and mortality in the high-risk groups.

Now, in terms of the con side, however, the adoption and implementation of the modified recommendations could simply create confusion. The second thing is that under the best of circumstances, it would require extensive effort to educate and implement. And then the third point is that by creating this kind of confusion, they could simply fail and they could also create a kind of backlash effect.

And I think the second thing in terms of the second option is to consider the timing. If the guidelines were implemented immediately or soon, in terms of the pros is that it would maximize the time that the public health sector could communicate about the new recommendations and why they've been made and it also maximizes the amount of time that vaccine providers have to adjust to the modified recommendations.

In terms of the cons of acting now in terms of adopting it, if in the fall time the actual supply problems are minimal, then what would -- what the modified recommendations would have created is a lot of unnecessary work and probably a lot of confusion. And the public health sector and the medical community, I would guess, would be susceptible to accusations that it had been crying wolf or crying that the sky is falling.

So this is the last slide. So I think that to summarize the options, the first option is simply to defer any action now. And if that option is taken, I think that the Committee still needs to discuss and decide upon what kind of threshold would have to be crossed for these kinds of actions to be taken. The second main option is to adopt the proposed modified

recommendations. And this could be adopted and implemented soon. Also, the recommendations could be adopted in principle but the implementation could be deferred. But again, if the decision is made to defer any implementation, the Committee would have to establish some sort of threshold for when action should be taken.

So I apologize, again, for the sort of disorder of the slides, but --

DR. MODLIN: Okay. Kaji, thanks. It looks like we have two major issues to discuss. One are the recommendations themselves, and number two, the timing at which they should be implemented, if at all. The other thing that needs to kept in mind is that the next time that this committee will meet will be in the third week of October, and even though we can arrange a meeting by conference call at some time in between, the logistics of doing that are not easy, particularly during summer vacation season.

Rick, did you have a comment?

DR. ZIMMERMAN: I have a couple of comments. First of all, the National Coalition Adult Immunization Steering Committee is having a meeting at the National Immunization Conference. Both of the National

Immunization Conference and the National Coalition Adult Immunization are meeting in July. So I would encourage that there be action, because there's a chance to disseminate information, but I also want to suggest that there's a third possibility. There's not just one and two, there's a third possibility.

That third possibility is to suggest that the campaigns be delayed for one month. Then instead of the campaigns all kicking off in October, in which case, many of them are likely to fail because they won't have vaccine, suggest the campaigns -- and this would be ask -- occur in November, the delay, at which point there's much more likelihood of being vaccine. And then we can establish a threshold about whether you need to change the recommendations themselves, but it seems to me the critical thing is there's not going to be vaccine for all the campaigns that are scheduled for October. And to delay that information from the public is very counterproductive because you're going to have campaigns called off at the last minute.

DR. MODLIN: Kaji, did you want to respond to that?

DR. FUKUDA: Actually, I think there are several people here who are involved in setting up these campaigns, and I think it might be useful to hear whether and how

much latitude there is at this point for delaying them back by a month and then making a decision upon whether to vaccinate slightly different at that time or not.

DR. MODLIN: Maybe we better ask Kristin Nichol, who's involved in this perhaps as much as anyone. Kristin?

DR. NICHOL: Sure. Actually, before I get to that specific issue about the campaigns, I'm curious to know if FDA or the manufacturers today can give us some sense for what the time line will be for us to get more specific information about (A) the nature of the delay that I am now assuming we will expect from all four manufacturers if they all bring vaccine to the market, and (B) when will we know about the vaccine supply. To my mind, there are two issues here. There's a delay issue, which I'm now hearing is a given, and then there's a supply issue, which I'm hearing is not necessarily a given. And I almost think about strategies in both categories as being somewhat separate.

So that's a comment and a question, actually, and I'm hoping that we'll get some sense for are we talking about not knowing until September 1 or will we know by July 15th or August 1st and what's the point of no return about both delay and supply. So that's just a

comment.

With regard to the issue of what kind of communication to send out right now and how this might influence campaigns, I would guess that many campaigns are very actively planning right now, but there is still a window of opportunity for them to at least receive an alert and go into a mode that they've maybe never gone in before, which is (A) at least plan for delay and (B) also potentially plan for vaccine supply shortfall.

So I would actually suggest, assuming we won't know definitively for maybe a month, that we think about some kind of communication going out now, just to put people on alert. But I would also agree with Rick, that there may be a third option, and what might be the message of something now. It might not be as specific as option two, but it might say the following: something to the effect that "Prepare for a delay because there is nearly 100 percent certainty that there will be delay. We suggest that you think about starting campaigns no earlier than November and otherwise continue to give vaccine if you get it earlier and you're lucky; (B) recognize that there may also be a shortfall and if there's a shortfall, start thinking now about how you might prioritize groups

according to highest risk for complications," without necessarily specifying either time line or which groups get it right now, because we don't know. If there's not a supply shortfall, then we are premature today in setting out specific recommendations.

And then the third is again a part of this alert. If there's going to be either a delay or a shortfall either to providers or maybe to the state health departments, if they might take the lead, "Think now about going into Plan B mode, where" -- how can you collaborate with other providers in your state or locale if you can start thinking about how would you either redistribute vaccine or reallocate your patients to different sites. And I think people can start thinking about that without necessarily realizing or planning that they actually have to implement all that. So a few comments.

DR. MODLIN: Thank you. Chinh?

DR. LE: Yes. Being one of the people who kind of coordinate the influenza vaccine for three million members, trying to coordinate 21 medical centers and 40-some-odd clinics, I know how much work has to go in advance and the posters, and mailing to patients and, you know, we actually mail influenza letters to high-

risk patients and so on, and I'm a little bit worried about postponing that until November, especially if you were to have an early epidemic in December or something like that. It takes a tremendous amount of time for an organization as ours to start -- I do understand your message, but I think it's much harder to do than we can sit at the table trying to figure it out. My thinking would be whether the Committee would feel that the postponing the implementation of the 50- to 64-year-old for next year would be one of the way out to decrease the demand.

The other comment I have is again the prioritization. It does make sense on paper, you know, if you are low-risk, get your vaccine in December and so on, but if you are -- if you are a Soccer Mom who brings in -- who brings in -- you know, and you wait in line for influenza vaccine program -- The shot clinics open on weekends and after hours to accommodate all the working people, and if you wait in line for 20 minutes and you are told "Come back in December," when you are bringing your emphysema mother, your asthma child and you're there for the vaccine, it's very hard for the provider to say "Come back in December."

So there are several implementation issue at the -- at

the clinic level that the practitioner will have to face. Despite rational guideline from CDC, which I would support, it's still -- it's not very easy to turn people away when they demand the flu shots.

DR. MODLIN: Dr. Levandowski?

DR. LEVANDOWSKI: Yeah, I'd just like to respond a little bit to what -- the issues that Kristin Nichol was raising a few minutes ago. And first of all, I just would like to say that I think our manufacturers do a really incredible job every year of putting together a vaccine which is basically a new vaccine because of the strain changes that are done. I think everybody should understand that as the amount of vaccine that's being produced has increased, it's still four manufacturers who are doing that and it just takes more and more time.

We're all sensitive to the stresses that this puts on the system and I can say that in past years, last year in particular, there were lots of concerns about the vaccine supply which turned out to be quite good. But it wasn't known at the beginning of the period of time what the actual number of doses finally would be, and although there were some delays in getting vaccine out there, ultimately I think was somewhere upward of 80

million doses that were distributed.

But what I'm trying to get to here is that the vaccine comes out in stages always and the more manufacturers there are putting out vaccine, the more that can come out, say, in July, August and so on. But ultimately, some of the issue here is going to be -- in future years as well, will be when the vaccine programs are operating and how likely it is that all persons and all users of the vaccine are going to be able to get their vaccines at the same time. I think there needs to be some understanding that it's not something that's all prepared and it's all ready at one time. It is being prepared over a period of time.

Now, to get to the point about delays, I believe that there are going to be delays, but again, it relates not only to -- it relates partly to what I was just saying, that there -- every year there are going to be these things happening, where some of the vaccine is coming out July, August, September, October. It's not -- It's not all going to be available at the same time.

And then as far as the supply, we will only know at the end how much vaccine was available. We're not -- We never know that until the end of the season, exactly how much is going to be produced. The manufacturers go

to great lengths to try to plan on how much vaccine they're going to make every year and they try to meet those targets, but there are these issues that relate to uncertainties about manufacturing, not just the vaccine strains but other things that come up every year that they have to respond to. And by and large, they do a very good job of that.

DR. MODLIN: So if I'm hearing you correct, you are -- would be somewhat a bit more supportive of the strategy as outlined in the draft MMWR article, which is sort of a staged delay in some respects, rather than a general delay as perhaps Dr. Zimmerman was suggesting?

DR. LEVANDOWSKI: Well, if you think -- if you think it fits the situation that we're in and we'll probably always be in, there may -- I would suggest that maybe there should be some consideration for such a strategy for the future as well.

DR. MODLIN: Thank you. Kristin?

DR. NICHOL: The -- Just to maybe speak on that again and -- And I don't organize programs as large as Chinh's, but the reason I was suggesting we consider some kind of general delay -- And last year, of course, we changed the recs. from early October to mid-October. The reason I'm suggesting that is that if there is a

delay in a particular provider getting the vaccine and they don't have it by mid-October, which is when they want to start, it's a true disaster. And, you know, the likelihood of getting the vaccine by November 1 is reasonably good and it's quite iffy by October 1 or October 15, my concern is that if we don't alert people to the fact that they might not have it by their usual start date, it's an even worse disaster than if they start in November and have twice the activity in half the time.

DR. MODLIN: So you might suggest a combination of both strategies. Is that what I'm hearing you -- given the sort of the pervasive uncertainty we have --

DR. NICHOL: I would suggest that we think about it. And this could go into the future. Maybe we should really be trying to concentrate most of our vaccination activities in the month of November going into December and when there's a vaccine supply shortfall separate from delay, although they probably always go hand in hand, then providers should think about, if at all possible, prioritizing vaccine delivery first to the highest-risk people. But I would hate to see us encourage providers to end up returning vaccine because they didn't give it to low-risk people.

DR. MODLIN: Other members. Jon?

DR. ABRAMSON: Yeah, there are a number of issues from a pediatric standpoint. We've been trying to deal with the issue of logistics and the more you narrow that window for young kids getting it done in a pediatric office, the harder it gets to get it done. Number two, for some of our kids, we've got to give them two shots and we see flu in December. Sometimes we see it even in November. So all those things affect our ability to appropriately care for children. So I think those all need to be factored in.

DR. MODLIN: Okay. Dr. Nordin?

DR. NORDIN: I'm speaking -- Although certainly our program isn't as large as Dr. Le's, but I'm speaking from the same position he is, which is that we're in the planning phases right now of a program for about 250,000 people and I think about the options. We -- To have clinic days, which we start advertising in August or something like that, and then to have no vaccine available or very limited vaccine available early would be very difficult to recover from. Whereas, the flip side would be bad also but not as bad. I guess the point I'm coming to is that we're in the planning phases right now and we'll be setting our dates within

the next two or three weeks at the latest, and I would urge the group to take action now rather than just deferring.

DR. MODLIN: Ben?

DR. SCHWARTZ: One of the comments that Jim had made earlier was that there were 14 million doses of vaccine that were distributed in the work place. And looking at the chart by age, most of these were in folks who were less than 65 years. I'm wondering if we know anything about the proportion of high-risk individuals vaccinated during work place campaigns and since 14 million doses is a substantial number, whether we wanted to -- whether we could focus more on that as a target in terms of delaying the work place and having the vaccine that's available being distributed through physicians, through managed care organizations, where it may be more appropriately targeted.

DR. MODLIN: If I heard the earlier presentations correctly, it sounded like the ability to control distribution is very limited. Is that not the case --

DR. FUKUDA: Yeah, John.

DR. MODLIN: -- Kaji? So that a strategy like that, where it might be desirable in theory may be very difficult to carry out in practice.

DR. FUKUDA: I mean, I think it's fair to say that we've reasonably extensively discussed the possibilities of redistributing vaccine or steering vaccines with the manufacturers and I think that the reps from the companies may want to speak up and give some additional details, but I think, in general, the vaccine which is contractually committed -- of which most vaccine in contractually committed. They sort of see that vaccine as being committed to whoever it's going to be sold to, whether it's an HMO or a large company or a small office, and that the ability to move that vaccine from that group and perhaps send it to somebody else is really something that they don't want to get into. And so, you know, is it possible for the public health sector to kind of try to wade in independent of the companies to do that? I mean, we've talked about that. Again, it bring -- it's just very complex.

DR. MODLIN: Dean?

MR. MASON: It may be for the consideration of ACIP that you'll be more influential in effecting the timing of delivery than in effecting the groups to whom it goes. And the reason I say that is, as Ben points out, the 14 million in the work place, they have a different

motive, and that motive is to keep their workers going in the production of that work place. We're not going to be able to deny their purchasing that product. There's also the wholesale -- wholesalers of this vaccine, who are interested in buying from the company and turning around and selling as a middleman to others who may not be as responsive to considerations such as high risk. So if 14 million go to the work place, which probably less than half almost assuredly, maybe less than ten percent are truly high risk, and if wholesalers who may not be as responsive to these considerations, it may be more of an appropriate focus to discuss the timing than our real ability to intervene with certain groups.

DR. MODLIN: Chinh?

DR. LE: I know that it's very difficult to predict when influenza hits in a community, but if statistically you could tell us like "Well, the chances in general over, you know, the season, over the years, that it's unlikely that influenza will come around November and early December," then I think we'll be very comfortable just kind of holding things back a little bit. But to start influenza vaccine in November with two doses, as Jon mentioned, and then be faced

with influenza in November, it's really a medical disaster as well. How -- What chances are we taking if influenza hits -- What's the probability, if you can give us that -- because we'll be willing to take a risk if that probability is small.

DR. MODLIN: I'm afraid nobody quite has the crystal ball that's quite that clear.

DR. LE: It usually is in January, isn't it? It hasn't been November.

DR. MODLIN: Kaji, can you --

DR. FUKUDA: Yeah, I'd really hate to make that -- that kind of prediction. I mean, I think that, Chinh, we can -- I mean, you know, in general, it's clear that there's much less chances for major flu activity to begin in November and October than in December, and it's more likely that there'll be substantial influenza activity in January. But having said that, I think when you go back instead and get away from sort of like general -- general patterns and you look at individual seasons, I think it's just very clear that there's so much variability in individual seasons that I would be very -- You know, other than going beyond some vague generalizations, I'd be very -- increasingly nervous about making any kind of statistical assumptions about

what's going to happen in this season. I mean, we can do that, but again, I'd be very nervous about saying that "because over the past 15 years we've seen flu begin in this time of year, that's the chances for this coming season," because it really has been very variable.

DR. MODLIN: Yeah. Walt, and then Rick, and then Chuck.

DR. ORENSTEIN: It seems to me, as we've been saying, there is some obligation to allow people to know that flu vaccine may not be available till late, and I think that needs to go out, I think, sooner in terms of the planning efforts. Granted, it will complicate lives, et cetera, but it seems to me that we just can't sit on this information, because I think it would be more problematic to have run a planned flu campaign and not be able to deliver on that campaign. I think we need to do it.

The question I guess I need to ask is on -- Granted, the difficulty with implementation of prioritization, is it not better to still have that prioritization out there as a guideline than not? That's the question I've got, is that there may still be some flexibility in the system and the question I would have for those

people who are actually involved in campaigns and warrant the peripheral side, is would it not be better to at least have the guidelines out there, even though we know, as you point out very well, Chinh, that it's going to be very difficult to implement in all situations.

DR. MODLIN: I think there's general agreement that it would, but I -- Let's -- Rick, and then Chuck, and then we're going to need to bring this to some closure sometime soon here.

DR. ZIMMERMAN: I want to bring us back to Kristin's earlier suggestion, because there is two issues. That's the issue of timing and then the possibility, which is unknown, of shortage.

If we delay the campaigns a month, providers can still give vaccine to high-risk people, but if we delay the campaigns a month, then we don't lose this issue of campaigns without vaccine. And that would probably mean they'll occur in early November to mid, because of the Thanksgiving holiday. And so that people will have time to (inaudible) immune response before the possibility of probably a December influenza disease season would occur.

I think the other part of that was to think of a

prioritization if a shortage were to occur, rather than to suggest a rationing system. And so then we can see if we need a rationing system delayer, but essentially, I think it's -- the option, too, moves us towards that idea of you really have to limit who you give it to, where if we just encourage people to think about prioritization if a shortage were to occur, that's a different issue. And we don't know whether there will or will not be. So I would encourage thinking about Kristin's suggestion of think about prioritization if the shortage occurs, rather than making the move to a system that could end up as a rationing system.

DR. MODLIN: I'd just like to remind people that there are some people, or particularly children, receiving dose at the first time that require two doses and a month apart. And so under those circumstances, you kind of have to take that into mind when you're thinking about how early one can start.

Chuck?

DR. HELMS: I'm hearing pretty clearly from everybody that release of information is critical here. I think the key question is coming down now to the options that Kaji put up there, particularly option two, and whether to delay implementation or not, whether the plan should

be put out there as something that would be implemented on a date certain if significant confusion still exists at that time or if the data clearly comes to -- comes forward as suggested, that it will happen.

And the question I'd ask, then, is, is there -- is it pragmatic to -- is it going to be feasible to wait that long to implement, or are we just -- should we just, at this particular point in time, not even consider the possibility of the delayed implementation and just say this is it, it's time to go?

DR. MODLIN: Thanks. I'm going to try to move on to wrap this up if we can. Kaji, the message that I'm hearing is that people generally feel that for planning purposes it's important to get the message out now, and I haven't really heard anybody say anything to the contrary.

DR. FUKUDA: No, and I would just point out that this is a public meeting and there are media representatives, and so to pretend that there is an option of not getting information out is --

DR. MODLIN: And secondly --

DR. FUKUDA: -- a little bit ridiculous. So the question is, what message --

DR. MODLIN: Right.

DR. FUKUDA: -- should go out and who should put that message out.

DR. MODLIN: I guess that was where I was going. The second message it sounded like we were developing a consensus around is, is that there should be some sort of recommendation that immunization campaigns be delayed on the average of a month and that there be some suggested prioritization for use of vaccine for the end user if, indeed, it turns out that there is a true shortage of supply.

Does anybody feel any differently than what I've just -- Well, okay, Jon?

DR. ABRAMSON: Yeah, I really am not sure that we can agree to delay it, just for the reasons I mentioned. Logistically, I don't know that pediatricians can handle that delay and still get all the kids immunized that need to be immunized and, too, we've got to get two shots into a lot of these kids. And it is not clear to me that we can do that in good conscience.

DR. MODLIN: Okay. I obviously struck a responsive cord.

DR. NORDIN: Can I comment on that?

DR. MODLIN: Sure.

DR. NORDIN: There's really two different processes here. We do an organized campaign and the first three flu clinics we have, almost everyone over 65 comes in. They come in -- If our first clinic is October 1st, October 1st the line is out the door. By the third clinic, it's a short line. The pediatricians -- The flu vaccine for pediatrics, it's a very different situation. That's delivered not in an organized campaign but in the physician's offices and should be dealt with as a separate issue.

DR. MODLIN: Okay. Thanks. Dennis?

DR. BROOKS: I'm more in line with -- I'm not really sure I like the idea of delaying anything, because it's always difficult to get our patients to come in, period, you know, for anything. I'm more in line with if there is a shortfall to use the proposal as a guideline for those who may need to ration it a little bit. But I -- The idea of delaying really kind of --

DR. MODLIN: Okay.

DR. BROOKS: -- is difficult for me.

DR. MODLIN: Well, I heard it the wrong way then. Okay. Fernando?

DR. GUERRA: I think in, you know -- And it's certainly been discussed in the Committee that it's important to

get the information out so that at least those on the front lines in both the public and the private sector can begin to develop some contingency plans, because I also feel that the train has already left the station and people are already calling to find out when it's going to start and it's going to happen. But I think there are a couple of other things that we can do.

I think it is incumbent on the public health side of things in communities, especially those with large populations, to develop a plan that would allow them to kind of get a better feel for how doses are being distributed and allocated in the communities. And it might also be helpful if the -- perhaps the CDC, the FDA, and the manufacturers could work together to see who has already placed orders. I know that there are some very significant orders that have been placed with companies that are not going to be able to comply with the request for that amount of vaccine and that perhaps having that information, we could maybe then begin to look at what the other supply has been into the companies. It probably will come close to being able to meet the request for vaccine, to see if there may be a little bit of give in that, to try to redistribute it so that at least we know that regionally most of the

regions in the country will have some protection at the outset of the season.

DR. MODLIN: Let me ask, then, if Committee members are -- it sounds like to me are then comfortable with -- pretty much with the language that's in the draft statement as is; is that correct? Bonnie?

DR. WORD: I think the one question I had, just to support what Dr. Abramson was saying, is there any way to word it so that to try to eliminate the difficulties that -- on those caring for children would encounter to make -- you can implement how to delay but exclude those caring for children?

DR. MODLIN: I would guess that children immunized according to recommendation actually represent a small proportion of the total amount of vaccine that's given. So it's not likely to have much of an effect, Kaji, but would it be reasonable to add something to the statement specifically regarding pediatric use for children that may require two doses? These are -- And actually it'd be even a much smaller number, because it's only really children receiving their first dose of vaccine.

DR. FUKUDA: Sure. I mean, so to make sure I understand, the sentence would be that clinics that

would be vaccinating adults delay by a month or some time period, but clinics and physicians who are vaccinating children ought to go ahead earlier because the special consideration.

DR. MODLIN: Is that reasonable?

DR. FUKUDA: All right?

DR. MODLIN: Rich?

DR. JACKSON: John, I think that's already in here. I mean --

DR. MODLIN: Okay.

DR. JACKSON: -- it specifically says children, that you start in October and November. So there's no real mention of that.

DR. MODLIN: Fair enough. It probably is. Thank you. Thank you.

DR. JACKSON: I think they're -- I think they're -- the emphasis on delay is notifications to providers that the vaccine may be, you know, delayed, and then delay mass immunization programs. So I think the providers' offices can prioritize based on this report.

One comment I have on the prioritization categories, even though intuitively they look -- they make sense, it does concern me about some subsets of the risk categories and specifically nursing homes. The

employees -- There's studies that show the vaccinated employees really limit the impact of the introduction of influenza into nursing homes and that's in here, but it's also visitors. I mean, visitors who are high-frequent to nursing homes are known to introduce flu in there. And I'm a little bit known -- or hesitant not to have that category in there as well if I know a family frequents, you know, every week to that nursing home, you know, I want to vaccinate that person.

DR. MODLIN: Good point. Peggy? All set. Okay. Fred, is it important?

DR. RUBIN: Just -- Yeah, I think so --

DR. MODLIN: Okay.

DR. RUBIN: -- because I -- Aventis Pasteur, speaking on behalf of the company, we provide about half the vaccine supply and it is very, very likely, and we intend to tell our customers that there will be a three- to four-week delay in vaccine. So we're expecting to reach at or very, very close to what we had contracted for and expected to make this year, but I think it's very important to -- for the Committee and reassuring to the Committee to know that if they say there's going to be a delay, it's a reality of the situation. So there will be a delay in shipment of

vaccine three to four weeks to people that are contracted to get it.

DR. MODLIN: Okay. Kaji, if I can maybe transmit, I think, the sense of the Committee -- I'm not sure we need to vote on this -- that there is an interest in getting information out on -- now, on a timely basis, in other words, publishing the draft article as soon as is reasonable, and secondly, that there's general comfort, I think, with the content of the draft statement without any major changes, although there may be some modifications that might be made along the lines that have been suggested by various members. I'm comfortable not taking a vote on this. Are others as well? I think we kind of have a consensus if that's the case.

DR. FUKUDA: John, just to clarify for my purposes --

DR. MODLIN: Uh-huh (affirmative), sure.

DR. FUKUDA: -- then, the information that we would be getting out would be specifically that delays are expected, shortages might occur, I mean, in essence. In terms of suggesting that a prioritization scheme is there, I mean, what's in the article already is okay --

DR. MODLIN: Uh-huh (affirmative).

DR. FUKUDA: -- and the primary modification would be

for adult clinics to consider delaying their clinics for about a month, but pediatric clinics and physicians ought to go ahead. I mean, if they --

DR. MODLIN: If they have the ability to plan to do so, yes.

DR. SNIDER: I'm not sure I heard "clinics," Kaji, what people described were more mass campaigns. And I understand that this is a -- maybe wordsmithing, but I think the concept was quite different. I think that people worry when they say "clinics," that my office should delay, and I didn't hear that from the Committee. What I heard was that campaigns to vaccinate all employees, et cetera, those are the ones that should be delayed.

DR. MODLIN: Right. I think that's fair. I'm sorry, I didn't -- Thank you, Dixie. Ben?

DR. SCHWARTZ: For committee members or liaisons who might have a tendency to wordsmith, Kaji, would it be reasonable to solicit comments, say, over the next week from the folks here? Would that fit with your time schedule for planning publication of an MMWR article?

DR. FUKUDA: Yeah. I'm -- You know, we had reserved a space in next week's MMWR pending the outcome of this discussion, and I think that it would be very helpful

to get input, written input specifically, from the members, and I think that we could delay the MMWR by another week or so. I think I'd also like to get input from the manufacturing side and, of course, we'll re-run the article by FDA and NIH and so on. So at best this will take a week or two. So I envision that the article might come out in two, perhaps three weeks, depending on what information comes in and how much back-and-forth there is needed.

DR. MODLIN: So if you're going to make a comment, in other words, do it very quickly.

DR. FUKUDA: Yeah. Please get it fast.

DR. MODLIN: Get your information to Kaji certainly as soon as possible.

Thank you. Let's take a break. Let's try to be back at 11:30, if we can, to get started. Thank you.

(RECESS FROM 11:11 A.M. TO 11:30 A.M.)

DR. SNIDER: John is going to be late, so we need to go ahead and get started, if the Committee members, especially, would come and take their seats and people would quickly terminate their conversations.

By the way, for those of you who need taxis, please see Gloria, Letarsha, or Gail at the back table at the break, the noon lunch break, so that they can schedule

those for you.

All right. We're going to have a presentation now by Steve Hadler about the Global Alliance for Vaccines and Immunization, otherwise known as GAVI. Steve?

DR. HADLER: Okay. Thanks, Dixie. I'll try to use this microphone. If people can't hear, let me know.

I'm going to brief ACIP today about a very promising development in international immunization programs, a new alliance to strengthen global childhood immunization and introduce new vaccines into the poorest countries. And this alliance is particularly important because it brings substantial new resources to childhood immunization that have been sorely wanting for many years.

I am not, per se, part of GAVI. I am right now on detail within the National Immunization Program to coordinate CDC's and NIP's involvement in GAVI.

Now, GAVI began last summer as rising out of the ashes of the Childhood Vaccine -- Children's Vaccine Initiative and was formed to support global immunization in new vaccines. GAVI is a partnership, and the emphasis is on partnership, of all the groups interested in vaccines. Probably the key partners are the World Bank, UNICEF, WHO, and the Bill and Melinda

Gates Foundation, but it also -- and the GAVI network includes other foundations, such as Rockefeller Foundation, the national governments which are responsible for delivering immunizations, donor countries, bilateral such as the U.S., the Nordic countries and so on, technical agencies, and I've been reminded, and this is a major oversight on the slide, that industry is a part -- is a part of GAVI.

Now, why GAVI? Challenges that have arisen for global childhood immunization during the 1990's are well known. Basically, during this last decade, since the Universal Childhood Immunization goal -- reaching that goal of 80 percent in the early 1990's, there was a shift in funding by donors to things other than immunization, donor fatigue, there was lack of sustainable funding within countries, and decreasing childhood immunization in many of especially the poorest countries that had either barely or not even reached the Universal Childhood Immunization goal. In addition, there was a failure to introduce some of the new vaccines such as hepatitis B and Hib into the poorest countries, and there was lack of progress in development of vaccines most needed for the predominant diseases in poor countries, such as malaria, TB, HIV.

There just wasn't a perceived market in the developed world and vaccine development was very slow.

This alliance was formed beginning last summer and set several objectives to meet these challenges: to improve the access to sustainable immunization services; to expand the use of all existing cost-effective vaccines, especially the new vaccines such as Hib and hep B; accelerate development and introduction of new vaccines; accelerate research and development for vaccines that are really needed in these poorest countries; and it is to address the funding issue to some degree, to make immunization coverage be considered an integral part of the design and assessment of health systems in international development, recognizing that immunization is usually one of the showcases of public health in developing countries is to make it be considered part of -- part of a measure of the quality of health care in these countries by the development banks and others who are -- who are pushing development and devoting a large amount of funds to this.

Basically, the organizers of GAVI set out to renew immunization in the 21st Century and to assure child -- all children have access to effective immunization

services, and these are pretty much the same goals I just stated: they're sustainable; they reach all children; have high levels of quality and safety -- And one of the emphasis of GAVI is on vaccine safety on introducing safe injections more fully into immunization globally -- to provide existing and new vaccines as they become available; and to facilitate the development and use of needed vaccines, even if there is not a big market in industrialized countries. They recognize that to renew childhood immunization, there needed to be improvements in vaccine infrastructure, which had been lagging during the 1990's. There had to also be improvements in financial tools that are available to the poorest countries and in resources available for research and development. Basically, GAVI is proposing much stronger coordination among all the donors and partners in immunization to work together and has both very short-term goals as well as longer-term goals. But there is -- One major goal is to make an impact now on childhood immunization programs through infusing funds to introduce new vaccines and to strengthen childhood programs. And this is starting this summer, the first funds will be made available. We want to expand the GAVI partnership

to bring in all the people who can and should be helping with this, and to -- but also look to the future. There's been some comments that GAVI has funding for five years -- Well, what happens after five years? -- and they're well aware of that and the issues of making sure there's sustainable funding for childhood immunization and for R and D is something that's on the agenda.

The organizational structure of GAVI, it's not a vertical structure, it's really a series of committees and working groups, but with some hierarchy within it. The GAVI Board is the highest level. There's right now 12 members, including the four key members: WHO; UNICEF; World Bank; and the Gates Foundation. But also, then, participation by the donor countries, two to three of those by client countries, several of those by industry, by NGO's and other foundations, by the research and development community, and by the technical supporters such as CDC. And there is a member from each of those communities that was initially appointed to the Board. This November, there will be a meeting of interested parties and there will be discussion and election of new members to the Board. The Board meets approximately every four to six months

and just completed a meeting in Oslow last week. There's a small Secretariat in Geneva that's headed by Tore Godal that really does coordination activities. It is not heavily funded. But the key -- The key group that's really driving GAVI right now and making it operational is what's called the Working Group, which is a series of eight members that meet monthly or more frequently to develop policy and operational approaches to reaching the goals. Again, the key members of that are the same, are representatives of WHO, UNICEF, World Bank, the Gates Foundation, and then one representative each of the donor countries, of industry and -- It's a relatively small group, eight members. Again, the makeup of this Working Group will be reconsidered this coming November.

In addition, there are task forces which are intended to discuss specific issues. There's one for country coordination led by WHO, which is now in the process of deciding how to provide technical support to countries that want to apply for GAVI funds. There's also one on advocacy led by UNICEF looking at how to better advocate vaccines and one on finance chaired by the World Bank and USAID, looking at long-lasting financing of immunizations.

Now, all of this leads to -- or the big difference between GAVI and the Children's Vaccine Initiative is that with GAVI, there are already substantial funds committed to reach these goals. Children's Vaccine Initiative never had that many funds, but GAVI began with a large donation from the Bill and Melinda Gates Foundation and which provides funds to directly help countries with immunization as well as to help in all the other aspects of immunization and to meet their goals.

The Global Fund for Children's Vaccine is developed to support immunization in eligible countries. It was established with a $750 million grant from the Bill and Melinda Gates Foundation to be used over a five-year period. It encourages gifts from other donors. This was meant to be seed money, huge seed money, but -- And just last week, Norway committed $125 million over five years to this. The U.S. government -- The President requested the U.S. government to provide 50 million to the fund this year and that's in Congress. Britain has just committed five million for this year and other European countries are considering donations. In addition, several of the vaccine manufacturers are donating substantial amounts of vaccine to the

initiative. I believe hepatitis B and maybe Hib.

Now, this fund, right now it's intended to have three ways that it can be spent, three sub-accounts: one to procure new vaccines, to help countries to buy hepatitis B, Hib, yellow fever vaccines, and possibly others; one for access and infrastructure, to help countries rebuild their infrastructure, improve routine immunization; and the last, for research and development.

Now, the research and development fund isn't open yet and that's been a bit slower to progress and most of the rest of what I'm going to say is going to focus on what's happening with the first two parts of the funds, but I'll come back to R and D at the very end.

GAVI organizers stress that this fund shouldn't be considered in isolation. It's a tool to help stimulate countries to assess, plan, and build their partners' support into a sustainable immunization program. It is not intended to replace either funds coming from countries now or those coming from other sources. And it's really intended that it could catalyze new funding by bringing people together in each country so that people can hear the country needs and actually provide funds.

And I guess the conceptual framework is that each country's national immunization service in the center is surrounded by its various partners, be they World Bank, WHO, UNICEF, bilaterals, NGO's, in these varied and different countries, but that these will be brought together in an interagency coordinating committee to agree upon common goals, to find real solutions to the funding needs, and with each of these partners doing what it does best to help out within each country.

Now, GAVI has been on a fast track. During this spring, they've been preparing -- Much of what I've just put up has really evolved during this spring. It actually -- The first meeting of GAVI Board members was last July. So they're on a fast track and they're on track to actually start making funds available next month. And again, funds will be made available to national immunization programs for two areas: one is procurement of these new, unutilized vaccines and the safe injection equipment needed to give them; and the second is for access and infrastructure.

Initially, the funds were granted mainly for new vaccines, but as they had further discussions with partners, they realized it's difficult putting a new vaccine such as hepatitis B into any kind of program

without giving some support for the infrastructure and putting it into a country that has 30 percent coverage is probably -- simply won't do what you want to do. So you can't give funds for new vaccines alone without helping support and rebuild the infrastructure.

Proposals for funds must come from national governments and the country eligibility are those with per capita income less than 1,000 U.S. dollars. There are about 75 in this category, excluding India, Indonesia, and China, at least initially, in part because they are all vaccine producers. Also, they could break the budget even of GAVI, although they are considering including these countries under special circumstances.

The eligibility criteria for applying for funds for new vaccines and immunization services accounts differ.

The new vaccine subaccount, as we've said, right now it's focused on these three vaccines, although it's -- as others become available, potentially they will also be included. But this will require good vaccination infrastructure and DTP3 coverage over 50 percent, a demonstrated burden of disease that justifies using the vaccine -- Yellow fever will not be given, except in Africa and South America -- a plan for introduction of the new vaccines, a plan for safe injections.

The immunization services subaccount, in contrast, is intended for countries that have coverage less than 80 percent, and that's most of the countries with GNP's less than a thousand, also have coverage below 80 percent, and this will require setting annual targets for increasing the number of children who are immunized and a multi-year plan which shows how the country intends to achieve this. Countries may be eligible for funds from both accounts or from one or the other.

The time line is that in February, through UNICEF, they elicited letters of interest from those countries that were potentially eligible, and 55 out of the about 75 countries did say they were interested. Application materials were distributed last month and the first round of applications are due on July 1st. The proposals will be reviewed during July and awards made during August.

There's another window for applications on October 15th. And then, subsequently, there will also be opportunities for countries to apply. So if countries have an inadequate application in the early rounds, they may be able to -- or they would be helped to improve their application so that they would be eligible for funds.

As I said, 55 countries have shown interest. The most interest has been shown in hepatitis B vaccine. This is driven a bit by the Gates Foundation, where there are a lot of ex-CDC people who -- with an emphasis on hepatitis B vaccine, but also recognizing this vaccine's been around for ten years and there's a major global disease burden still to be met. There are some who are interested in Hib vaccine and there might be more if there was better estimates of disease burden, and some with yellow fever vaccine. Among the countries with no interest are many of the ones that are really very war-torn now and have no vaccine infrastructure, such as Afghanistan, or no structure outside of what NGO's are doing.

The application procedure is not a simple one. It has three major criteria or components: a five-year plan for immunization, really laying out the game plan of what they're going to do and including what they're doing with polio eradication, because the intention is not to disrupt the final stages of polio eradication; a functioning interagency coordinating committee to bring the partners together and have agreed-upon goals and that these -- this needs to be a functioning committee with terms of reference and monthly meeting; and a

recent assessment of immunization services, again knowing what is working and what is not working and what's it going to take to improve it.

The application is submitted by the government, but the ICC members are asked to endorse the application. And part of the goal is to bring all the partners together so people know who's giving for what, where the gaps are, and have people start to fill gaps that are there.

The application procedure, again, will require a lot of basic information about health services and the immunization program status and funding, the assessment, the multi-year plan, their plan to introduce new vaccines if they're applying for it in their unmet needs, as well as who the money will be channeled to, whether to the government itself or to donors.

GAVI -- Right now, the plan is that funding would initially be for a several-year period, recognizing it's difficult to make an impact in the first year.

But it will be monitored and outcome-oriented, looking for the number of children -- the increase in the number of children vaccinated, ideally verified by either covered surveys or audits, looking also at financial sustainability, encouraging governments to

begin to pick up some of the funds that GAVI is providing and quality indicators and discussions are right now that if at the mid-term review a country is not producing changes in immunization coverage, than a certain component of their funds would be stopped. That's pretty much an overview of the process of actually getting funds out to countries very quickly.

A few words on the research and development part, which many of you would be interested in. There is a research and development task force, which is just, I think, working on its terms of reference. What I understand is they -- they're still trying to decide what to do, what their position would be in the, I guess, R and D field overall. Myron Levine is in charge of this. Again, I haven't spoken with him directly, so my information on this is sketchy. I understand they may select one or two orphan vaccines which are part way along development but not yet there and push those.

But what I wanted to emphasize is that other Gates Foundation funds are -- have been generously provided in a number of areas and are really -- I guess they've just swollen the pot for R and D on vaccines immensely and give a potential for major developments in the next

several years. The Gates Foundation has its own children's vaccine program. Mark King is now head of that. And they've received $100 million over five years to support childhood immunization and development of new vaccines. They're providing money to WHO for their -- to help put new vaccines technical officers in regions. They've provided some support to World Bank, I believe to UNICEF. They're supporting working group on vaccine development for I think diarrheal disease and so on.

In addition, the Gates Foundation has given money to other areas to stimulate development of malaria, TB, HIV vaccines, 50 million each. Gina Rabinovich is now in charge of working with the malaria vaccine development. In addition, I understand they've given money for neonatal tetanus control. So the funding that's come in for global immunization is very large by I think any of our standards, but is a wonderful opportunity to really move the immunization field forward.

So just a few conclusions is that GAVI really brings major new resources for immunization that are much needed that were missing during most of 1990's, except for perhaps polio eradication. The funding is really

focusing on new vaccines and infrastructure. It really has the opportunity to really invigorate childhood immunization programs globally and to provide a firm platform for adding the new vaccines that are coming down the line. It will require very strong technical support. There's no doubt that WHO and national resources and all the partners who've been working, especially in the Working Group have been stretched very thin. It will continue to be -- to stretch -- The partners now is -- we're in the process of identifying people who can help with planning, with technical assessments of program, disease burden, with monitoring, and there will be a real need to build the technical capacity in the partner countries so that the countries themselves can pick up this as it progresses. And lastly, there was a handout yesterday. Hopefully, most of you got that. One was one page from the GAVI web site and then a brief summary that we had put together, but just for those who were interested, this is a place where you can find out more information more quickly about what's going on:
www.vaccinealliance.org.
So I'll stop here, and if there are any questions -- I think Tom Vernon had wanted to make a comment.

DR. MODLIN: Questions for Steve? We'll start with Tom. Go ahead.

DR. VERNON: John, if I may, a personal note on an attribute of GAVI which is relevant to us in the U.S. today, and it's one to which Steve has referred. The effort, beginning in fact, with the Children's Vaccine Initiative, thanks to the leadership or Roy Whittis (phonetic) through the 1990's to bring industry to the table as a full partner, that is an attribute of GAVI today. At the Board level, the industry representative is Jon Jacque Bertrand, the CEO of Aventis Pasteur vaccines. On the Working Group is Dr. Tim Cook of the Merck vaccine division. And indeed, it is a full collaboration with industry there at the table.

This is relevant to us today in the U.S. because there are a few in Congress and elsewhere who are mistrustful of the relationship between and the other partners in the immunization enterprise here in the U.S. And this is despite your sterling personal ethics and despite the carefully wrought checks and balances which we have in place in the event that there would be slippage. Yesterday we saw a demonstration of this collaboration in thimerosal, thought leaders, you, regulators, CBER, the implementers, NIP, in the

hepatitis branch, and the producers, the companies. Let's resolve in the GAVI model that we not be pressured into a retreat from the kind of collaboration which we have achieved and must continue to achieve as full partners all. Let's resolve to preserve and further promote the partnerships that are so important to the immunization of not just the U.S., but the entire world, and think of the way in which GAVI is operating today as an example of that kind of collaboration.

Thank you very much.

DR. MODLIN: Tom, thank you. Other comments, questions for Dr. Hadler? Fernando?

DR. GUERRA: Yes. Steve, thank you for the information. I didn't see the Rotary International listed on that. Is that a member of this effort as well?

DR. HADLER: I'm not the best person as the -- There -- I think GAVI would very much want Rotary as a major donor to be part of it. It is not yet, and I guess you've seen the positive side. There are questions in some people's minds, how is GAVI and polio eradication going to work together. There's concern from the polio eradication people that GAVI

will distract countries from finishing polio, and that is a real concern. You can see all countries want to be part of GAVI and they want to add hepatitis B, whether they wanted to last week, they want to now. And so there is a real concern.

There have been efforts to start to bridge that. The Working Group met with the polio consultative group last May and began to discuss working -- making sure -- working together and ideally, it should be able to be synergistic, but there has been something of a gap up to now. From what I just saw from the minutes of the Oslow meeting, which if people want, I can send out -- I can give to Gloria to send to the Committee. I just got them this morning. They did discuss the need for GAVI and polio to work synergistically and that the Working Group of GAVI needs to keep working with the core polio group.

All that said, I understand Rotary was invited to the Board meeting but may not have gone, and I don't know anything more than that. But obviously, one would want Rotary to be part of it. That has not yet happened to my knowledge. I'm not sure if anyone else knows more than that.

DR. MODLIN: One more comment. Bob Chen?

DR. CHEN: Just briefly, that I'm very pleased that Steve mentioned that sustainability will be one of the issues that GAVI will focus on, that this is a real problem in dealing with developing country immunization programs, that in my career in immunization so far, this already is perhaps the third attempt of this with UNICEF, starting with the Universal Childhood Immunization Initiative, the Children's Vaccine Initiative, and now GAVI. And the main problem historically has been that basically with donors, they only have a certain number of years of a certain initiative, then they need to move on to another more exciting and juicy problem. And so, hopefully, you know, perhaps an endowment of some Microsoft stocks before it splits or something might be a long-term investment so that we truly have a sustainable investment in these efforts.

DR. MODLIN: Thanks, Bob. Steve, thanks very much. The next item on the agenda is a progress report on the Vaccine Identification Standards Initiative, VISI. Dr. Weniger, Bruce Weniger, is going to present that.

DR. WENIGER: Thank you for this opportunity to update you on the Vaccine Identification Standards Initiative, or VISI, as we call it. We've presented before to this

committee, but it's been quite an elephantine gestation. So there may be some new members who are not familiar with it. And we sent you some materials in your packets a few weeks gap which are now somewhat outdated, but you update the details and the refinements that have occurred since then at the web site.

The Initiative is driven by a growing problem we have in vaccine safety surveillance of errors and omissions in documenting the vaccinations that children or others have received in their medical records. And if you go to our background and rationale page, you'll see a lot of the details for this and illustrations of it.

There's also been an increasing burden on providers in carrying out their legally-mandated requirement to transfer into the medical record information identifying the vaccine that was given, including the lot number. And of course, these are the -- these are the data that then eventually ends up in immunization registries and in our vaccine safety monitoring systems and we're reaching levels of missing and erroneous data anywhere from 10 to 20 percent in them. In addition, in general, there's a lot of increasing concern over

medical errors in the health care delivery system. Now, this initiative is the kind of collaboration intersectorial (sic) of various partners in the immunization system that Tom Vernon had alluded to. Our participants include not only CDC and FDA and the vaccine manufacturers, but state health departments, professional organizations, health care provider organizations, the immunization registry community, Uniform Code Council, the people who assign those bar code numbers and participate in an increasingly global system of product identification, the bar-coding software/hardware industries, and some international observers. And the details of our meetings and minutes are available on the web site.

These are the seven key components that VISI now has. And we're now reaching the final stage of this process. So I wanted to illustrate what they are. The first one is peel-off bar-coded stickers on every vaccine vial or prefilled syringe. And here's an illustration of a mockup we made of such a sticker based on a prefilled syringe sticker that already occurs on Wyeth's Tetanus Diphtheria Toxoid vaccine, although it's not at the current time a peel-offable one. But what we've done is assigned -- Printed this additional information on

it, and the VISI specifies at a minimum -- let's see, one, two, three, four, five, six items to go on a peel-off sticker: one would be the lot number, of course; one would be the expiration date, of course; one would be the National Drug Code which uniquely identifies every pharmaceutical product in the United States; one would be the abbreviation for the vaccine if there is not sufficient space to spell out the full generic name for the vaccine; one would be an official abbreviation for the company, if there's not sufficient space on what might be very small labels to identify the company; and then a reduced space symbiology, or RSS bar code that can produce in a very small
area -- I don't think we have a scale here, maybe we do a little bit down here -- a very small area all of the numerical information that I've just described, the lot number, the expiration date. So if a pediatric practice has a bar-code scanner, a sophisticated one, they could scan this, or at least if an immunization registry has one, they could read the numbers in without any transcription errors.
The next -- Here's an example of what was developed in Sweden by Pasteur Merieux MSD, now Aventis Pasteur MSD, of -- of their multiple layers of peel-off stickers on

vaccine vials in which -- but we don't have the actual photograph of a vaccine vial. They're actually, as you can see over here -- one, two, three, four separate stickers that are superimposed on each other that contain bar-coding and the key numbers that can be peeled off and placed on various places, various forms and so forth.

The next component is to have full bar-coding with not only the National Drug Code, which already occurs on vaccine cartons, but also the lot number and the expiration date, so this can be pulled into electronic records automatically without having to open the box and look at a peel-off sticker. And let me illustrate that. This would be an example of the National Drug Code that will be preprinted on the carton for any specific product, and then the challenge would be, what would be new, would be to have an additional bar code with the lot number and the expiration date printed on line during the filling process, when they know what the lot is going to be and what the expiration is going to be for that vaccine.

And the challenge remains that the current printing equipment that manufacturers use to print on line the lot numbers and the expirations dates are not yet -- do

not yet have the resolution to produce very small bar codes. But we're working with the industry and have meetings scheduled later this -- in the end of July to bring in some experts on the high-resolution printing on line.

The next component is if you're going to have peel-off stickers for practices that don't have bar codes, paper practices that have not completely made electronic their medical records, we came up with a form that these stickers can go into that can be used both if you have a sticker and if you don't have a sticker. And here's a mockup of the form. Let me see if I can zoom in to show the fields here.

There would be a -- basically, a place on the form where you could put the sticker if you had one, and if not, then you can manually fill in the lot number, the vaccine abbreviation or brand name, and click on your manufacturer. And then it also has other information that exists in forms, like the American Academy of Pediatrics has, that are often desirable on forms, the site where the vaccination took place, including the right or left leg or limb, the source of the vaccine, initials for the vaccine information statement, and the initials for the administrator of the vaccine.

The next component was if the National Drug Code is going to be the unique number that identifies every pharmaceutical product, to date, there's not been a user-friendly, easily accessible way to look up what is the vaccine associated with that NDC number, which appears on every vaccine today and vice-versa. So we created a National Drug Code database search engine.

So you could go to this web site and if you have a number that comes in, it's a ten-digit number, you can type in the number with or without hyphens or any sub-field from that number, or the name of a manufacturer, or the name of a vaccine, and it will immediately give you all the choices of all the records that are hit by that search.

Now, currently, we have about 151 separate records in the database. I think we may be missing a few, but I think -- when we think about it, there are not that many vaccines in existence and I think clearly far fewer than 200 would be in this database. So I'm going to give you an example what the retrieval looks like when you get a hit. This is the DTPa Certiva vaccine from North American Vaccine and all the fields will give you the NDC number for it, will give you the strength, how many doses are in it, is it a prefilled

syringe, is it ten single-dose vials, is it one multi-dose vial, and so forth.

The next component is to try to help the physicians and nurses particularly in the clinic obtain the information they need quickly from the vaccine package. If you look at existing vaccine packaging, the key information is often in different formats, on different sides of the box if you want to know "Are there any egg proteins in this vaccine," "What" -- "Is this a ten" -- "Is this a box of ten single-dose vials or is this a box of one multi-dose vial with ten doses in it," and so we mimic the nutrition facts that we find on nutrition labeling to create a vaccine facts sidebar. And we've made mockups for about a half dozen or so vaccines. Here's an example from Wyeth-Lederle's FluShield, in which we've tried to organize all this information that now exists on the boxes but in a more systematic fashion so the nurse can quickly find out the information he or she is looking for. And interestingly, the FDA is now in the process of mandating a similar drug facts box for all over-the-counter drugs sold in the United States and these will be appearing on all boxes of pharmacy -- of over-the-counter products by February of 2001. So this, I

think, is something that we feel could be very useful, as well, to health care workers.

Here are some examples in which you have the type of vaccine, the full generic name, and the official abbreviation, the brand name, the manufacturer's abbreviation, National Drug Code, how many doses, and what's the volume, and the storage requirements. We think we need another field here, and we think there's more work that can go into this, and that's a field for packaging. What kind of a package is this? Is this is a box of one prefilled syringe or a box of five prefilled syringes? Is it -- Because sometimes you want to know without having to open the box and find out.

In addition, all the dose and administration information, the dosing, is it intramuscular, subcutaneous, any cautions involved, and any trace components, does it have thimerosal, does it have tissue culture cell lines that it was grown in, and so forth. And other examples, we have for Engerix-B. We have basically samples from all the major manufacturers, Havrix, Ipol, and various others.

The next component that is supportive of this, is if we're going to have very, very small peel-off stickers

without a lot of space to spell out the full generic name of the vaccine as well as the name of the manufacturers, then come up with standardized abbreviations for both vaccines and manufacturers. And for the vaccine abbreviations, we've followed the European precedent that was attempted to come up with a format for vaccines and went globally around trying to come up with a system that works for all vaccines and not do it on an ad-hoc basis every time a new vaccine comes along.

We have certain guiding principles. One is that it's basically a root of three capital letters that identifies the disease or the immunological agent you're protecting against, and then the use of subscripts to more precisely -- if you want them and optionally to define the types of vaccine you're referring to. And the principles for naming them are -- One, of course, is that we're going to grandfather-in all the common, accepted, widely recognized abbreviations, BCG, TT, DT, DTP, and so forth. But when naming new abbreviation, to use various principles: onomatopoeia; intuitiveness; specificity; consistency; and economy.

And I'm going to just comment on economy. Aside from

the grandfathered abbreviations that use "V" to stand for vaccine and virus, it seems when you only have three characters and you're trying to identify specifically a vaccine, you don't want to waste one of those three spots for a "V" that simply stands for vaccine, because that's all we're talking about. So that would be an example of trying to get the maximum amount of information in a limited amount of space. And then the specificity is described for how you would identify different types of vaccines with subscripts and various formatting specifications, such as how would we notate combination vaccines, how we notate simultaneous vaccination, and the user flexibility to add -- to specify the types of conjugates that are used and the serotypes or seed strains that are used in the vaccine, the valency of the vaccine, the order, when you have -- as well as the manufacturer of the vaccine, and then the order in which these various specifiers would be added as subscripts, and then finally, a long list of every vaccine we could think of, not only currently, but from the past and even into the future vaccines that don't yet exist, and a suggested abbreviation for them, from adenovirus down to yellow fever.

And the final component is to standardize the abbreviations for the manufacturers. And this is a rather confusing field with the speed with which these companies are being absorbed and merged into one another and their corporate identities are changing. We had made a list that includes both historical abbreviations and then indicated when they're no longer active or they've been absorbed into another company or another abbreviation, and everything from Abbott Laboratories, Adams Laboratories, Alpha Therapeutic Corporation, and of course, API, down to some of the ones that are no longer manufacturing, like Lily Vaccine, just for historical purposes. So this might be used not only in current medical records but in scientific communications and publications, both current and historical.

And these are the next steps we see in this final stage. One is we're not satisfied with those vaccine facts you saw before. We realized after making those mock-ups -- We took the language directly from the boxes of these sample vaccines, and we realized there's a tremendous variation in how each company says the same thing. And we think it might be useful to develop some standardized language. Some companies say, "Rx

only." Other companies say "Federal law requires," you know, "prescription by physician" and so forth. And some say, you know, "Store it at this temperature." Others say, "Refrigerate it at this temperature." So we think we could come up with some standardized language for each of those fields, and we'd like to work on that.

But we're ready, I think, at this point, to announce this for -- to start soliciting public comment for a 60- or 90-day period, and then basically to revise that -- and look at that public comment that comes in and revising the drafts, the specifications, as appropriate. And at the same time, we'll need to be helping bring together the bar-coding and printing industry with the manufacturers to solve the problem of printing such small bar codes on there as peel-off stickers.

And then ultimately, we need to find the resources to pull it together with some editorial and web graphics support to reformat the narrative text. And there's quite a few textual details that I haven't shown you that you can download if you wish. And then ultimately, to publish this, and finally, to identify the long-term responsibilities for ongoing maintenance

of this National Drug Code database and the abbreviation list, which, as you know, we're constantly changing. Pretty soon, Glaxxo is going to merge with SmithKline and we'll have to figure out what that name will be and what abbreviation that merger will get.

So I think that's it.

DR. MODLIN: Thanks. Any questions for Dr. Weniger? Chinh?

DR. LE: Bruce, is participation of the vaccine manufacturer voluntary or do you have any teeth in terms of enforcing -- because eventually, unless it is a universal type of implementation, it's going to be falling through the cracks.

DR. WENIGER: This was an entirely voluntary initiative. Obviously, the FDA has the authority to mandate whatever it wants, but we -- what we wanted to avoid is many of these components, people are asking the companies to produce and already some companies have peel-off stickers. Merck has one on some of their pre-filled syringes. Aventis Pasteur has one on their TriHIBit. But we wanted to avoid a vulcanization, which every company approaches how to do this in a different way, and then they wouldn't be compatible if you put them on a common immunization form or sent them

to an immunization registry.

And so it's been voluntary, but what I think will happen is once the first company starts coming out with some of these improvements, I think the market will indicate if the doctors like these peel-off stickers that they can put right in the chart, that the market will drive the other companies to catch up. And having these common standards will make sure that once they're on a form that's, say, mailed to an immunization registry for scanning into the system, it will be one that will be -- all these stickers and other components will be interchangeable.

DR. MODLIN: Dave Fetson?

DR. FETSON: David Fetson, Aventis Pasteur MSD.

Since the companies that make the vaccines are, for the most part, international companies, to what extent is this process, which is voluntary, involving people and representatives from other countries, including health agencies such as yours?

DR. WENIGER: Well, at this point, although the National Drug Code number fits into a larger global system -- And we are proposing that the current bar code that exists on the package, which is only a U.S.-based one, be substituted for a newer one that

incorporates this same data but can be recognized globally. But the reality is that outer packaging is unlikely to be used the same in other countries because it has the National Drug Code, which is not necessarily the same code in other countries. So I think we've had a mostly domestic focus on this.

We had individuals from other countries involved with vaccine packaging -- you know, involved in this initiative, but we're thinking at this point mostly domestically. We would welcome input from other countries in terms of feedback on abbreviations, other manufacturers that are not listed. But I think the reality of the U.S. market is that the packaging that occurs for the U.S. market would need to be changed to satisfy other markets, and so we're really focusing on our market for the time being.

DR. MODLIN: All right. Bruce, thanks very much. I know a number of immunization managers are looking forward to seeing this become a reality.

The final item on this morning's agenda will be focused on rotavirus vaccines and will be led by Dr. Paul Offit, who will begin with the summary report of the WHO meeting that was recently held on rotavirus vaccines.

DR. OFFIT: In February of this year, there was a meeting held by the World Health Organization in Geneva entitled "Future Directions of Rotavirus Vaccine Research in Developing Countries." And for those of you interested in seeing an excellent summary of the whole of that meeting, one is available from Joe Breze (phonetic). What I want to do is just focus on one selected aspect of that meeting, specifically the reaction by World Health Organization of the ACIP's decision to withdraw its recommendation on the rotavirus vaccine.

And there are two issues that I'd like us to consider. The first is consideration of the risk-benefit ratios of Rotashield vaccine in the United States; and the second is strategies to encourage the use of Rotashield vaccine in developing countries when the vaccine is not recommended for use in the U.S.

So let's consider first the issue of risk benefit. The ACIP was criticized by WHO members for failing to consider the risk-benefit ratio of Rotashield in the United States. This was seen as a lost opportunity. Because rotavirus disease is ubiquitous, a decision not to give a vaccine is a decision to allow for the often severe consequences associated with natural infection.

Therefore, the decision not to give a vaccine is not medically neutral and deserves discussion of benefits and risks.

So want I want to do over the next three slides is just go through what is admittedly a crude analysis, and I'll try and explain the assumptions that are made in each case.

First is to assume a risk of intussusception of one in 4500 vaccine recipients. This is the original data generated by the CDC. And in the analysis below, I'm going to do estimates per million children.

Now, if you just look initially on the line for intussusception, the rates for intussusception, the attributable risk for intussusception would increase in the vaccinated group by about 260 children per million vaccinated. The number of doctor visits would be decreased by about 113,000, assuming about an 80 percent protective efficacy against moderate the severe disease, which is a published number.

Hospitalizations would decrease by somewhat less than 16,000, assuming again a published statistic of about 95 percent protection against severe disease. However, I included under vaccine the 260 excess hospitalizations that would be created by vaccine, and

I don't mean to make equivalent hospitalization for dehydration and hospitalization for intussusception, because they are certainly different in that a certain percentage of children hospitalized with intussusception go to surgery. That's not the case with hospitalization from dehydration.

And then on the last line, the number of deaths from the vaccine would be decreased by five to 11 per million, making the assumption of 20 to 40 deaths per year for rotavirus disease. This has been presented to us by Dr. Glass and also there was one death per -- roughly per million children vaccinated from intussusception caused by Rotashield vaccine.

Now, there are probably two assumptions in there that are limited. The first is that all rotavirus vaccine deaths would be prevented by Rotashield, because there likely would be some deaths that would occur in the less-than-six-month-old child who's not fully vaccinated. And I think it's also probably incorrect to assume that there would be intussusception deaths from a Rotashield vaccine given that usually deaths and, frankly, surgery from intussusception is a consequence of the failure to recognize the disease. With the Rotashield vaccine, the risk is quite discrete

after the first and second dose occurring within one week of those doses and so the likelihood is that intussusception following that vaccine would probably be recognized fairly quickly and would be less likely to result in either surgery or death.

On the next slide, I assume a risk of intussusception of one in 12,274, which I think Dr. Chen in the talk following mine is going to tell you about. That's a more recent attributable or assigned risk. And now you see that under intussusception, the -- there will be, then, an attributable risk of about 95 children with intussusception per million vaccinated, the other number's staying roughly the same.

Lastly, there was a paper presented at the Society for Pediatric Research by Martha Hellams, where she, looking at a cohort of children in Virginia, found that the peak of intussusception in Virginia was in April and really correlated directly with the peak of rotavirus disease, at least in her state. And she made the statement that rotavirus disease may, at least in part, be a cause of intussusception.

Now, these data, I think need to be interpreted with caution in that they were presented only as a poster and have not been submitted for peer review. But at

least it brings up the theoretical possibility that rotavirus disease may be a cause of intussusception, even a small cause of intussusception, and if that's true, then one could argue that vaccine may also prevent a certain degree of intussusception. So you could argue that the vaccine could both trigger and prevent disease.

Now, if that's true, it would be interesting, then, to follow these children up through the first two years of life post-vaccination, a time when intussusception most commonly occurs, to see whether there is a definable increase in attributable risk. If there's not, then obviously the numbers that we're looking at would change dramatically.

So I would say that to conclude this part, the data needed to have, I think -- what we need to have, which is a discussion to the effect that I would ask for the following: one is final data on the attributable risk of intussusception from Rotashield vaccine; in addition, I think rates of severe adverse events from natural rotavirus infection, including severe adverse events other than death; and then finally, a determination of whether the Rotashield vaccine prevented intussusception, I think more accurately in

the first two years after vaccination. And hopefully, those data will be available to us soon.

The second issue is rotavirus disease in developing countries. Rotavirus, as you know, is responsible for about 660,000 to 800,000 deaths per year in development countries. Therefore, every day approximately 2,000 children die from rotavirus disease, which is more than one child per minute. The risk-benefit ratio for rotavirus vaccine in developing countries will no doubt be very different than that in developed countries.

Just to refresh your memories to what we said in our draft statement, we've shown that here. "The worldwide burden of rotavirus disease remains substantial, thus the ACIP's decision may not be applicable to other settings." Where the burden of disease is substantially higher and where the risks and benefits of rotavirus vaccination could be different, we certainly considered our obligation, but the fact of the matter is is that our principle charge is to -- is to recognize and deal with the health of children in the United States, but there is no doubt about the fact that a recommendation that we make for children in the United States have an impact on use of vaccines in developing countries.

So the fact is that Rotashield vaccine will not be used in developing countries if it's not used in developed countries. Therefore, the vaccine that's likely to prevent rotavirus disease and deaths in developing countries is not available. This technology is, unfortunately, sitting on a shelf. And I guess I would ask us, "Is there any way that this could have been avoided?" I'm going to make three probably somewhat naive suggestions as to how I think this could be avoided potentially in the future.

The first is I think it's of value to encourage vaccine makers to do large safety and efficacy trials in developing countries prior to licensure. With these data, developing countries can make an informed choice about the risk and benefits of a vaccine in their country instead of extrapolating data from developed countries.

Second is I think it would be of value to encourage incentives for vaccine makers to manufacture vaccine for developing countries, even if the vaccine is not recommended for us in the U.S., hopefully with the strength of the data that I mentioned in the previous slide. And one can consider sources of funding for this from, for example, the United Nations or, as just

was presented to us, GAVI.

And lastly, to encourage incentives for vaccine makers to assist in vaccine manufacture locally. I think especially one needs to consider the development of less expensive technology, for example, cell lines or substrains that are able to produce a maximum number of vaccine doses per unit volume, and in addition, perhaps a consideration as we would have here, a four-bound or quadra-bound vaccine, a vaccine which would contain one or two serotypes that would be most likely to effect the disease locally.

So I would conclude by saying that I think there is a need for the ACIP to discuss risks and benefits of Rotashield vaccine when final data are available and that there is -- I think we should use our influence to encourage strategies to enable rotavirus vaccines to be available for use in developing countries, even if the vaccine is not recommended for use in this country. Thanks.

DR. MODLIN: Thanks, Paul. Did you want to entertain --

DR. OFFIT: I would say probably the best thing is to have Bob present --

DR. MODLIN: Fine.

DR. OFFIT: -- and then we can all do it.

DR. MODLIN: Sounds good.

DR. KRAMARZ: I'm going to talk -- I'm going to talk about three issues from our analysis of rotavirus vaccination and intussusception.

The first is the possible role of wild rotavirus in causing intussusception and this will support the biologic possibility of the vaccine causing the same, and so if it is true, then the vaccine not only would not only cause but also to some extent prevent intussusception disease. And I'm going to use the approach of Dr. Parashar, who observed that diarrheal diseases approximate quite well wild rotavirus infections.

The second issue that I'm going to discuss is the status of the managed care organizations follow-up study to address the so-called triggering hypothesis that says that the vaccine may only trigger intussusception in children who are disposed to it. And if this is true, then we should see in the long-run compensatory decrease in the risk of intussusception. And the third issue that I'm going to talk about is attributable risk. There is some confusion about the numbers here, and so there will be a separate meeting

devoted to this issue, but I'm going to briefly show you what we have now.

As you remember from yesterday, the Vaccine Safety Datalink is a collaborative project between CDC and four large HMO's on the west coast of the United States. If we use this database and the ICD-9 codes for diarrheal diseases that approximate wild rotavirus infection, we use hospitalizations and emergency department visits databases of the HMO's. But here is the result.

On this graph, this graph show season of distribution of diarrheal diseases events in separate sites. On the "Y" axis, you see the rate of diarrheal diseases, hospitalizations of emergency room visits, expressed as cases per thousand child years of observation. And this goes from south to north, from southern California through northern California, north to Portland and to Oregon and Seattle, Washington. You can see that there is a distinct peak of diarrheal diseases events from between December and February, March, and then the peak moves from December towards February, moving from south to north, which is quite consistent with what we know about the wild rotavirus infection epidemiology.

On the next slide, I'm going to superimpose these

graphs into intussusception. We used the Vaccine Safety Datalink on six years of observation and we found 164 cases by automatic search of history using the ICD-9 for intussusception during the first year of life and then we confirmed 131 cases of this 164 by medical record review.

Here, you can see the graph with both graphs. The yellow graph is -- shows the rates of diarrheal diseases events. The left screen shows the extent. And then the blue line shows the intussusception rate with the values are shown on the right, the "Y" axis. So you can see that the peaks of both the virus don't coincide. But I'm going to show you another slide where I have it all on one graph on the four sites merged. Intussusception is a rare event, so with all four sites, we have more stable rates. So, again, the peaks don't coincide. But this is just ecologic analysis and we are going to have -- We have another analysis in progress, which is an individual analysis where we did the same as what we did for rotavirus vaccine, but instead of having vaccination as an exposure. We used diarrheal diseases events as an exposure and we are going to compute rates of intussusception in relation to the event, which is

diarrhea.

Now, I'm going to talk for awhile about the second issue about -- to update you on the status of the follow-up analysis of the managed care organizations study of rotavirus vaccine and intussusception.

The first stage of the study, the observation period ended on July 16, '99, and we found this increased risk shortly after vaccination. But to address the triggering hypothesis, whether this is a compensatory decrease later on, we were able to follow one site, one of the bigger sites of the study, which is Northern California Kaiser, until the end of '99. It was of vaccinated children with more than 12,000 participants but contributed 20 percent of observation -- total observation time to the analysis. One more case was found after July '99.

And in unvaccinated children, which contributed most of the observation of the analysis, also one additional case was found beyond July '99. And by statistical methods, there was no significant decrease -- no significant difference between the rates of intussusception in both cohorts in the follow-up period. So we didn't observe this compensatory decrease. There was no difference.

However, these are the results from just one study site. It's a bigger study site. But we will have the results from -- hopefully from all of them, all ten sites that participated in phase one, interested in participating in the follow-up analysis. And the principal investigator suggested a 12 months follow-up instead of six months to be able to fully address both triggering hypotheses and the possible role of wild rotavirus in causing intussusception.

However, even if we stop observation, which we plan to do on July 16, 2000, there is almost a processing delay of the data, the claims data, arriving at the HMO's and we expect to be able to do the computerized analysis at the earliest in October, 2000. We will use similar methods than in the first -- I mean, the first phase of the study. We'll do first the computerized data analysis, but we'll have to do, also, chart abstractions and the analysis of chart-abstracted data, because in the first phase of the study, the validation rate was not very great. It was 61 percent. But we will (inaudible) search as a tool to find intussusception cases, because we didn't use anything in the first phase of the study. All the cases were found by computerized diagnostic search.

So, in summary, Vaccine Safety Datalink data don't confirm the association between wild rotavirus and intussusception. However, it's an ecologic analysis and we will -- we hope to have individual-level analysis results. And the follow-up data today don't support the triggering hypothesis, but again, we will have more complete results from all the study sites.

Now I'm going to spend some time explaining the issues of attributable risk. This is -- As you remember, this is the slide that I had shown in October '99, where we have the computerized data analysis from the managed care organization study hoping to search on rotavirus vaccines. And we have -- At that time, we have nine cases within the three weeks after vaccination. Here are the rates of intussusception in particular risk windows expressed per 100,000 to the person observation. This is the background rate that we used at that time that we computed, and here are the relative risks adjusted for age.

So to compute attributable risk, we used this equation. We have two variables here, the relative risk from this column, and number of cases for each (inaudible) from this column. Because relative risk is just a division of the rate in each (inaudible) by the background rate,

this number depends strongly on the background rate search. So at that time, last year, we had one case of more than 7,000 vaccinated children, one excess case in addition to background.

Now, on this side, you can see what we have now, the confirmed case. We had six cases in a three weeks' window after vaccination. In the background rate after discovering some cases as known cases, dropped to 25 per 100,000 persons observation. The relative risks remain quite similar, but this change in the number of cases in each stratus and especially changing the background rate changed the result of this equation and now we have about one case per 11,000-plus children.

The take-home message from this is that this computations are strongly dependent on the background rate.

Thank you.

DR. MODLIN: I'd like to open it for just a few minutes for questions, either Dr. Offit or Dr. Kramarz. Comments? Chinh?

DR. LE: I'm glad the issue of rotavirus vaccine is back on the -- on the table. My question is, even if ACIP were to reconsider the cost analysis and so on and would make another attempt to make recommendations, I

remember one day before we made the recommendation to withdraw the use of the vaccine, the manufacturer has already withdrawn the vaccine from the market. And I just wonder whether there is any -- in the atmosphere of the medical/legal issues with vaccine liability, there's any chance in the U.S. that Rotashield will come back, even if we make a recommendation on cost analysis.

DR. MODLIN: I'm not sure you're asking the right person, Chinh, but Peter -- If Peter is here, would he be willing to take a stab at that? Peter may have seen this on the agenda and caught an early plane. Anyone else from Wyeth that would like to respond? Or Bill? Please, of course.

DR. EGAN: Yeah, although not from Wyeth.

DR. MODLIN: Okay.

DR. EGAN: Yeah, I should mention that the vaccine is still licensed in the U.S. The license was neither suspended nor revoked, nor did Wyeth, you know, request that the license be recalled. There has been no distribution of vaccine, however. So the -- So I hope that answers your question, Dr. Le.

DR. MODLIN: Thanks. Ben?

DR. SCHWARTZ: I have a question for Paul.

You were talking about the risks and the benefits of vaccination, and in discussing that issue, you compared numbers of cases, numbers of deaths. You did this all very scientifically. I think, though, that what we're facing is a public health issue, not just a scientific issue. And we've spent a lot of time at this meeting and at previous meetings talking about confidence in the vaccination program. In fact, there was a story on NPR this morning about the recommendations for pneumococcal conjugate vaccine, and rather than focusing on what a great benefit this vaccine will be to public health, the story began with an interview of the -- of a mother of a child who had intussusception following rotavirus vaccine and then followed with an interview of a physician who administered rotavirus vaccine who admitted that he was going to be hesitant now about implementing new vaccines.

My question is, when you talk about the risks and the benefits of a vaccine, and when you talk about the decisions of ACIP and of the Public Health Service, how do you weigh in public confidence in the vaccination program and the impact a decision may have on the future and on new vaccines that may be introduced?

DR. OFFIT: Now, I think our task is actually a fairly

simple one, which is to make the recommendation that we think does the most good for children in this country. I mean, when I was a house officer, I saw an eight-month-old child come into our hospital who had had diarrhea and vomiting and fever for one day and had followed the physician's advice of trying to take, you know, one teaspoon, you know, frequently of fluid. It was good advice, but the child was severely dehydrated and despite, you know, Cloysis (phonetic) as an attempt to hydrate the child, the child died. And similarly, we had a child admitted to our ICU about two months ago who required press support. And so who represents those children? I think we represent those children. And the question is -- The fact is that 20 to 40 children die from rotavirus infection a year, that a tremendous number of children are hospitalized every year with rotavirus, and I just think -- I'm not saying that our decision was the wrong one. I don't think it necessarily was the wrong one, I just think we need final data. But I do think that we need to educate the public about what is the impact of this disease so that they can understand what the disease is. And if we think the vaccine is important, then part and parcel of that is letting people know just what it is that that

disease is doing out there to best further their health.

DR. MODLIN: Dr. Abramson?

DR. ABRAMSON: Yeah. Paul, I would take a somewhat different tact and then argue that whether the incidence of intussusception is one in 5,000 or one in 10,000 due to the vaccine, we need a safer vaccine. And even if the incidence of real disease in intussusception is one in 5,000, one in 10,000, the better vaccine, the vaccine we need, is a vaccine that will decrease that incidence also.

So from my standpoint, this was a first -- whatever you want to call it -- first goal, and I realize there were other vaccines that have been tried to be developed, but what we really need is a safer vaccine.

DR. OFFIT: I mean, if I could respond to that briefly. I think that vaccine -- Maybe there will be a safer vaccine and maybe there won't. I think what we have to define with this vaccine is whether or not -- exactly what is its level of safety. And safety -- The definition of safety is that its benefits have to clearly and definitively outweigh its risks. And that's why I think the two-year follow-up study that will allow us to look at -- to answer the question,

"Were those million children that were vaccinated, when one looks at their risk of intussusception, was it statistically -- was it higher, clearly, definably higher than the group that didn't get vaccinated?" Once we have that information, I think then we can really answer the question as to how safe this vaccine is.

The other vaccines that are being developed are several years away and during that time, there are going to be, you know, 20 to 40 children to die of this disease every year. So I agree with you. I think we need to make the safest vaccine possible, ultimately. But, you know, that's -- that's an unknown.

DR. MODLIN: Dr. Zimmerman?

DR. ZIMMERMAN: These questions are not easy, and I don't claim to have the answer, but I think that there is an issue of public confidence. I think there is a shift that's occurring in the way society thinks about truth into much more of a relativistic view of truth than perhaps I hold myself, particularly as an epidemiologist schooled in western civilization, western thought. And as we saw with polio, there became a sense of shared decision-making, and I think with some vaccines that have a risk and a benefit that

there's going to have to be a consideration of beginning to make shared decisions. As much as I may like to make recommendations that are hard, we may have to move into more shared decision-making. And so that adds another dimension to our thoughts.

DR. MODLIN: Chinh?

DR. LE: I'm not a vaccine researcher into vaccine design and so on but, you know, we should also remember that the vaccine was licensed to ten to the fifth dose and there are studies which ten to the fourth dose seemed to be just as -- just as good, and this is a lot difference in virus that goes to bowel. Perhaps Roger and others can see whether one could provide the study for small dose and get the clinical efficacy that reduce severe disease and get away with higher side effects, intussusception, for example. I mean, this vaccine could still be revived in a different form.

DR. MODLIN: So, Roger, the question is if we give -- ten to the fourth, are we going to have less intussusception?

UNIDENTIFIED SPEAKER: This might be a reason- -- Is this on? -- might have been a reasonable vaccine with two changes that might have changed this risk considerably. One was the dosing issue, and I think

there's been some concern that much of what goes into that vaccine is killed antigen as opposed to a live virus, and there may be a bolus of -- a much larger bolus of killed antigen. The other is the age. This was opened up to children two to six months of age. We have precious little information on children from six to eight weeks where the attributable risk and the background rates of intussusception are much lower. However, to do any further testing of this vaccine would require studies that will be in excess of 50,000 to 100,000 people, and knowing that the vaccine has this problem to begin with, even if we could reduce the risk five-fold by giving it at a younger age or at a lower dose, would still make this a very expensive gamble for someone to pursue.

So we may well have a vaccine that would have much lower risk, but we don't have the ability or the financial wherewithal or the confidence to test it at either of those different strategies, lower dose or earlier time. Especially in developing countries, the earlier time is critical, because we have some preliminary data that newborn immunization can be effective, and that's a time when no intussusception occurs, generally the incidences are very, very low.

DR. MODLIN: Thanks, Roger.

I think -- Even though I hesitate to bring this to a close, I think we must because of the time. I think -- I want to thank Paul for bringing this before the Committee and make the observation that he's brought up some very important points that I think it's going to be important for us to keep before the Committee in the future and we certainly will intend to do so. And it'll be also nice to see the information from Dr. Chen's group develop and review those at some very early future meeting.

Let's break for lunch and let's try to --

DR. CHEN: John?

DR. MODLIN: Yes? I'm sorry.

DR. CHEN: If you don't mind, let me just make a quick personal note to Kramarz --

DR. MODLIN: Everybody hold on for just a second, please. Bob?

DR. CHEN: Thank you. Kramarz is getting on the plane tomorrow to return to his native Poland to head up their -- be the Deputy Director of their sanitary and epi system, and I want to acknowledge all the help he's provided NIP during his three years in the United States and wish him the best.

(APPLAUSE)

DR. MODLIN: Thanks, Bob.

Let's return at 1:45.

(LUNCH RECESS FROM 12:54 P.M. TO 1:53 P.M.)

DR. MODLIN: While people are taking their seats, I would like to mention the fact that even though Dr. Chinh Le will be leaving the Committee at the end of this meeting, his influence will live on. Chinh is the one who has raised our consciousness about the possibility that some children can be immunized possibly with a simpler immunization, with smaller numbers of doses. We had our first meeting last night of the work group to begin to explore this and the work group will continue its work and at some point in the next year report to the Committee on looking at least the possibility, the chances, of reducing a number of doses in the routine childhood immunization schedule for some antigens.

Let's go on with the agenda as planned. And we have Dr. Weniger back who's going to give us -- make sure I get this right -- update on the status of high-speed needle jet -- needle-free jet injectors for mass immunization. Bruce?

DR. WENIGER: Thank you for this opportunity to come

back again on an entirely different subject from this morning. I'd like to brief you this afternoon on the current status of high-speed needle-free vaccine devices, often known as jet injectors or jet guns. But that latter term, "gun," I think is inadvisable. These -- Some of these older devices are frightening enough for children when they see them that we don't need to use that term. And then I'd like to explore the implications for whether or not we are ready to deal with a mass immunization campaign for either pandemic influenza or a bioterrorism incident.

I'll cover first some history of their use and their capabilities and how we've relied on them in the past for many major campaigns, and then I'll deal with the key issue regarding their safety in potentially transmitting blood-borne pathogens between consecutive vaccinees. And in that respect, we'll cover some work in progress in trying to develop a reliable, valid, and sensitive method to evaluate their safety. Then I'll briefly review their recall by the military, U.S. military, in 1997 and the evolving policy of WHO toward them since that time. And next, I'll present some efforts to develop substitute devices of inherently safe design using disposable cartridges. And then,

finally, I will present a simple mathematical model that reveals the additional challenges I think we would face without such high-speed devices in trying to vaccinate a large segment of the population within a short period of time. And then I'll present some conclusions and recommendations on how we might try to overcome this problem.

This is the Ped-O-Jet type device, trademarked brand name, which has been by far the most widely tested and used model since such devices were first developed in the early 1950's under military contract. It's capable of vaccinating at rates of up to 600 and even 1,000 patients per hour, literally as fast as one can press the foot pedal to fill the chamber and pull the trigger. Vaccine is drawn by suction from 50-dose vials, or larger if you can get any, through tubes and check valves into its internal chamber here. And then a heavy metal spring, which is cocked by hydraulic pressure here, is released to force vaccine at high pressure through a small orifice in the nozzle, literally drilling its way without a needle into the patient's subcutaneous or intramuscular tissues.

And there are literally tens of thousands of these devices in the basements of national and local health

departments in the United States and ministries of health around the world. And I thought I might want to just demonstrate to you the speed capacity of one such device from CDC's warehouse. There's a -- The foot pedal comes in a box down here. One presses on the pedal and then fires. And as fast as you can press again, you can vaccinate the next patient, the next patient, and the next patient, if you had them all in line as the military likes to do.

In some mass campaigns, I think they actually ask the patient to do the pressing so the health worker doesn't get exhausted from all that pushing on the pedal.

Now, in the 1960's and 1970's, the world relied on these devices to deliver literally hundreds of millions of doses of both measles vaccine and smallpox vaccine and in simultaneous campaigns to control measles and to eradicate smallpox in west and central Africa.

Sometimes, as shown here, separate devices were used to deliver the two vaccines into each arm and at other times, a combined measles-smallpox vaccine was delivered by one device.

Here, the U.S. Surgeon General Stewart, in 1968, administered the 25 millionth dose of smallpox vaccine in west and central Africa, here in Ghana, actually.

And in the five years between 1967 and 1972, a total of 153 million doses of smallpox vaccine were administered in west and central Africa, most of them by jet injector.

In Brazil and other South American countries, since the 1960's, the device has played an important role in delivering, again, literally hundreds of millions of doses of vaccine at high rates of speed for smallpox eradication, as shown here, and for efforts to control yellow fever, meningococcal disease, tetanus, diphtheria, and measles.

In its 1987 measles campaign not shown by this graph, the Sao Paulo state in Brazil alone delivered five million doses of measles vaccine by jet injector out of a total of 8.5 million doses during that year, achieving 95 percent coverage for measles protection in that state.

And in the early 1990's, Brazil bought 5,000 Ped-O-Jet devices and used them to vaccinate 48 million children from nine months of age to 14 years of age in their successful "Catch-up and Keep-up" campaigns for measles control, as illustrated here by how remarkably they have reduced measles incidents in that country in South America. And even here in the U.S., we've relied on

their speed of use in mass campaigns with injectable polio vaccine in the 1950's, too early to appear on this graph of biologic surveillance which didn't start until 1962, to vaccinate against polio with the injectable product.

Notice here this skyscraper in 1976 and this sort of light blue vaccine here, which is influenza vaccine. This was the swine flu vaccine in which 85 million doses were distributed in the U.S. that year. And although I have had trouble finding some exact numbers for how many of those 85 million doses were delivered by jet gun and by needle and syringe, anecdotally, a substantial proportion of them were delivered by these Ped-O-Jets. And perhaps there's some old-timers in the audience here who can provide a little more insight into their -- the campaigns for swine flu back in 1976.

Now I'd like to describe the increasing concern over the last decade and a half for the safety of these multiple-use nozzle devices or devices defined as those which reuse the same fluid pathway between patients.

Fifteen years ago, in 1985, another high-speed device, the Med-E-Jet shown here, was implicated in an outbreak of hepatitis B in a weight-loss clinic in California. The device had been used to administer human

gonadotropin hormone injections to patients trying to lose weight at one branch of a weight-loss clinic in Long Beach, California. And over the period of the epidemic, several dozen confirmed cases of hepatitis B were identified and were linked epidemiologically to receipt of injections from the device. Now, there was no evidence of any problems in other branches of the same weight-loss clinic throughout California that were using the same type of device to deliver the hormone.
Now I'd like to review some of the safety testing that took place at that time in the 1980's and then subsequently in the 1990's in more recent work.
Soon after the California outbreak, Walter Bond in CDC's Hospital Infections Program studied and compared both devices, the one involved with the epidemic in Long Beach, the Med-E-Jet, and compared it to the Ped-O-Jet model that you just saw demonstrated a few minutes ago. And you may notice that they have somewhat different designs. There's sort of an internal sleeve on the Med-E-Jet here where it's a solid front end here with a sapphire orifice in the center.
That group injected hepatitis B surface- antigen-positive chimpanzees with the devices and then looked

at subsequent injections from the injector put into sample vials -- In other words, they literally shot the next dose into a sample vial -- representing the next person in line who might have received an injection during an immunization campaign. But in this in vivo model, they were unable to detect any hepatitis B surface antigen in any of those subsequent ejectates. Now, of course their technology at that time was -- for detection of very small quantities of anything didn't have the benefit of TCR and other techniques. And because only perhaps a very rare injection would transmit from one patient to another, more than the samples they were prepared to do, they also did some in vitro studies in which they artificially contaminated the nozzles of these devices with fluid containing hepatitis B surface antigen and then they again injected into sample vials and looked for hepatitis B surface antigens. Sometimes they swabbed the nozzle as the manufacturers recommend between patients to remove any blood or splash-back and sometimes they didn't, representing noncompliant use as it's called by negligent health workers.

And as you can see here, regardless of whether swabbing or not swabbing was done, for both devices, there were

detectable hepatitis B in a proportion of the next ejectates coming from the device as well as the nozzles' exteriors contained detectable hepatitis B, although not the interior for the Ped-O-Jet, nor the nozzle for the Ped-O-Jet. And you can also see that the Med-E-Jet did have substantially higher rates of these detections compared to the Ped-O-Jet.

Now, five years later, in Brazil, Glacus de Souza Brito of the Ministry of Health of Sao Paulo State and colleagues studied the safety of their Ped-O-Jets during actual routine vaccination programs in humans. After an injection of a patient, the next dose of vaccine was squirted into a sample vial. And using at that time inexpensive but rather insensitive techniques of the urine dip stick for doing a routine urinalysis, they were able to detect blood, occult blood, in roughly one percent of all the next injections after these three studies. And clearly, that level of sensitivity of a urine dip stick is many-fold higher than what would represent an infectious dose of hepatitis B. And let's talk about that for a second -- And we'll talk about that in a second.

Later on in the 1990's, with WHO's support, the Public Health Laboratory Service of the United Kingdom

developed a new protocol for evaluating the safety of these devices, an animal -- another animal model, and similar to what Walter Bond did with chimpanzees and Glacus did with humans, they collected the next ejectate after an in vivo injection of the experimental animal, in this case, a calf. And then they used a direct ELISA antibody assay to detect bovine serum albumin as a marker for blood, and they constructed calibration curves from known dilutions of that animal's blood in order to report a -- the concentrations found.

And the Public Health Laboratory Service basically tested four different devices. I've just labeled them A, B, C, D in here. And we borrowed this methodology and did it with the University of Florida on one of the devices in both calves and pigs. And the University of Florida tested another device as well on cows and pigs. Then the Brazilians went back and they tested it on humans again, but this time, they sterilized the device between the subjects who were hepatitis B carriers. And let me digress for a bit on how we came up with the desired level of sensitivity of this assay and the presumed criteria for a positive test. And it's entirely based on Walter Bond's observation that a

hepatitis B carrier chimpanzee has 100 million chimpanzee infectious doses per milliliter of blood and just by mathematics, this converts to an estimated infectious dose volume of ten pikoliters of blood, which is a very, very small quantity. And hepatitis B is probably a good model to use because it's one of our most contagious blood-borne infections, roughly 100 times as infectious as HIV judging from needle-stick accident surveillance.

Now, in Florida, we wanted to bridge the calf model in London to an experimental animal that we felt would be easier to handle than calves and whose skin is reportedly closer to human skin, and that's pigs, but we were wrong on both scores. It takes actually two burly veterinarians to give these 60-pound pigs a bath and to clean the injection site before the study. And then we also noticed a particular resistance to injection by the tough layer in pigs of this age in about one third to half the injections. Some of the injectate phosphate-buffered saline leaked out and dripped down the skin no matter how tightly the skin was pressed with the device and even though the bruise marks that we -- that appeared within a few minutes indicated that some of the dose did actually get into

the animal.

So we have concluded, for future studies, much younger pigs should be used. And this observation was later confirmed by European veterinarians with experience administering the jet injectors to animals.

So let me summarize these studies, and some of the results are proprietary and they've not yet been published. So I'll just give you a real overview on them.

A total of five different devices have been studied in three sites on three animal models, with and without swabbing the heads between the injections. And essentially, one of the results we learned was that the assay is not very sensitive and it doesn't really behave at the

low -- at the desired concentration levels that we're looking at, the 20 pikoliters per ml. Also, they -- it has a problem with some kind of contamination occurring occasionally when blinded positive control -- I'm sorry -- when there were false positives detected, perhaps from contamination in the animal pen or in the lab.

But another factor is that it's under-reading the true concentrations based on blinded positive controls put into the assay. But nevertheless, so we can assume

whatever the results were, the actual concentrations were probably higher.

In all cases, for all the devices tested, at least one of the injections occurring was above a reasonable cutoff or unclean in series of up to 100 injections. And I guess the most important issue is the uncertainty over what is the criteria for safety, what would be the criteria for safety of these devices. Would FDA require that 100 consecutive injections be clean or zero-contaminated injections after 500 tests or after 1,000 tests? It's very hard to prove a negative. And the FDA has not yet been presented with a manufacturer trying to newly license a device today, given all we know about them. So that's a major uncertainty in the field.

Now, as a result of some of these studies, as these studies were leaking out, the results were leaking out, the manufacturer of the Ped-O-Jet, which was the supplier of both devices and spare parts and maintenance to the U.S. military became alarmed and concerned about liability issues. And as a result, in late 1997, they notified the Department of Defense of their intention to withdraw from the market. And DOD immediately recalled them from use throughout the

military system, where they had been in use for many years. And they basically said it was a cautionary measure, noting the absence of any confirmed cases of disease transmission over 35 years of military use by them. And as a subsequent consequence of that, the manufacturers of the large-dose, 50-dose vials of meningococcal polysaccharide vaccine, Td vaccine, and yellow fever vaccine stopped making these large vaccine vial formulations.

Then in April 1998, the Armed Forces Epidemiology Board, which serves as an advisory body to the military similar to what ACIP is to CDC, looked at the issue and recommended that the DOD put effort, money, resources into developing a new, safe high-speed device. And a few months later, the Navy Bureau of Medicine actually approved a slow-speed needle-free device for use in their immunization programs, but it doesn't solve the speed problem.

Now, in the interest of time, I won't read these quotes of the current WHO policy, but at the moment, based on this 1998 statement, WHO no longer count, condones, or recommends the use of these high-speed reusable-nozzle devices for immunization until they can be shown to be safe. And I've already mentioned the challenges in

doing that. The CDC policy is based on ACIP's recommendation on general immunization in 1994, and it takes a more balanced view that the small theoretical risks of blood-borne disease transmission must be balanced against their advantages in epidemic situations and leaves it to the health authorities to make that judgment call when you're facing a serious epidemic and you need to vaccinate people quickly.

Now, what are some of the ways out of this dilemma in finding effective substitutes for these devices that are now in limbo? There is a new generation of needle-free injectors that began to appear in the 1990's utilizing disposable cartridges, one -- use-once-only syringes. This Biojector model, for example, is one that the military has begun to use. But it still requires the individual to manually fill the syringe or cartridge in the traditional way, which it basically makes it as slow as a needle and syringe.

This one is powered by CO_2 cartridges, although the military has rigged them up to permanent tubing to huge CO_2 tanks. That avoids the need to open the device and replace the cartridge every 10 or 15 injections. And this is the only current new-generation device that's labeled for both intramuscular or subcutaneous

injection. And that difference is determined by the syringe that you choose, which has a different orifice based on your -- the intended compartment you would like to deliver it to.

And I'd like to just demonstrate quickly how it works. The syringe comes in a standard packet like a regular syringe. You basically fill it like a regular syringe, either with a vial adapter without a needle or put a needle on the end of it. You insert it into the end of the device. You can choose -- choose the right end; twist it; hold it firmly against the patient; and then vaccinate; and then remove the device and replace it with the next one for the next patient.

This is another FDA-cleared device with disposable cartridges that's now on the U.S. market, the Injex. And it uses an internal metal spring which is compressed with a separate cocking device. But this one is only powered for and labeled for subcutaneous injections. And let me demonstrate this one here. I've prefilled it already. Put it against the patient, hold the skin firmly, and then inject.

Now, for the last few years, CDC has been applying available but rather limited research and development funds on two parallel tracks. One track is to try to

rescue the existing Ped-O-Jet type devices from their limbo status by refining the animal safety testing I described and seeing if re-engineering their front ends with disposable parts would solve the problem. And to date, we haven't seen any clear evidence of success, although we've able to reduce the frequency of contaminated injections by doing so, but not down to zero, as I mentioned early.

But research limitations and competing priorities for these funds makes this a rather slow track. A higher priority track is to support the development of high-speed disposable cartridge devices which don't yet exist that would be of inherently safe design. And in this fiscal year, we expect to award at least two contracts for such work. One through SBIR program and one through an ad hoc request for proposals, which is now on the street with deadline of June 29th, I believe.

And what we envision is some kind of a machine gun belt or magazine that would automatically feed the cartridges into the chamber and then expel them after each injection, hopefully as fast as you could use the Ped-O-Jet. But the amounts of money available for this program are unlikely to carry through a device to

successful commercialization at any kind of an expedited pace.

Now, two key challenges remain in this area. And one is to avoid the delay and burden of having the end user manually fill the cartridge. Even if the device is quick, it still takes a lot of time to manually fill these proprietary cartridges. A more elegant solution would be to get the vaccine manufacturers to prefill their vaccine into cartridges at the factory, but there are unfortunately many disincentives for the manufacturers to do this.

One is the lack of a universal standard for cartridge size and interface. Another is the need for prolonged and expensive stability studies in the likely kinds of plastic, usually polypropylene materials that these cartridges would need to be made of. And another disincentive are really questions over what is the size of the market, can they recoup their investment, and how much would UNICEF buy for mass campaigns, and would they buy any at all or put out for tenders this type of a product. Another issue that we face is the fact that the next major eradication campaign will be measles, which requires a mixing step to do that, and we'll get back to that in a minute.

Now, actually, Pasteur Merieux Connaught was well on its way to solving the prefilling challenge a few years ago when they invented this Imule cartridge shown here and prefilled it with several vaccines, hepatitis A, typhoid, tetanus toxoid, DTP_w, and influenza vaccine. And this is their Influenza Vaci-Grip product, and they also developed a jet injector to shoot the device -- to shoot the cartridge, and here's a closeup of the prefilled cartridge.

Basically, the cartridge is the vial that arrives from the vaccine manufacturer and, as you can see, it's actually even smaller than the typical type one vial that single-dose vaccines come in. So it's quite efficient in terms of saving refrigerator space. And instead of being closed on the bottom like a vial, it has a -- the plunger seal or optirator at the bottom, the vaccine, and then at the top, once you take off the protective cartridges, the orifice opens. But, alas, business considerations have led PMC, or now Aventis Pasteur, to abandon this project and we feel that's very unfortunate and we hope that someone else in the world might pick up this idea where they left off.

Regarding the auto-reconstitution issue for vaccines like measles, it seems a solution for jet injectors

would not require real rocket science. For example, here's an existing German product. Actually, they make the syringe and try to convince vaccine manufacturers to fill it. But it's a manual syringe that's prefilled with a liapolozied (phonetic) pellet over here, illustrated over here, and here in closeup, as well as the -- the diluent also further back in the syringe behind a separator seal. And as the plunger moves forward, the liquid diluent reaches this bypass section in the wall of the syringe and allows the liquid to pass around the seal and get into the front part of the chamber, where the pellet is located. And then it's shaken for a second and then the injection proceeds with the dissolved vaccine. So we feel this type of technology could be developed for jet-injector cartridges.

And finally, I wanted to talk about the main message today, which is that without these high-speed vaccination devices, we may not be prepared to deliver vaccines quickly enough in the case of a pandemic threat or bioterrorism. And let me illustrate this theory with a simple mathematical model of manpower, nurse power.

First, let's compare how many doses a vaccinator might

be able to deliver with either conventional needle and syringe or a jet injector. Several time-motion studies have been. Chuck Lebaron, et al, at CDC, Paul Copeland at Merck, in which they've estimated that the average time it takes to deliver an injection in a clinic is about one minute and a half, or 90 seconds. And what I've done is arbitrarily divide that time into half of it for patient flow, paper work, band-aids, those kind of things, and the other half of that minute and a half on the actual act of filling the syringe from the vial and injecting the patient. And of course, the paperwork side, the logistic side would be the same between the two systems, but that I assume the jet injector could do in five seconds what it would take 45 seconds with a needle and a syringe, as was demonstrated earlier.

Now, given that, if we can calculate that an RN can vaccinate 40 patients per hour versus 72 per hour with a jet injector, and if we assume in an epidemic crisis we could get someone to work six hours a day doing nothing but vaccinating, that would be 240 vaccinations a day with needle and syringe versus 432 with jet injector. And if we can get this RN to work five and a half days a week, it is an epidemic, of course, and

lives are at stake, that would be 1320 needle injections per nurse versus 2376 with the jet injector. Now, we can stockpile vaccine and we can stockpile syringes and other supplies, but one thing we cannot stockpile is manpower. So let's consider where we will beg, borrow, and how many we can draft into an emergency vaccination campaign.

So just looking at the U.S. population, in 1996, there was about 265 million and at that time, the Bureau of Health Professions in HHS did an estimate of the RN population of the U.S. It's about 2.5 million, with only about 2.1 of the million actually employed in the field. So I've taken an arbitrary 2.3 million as the actual total number of nurses in the United States that might be used, and assume that you would have to be a -- an RN or a qualified medical practitioner to deliver a vaccine. And then I took a hypothetical city population of, say, a city of three million, which happens to be Atlanta's population, and assume the same ratio of nurses in the population, that we would have 26,000 nurses in Atlanta.

And in the event of a pandemic or bioterrorism attack, how many people could we divert from their regular jobs, taking care of the victims of this pandemic in

clinics and hospitals to work on a vaccination campaign? If we assume that we can recruit one half of one percent of all these RN's, in the city of Atlanta, it might be 130 nurses. In the U.S. as a whole, 11,500 nurses. It would take, using needle and syringes, about 17 and a half weeks to vaccinate every person in the population with one dose of vaccine and a little more than half of that with jet injectors.

Obviously, if we could recruit more, the times would be reduced. If we can get five percent of all the nurses recruited for this mass campaign, it would only take 1.7 weeks versus one week. But I think we have to consider that there are going to be many competing demands on these health workers to do this, not only in their regular jobs, but taking care of sick family members as well. So I think we have to recognize that in such situations, we need to take as much advantage as we can of ways that we can speed up this process if one of these events, heaven help us, actually does occur.

So, in conclusion, the future is uncertain for classical jet injector devices with reusable fluid pathways. Can they be re-engineered and proven safe to satisfy the FDA? And second, as of the moment, there

exists no proven licensed device of unquestioned safety that's capable of the high speeds that we're talking about, 15, 20, 30 patients, perhaps, per minute for either pandemics or bioterrorism.

Also, the amounts of money that have been available to date have been relatively small, and so the recommendation is that we need to increase our attention to this phase of the response to these threats, we need to figure out ways to provide incentives to manufacturers to work on prefilling injector cartridges, perhaps by making more obvious the huge market demand that would be there, not only for pandemics, but also for measles eradication. We're going to be needing literally hundreds of millions of doses of measles vaccine delivered over the years ahead. And so I would hope that some of the resources now devoted towards planning for pandemics and measles eradication and bioterrorism can be used to fix this weak link in the chain of our preparedness.

Thank you.

DR. MODLIN: Thank you, Bruce.

Any comments or questions for Dr. Weniger? Dr. Jackson?

DR. JACKSON: Just a very quick comment. While in

service in the Vietnam situation, we had the opportunity of using the jet injectors on about 1,400, 1,500 men a morning. I didn't hear you say one problem that we did have from time to time and always seemingly in an officer of high rank, and that was the slipping of the gun on the skin, creating what could look like a knife wound. And it was rather interesting. It was someone who was passing out most of the time and it was usually an officer who would always get up and give us a hard time. You didn't mention that at all, but what's your experience there? Do you -- Have you -- What's the most recent?

DR. WENIGER: Well, I didn't go over it all because of time interest and the whole clinical efficacy and safety of these devices, but that's a known and reported complication and the recommendation is to firmly hold the patient's arm and fix the device, because if it is moved as the injections occurring, it can function as a knife and cause lacerations. So it needs to -- The arm needs to be fixed relative to the device with the vaccinator's other hand. But it's a relatively rare complication.

DR. MODLIN: Chinh?

DR. LE: Bruce, that was a very interesting talk. Just

want to know, what did you have in those vacc- -- in those syringes? Was that vaccinia or like anthrax four?

DR. WENIGER: Well, I have tested all these devices except the Ped-O-Jet, which is a little hard to handle, and I don't have the ability to sterilize. I've tested all these devices on myself with sterile saline and I've been rather surprised by how pain free they are. The most -- Most of the pain is just holding hard enough against your arm that you don't, you know, slip. But I think it's the nature of the drug that you're -- or the vaccine that you're delivering that does cause pain.

And in most of the studies, the good studies that have come out, the side effects, the reactogenicity, tends to be somewhat higher with needle-free devices than with needle and syringe, probably because they're leaving some off vaccine in the track through the skin and through the subcutaneous tissues and they're more irritating. So in general, I think that there is a higher rate of side effects, but it's tolerable for the most part. It's a reasonable tradeoff.

DR. SNIDER: But Bruce, what did you expose us to?

DR. WENIGER: Oh, what did I expose you to? Basically

the same water that's in your pitcher over there. For this device, for the Ped-O-Jet, I used this sterile saline.

DR. MODLIN: Bruce, how can the Committee be of help to you at this stage? We appreciate the update and the information --

DR. WENIGER: Well, I think basically moral support, and you know, there are huge amounts of money. I think they're spending $40 million to make smallpox vaccine. Smallpox is no longer -- You no longer need these devices for smallpox if you're going to use a bifurcated needle, which is much more efficient and as rapid as this. But if a new smallpox vaccine is made that does require injection, traditional injection, seems if we're spending $40 million or upwards to stockpile vaccines and huge amounts of money for bioterrorism that we ought to be diverting some of these resources into developing this new generation of devices. And to my knowledge, the military has not yet responded to the AFEB's recommendation that they put some R and D funds into this as well.

DR. MODLIN: Thanks. Chinh?

DR. LE: Bruce, I think another advantage of pursuing the research on that is actually for routine clinic

use, because now that OSHA recommend or mandate some of the safety devices -- safety needles, it's getting very, very expensive. It costs us $.60 more per syringes and if there is any device which is needle-free, I think that probably would be very, very well welcome.

DR. WENIGER: Yes, these new Occupational Health regulations that are going to basically make traditional unprotected needles unusable or not satisfying the regulations are leveling the playing field between the cost of these devices. I think currently the Biojector syringe, the disposable part, is about $.50 a pop and maybe that will come down with quantities, but -- So it's becoming a little bit more competitive with these fancy safety needles where the needle disappears or is automatically covered.

DR. MODLIN: Bill?

DR. EGAN: Bruce, you mentioned the -- about the possibility of transmitting blood or disease, you know, through the use of these injectors and gave a figure of about one of -- one in 100, one out of 100, and I was curious to know if you have any thoughts about what you consider would be an acceptable level.

DR. WENIGER: Well, I don't -- I wasn't implying that

the actual rate of disease transmission is one in 100. I think it's probably much -- much, much rarer, if it occurs at all. And these are all hypothetical concerns for the most part, except for that one epidemic in California with the device that had internal channels that probably held the contamination.

It's a tough call, because in the developing world, it's believed upwards of half of needle injections are unsafe. They're either unsterile, they're causing abscesses, toxic shock, and so forth. They're transmitting hepatitis B and HIV between patients now because of improper practices. So a needle-free system could ultimately solve that.

It's a tough call. I would say if you found zero out of 500 or zero out of 1,000, that would be reassuring, but look at what we had with Rotashield. I mean, one out of 11,000 problems caused us to withdraw the vaccine from the market. So it's a tough call that you're going to have to make if anyone tries to bring such a device to you today.

DR. MODLIN: Dr. Trump?

DR. TRUMP: Just one comment about the -- Your model used registered nurses as the population to be giving immunizations. In the military, we had routinely used

corpsmen, medics. One of the disadvantages of having lost the use of the jet injector is we no longer are training them in the mass immunization skills. That was at least through recruit training or through mass flu campaigns, was a way for having a population that was trained to use these devices. Obviously, without the device, we don't have the trained population either.

DR. MODLIN: Thanks. Let's -- Bruce, thanks very much. We sure do appreciate your --

DR. SNIDER: If I could just make one comment about the risk issue.

DR. MODLIN: Uh-huh (affirmative).

DR. SNIDER: I think it would be useful, Bill and Bruce, to look to the blood and blood products discussions around the -- what is acceptable risk for those products and consider how that's being done and what numbers people are using to determine what's acceptable risk for blood and blood products, because I think we wouldn't be in a very good position if we came up with some substantially different standard.

DR. EGAN: No, I think that's a very good model.

DR. MODLIN: Okay. Bruce, thank you.

DR. WENIGER: Thank you.

DR. MODLIN: Let's go on, and the next item on the agenda will be an update on the recent meeting that was hosted by the American Academy of Pediatrics in Chicago on vaccines and autism. And Neal, are you going to be leading off? And

with -- along with Dr. Frank Destefano.

There are the two of you that are on agenda and I'm not certain -- While Neal is coming to the podium, let me just mention that at the end of the day yesterday, the long discussion on thimerosal, one of the things that we neglected to do that was on the agenda was to spend a few minutes discussing future research needs for thimerosal. Let me take the prerogative of speaking for the entire committee and saying I think we all would strongly support future research in this area and do. It's absolutely critical and we would hope that we'll see the fruits of that research at future meetings, but I did want to add that to the record.

Neal?

DR. HALSEY: Thank you very much, John. I'm going to talk about a meeting that was held, a workshop, on the 12th and 13th of June in Chicago under the auspices of the American Academy of Pediatrics. The meeting was supported financially in part from the Centers for

Disease Control and Prevention. The title was "New Challenges in Childhood Immunization," which may be the first in a series of this type of review that the Academy will undertake.

The objective of the meeting was to review the available information on hypothesized associations between measles, mumps and rubella vaccine and inflammatory bowel disease and MMR and autism. The issue has arisen because of three hypotheses that have been generated primarily in the United Kingdom by investigators there: first, that measles virus can persist in the intestinal tract and possibly contribute to chronic inflammation; second, that concurrent exposure to more than one childhood viral infection can increase the risk and severity of autism; then third, that the use of MMR has resulted in an increase in autism.

The panel that is reviewing this has agreed to you to review the causal criteria that were alluded to in part yesterday in some of the discussions that we had. And these were first developed more than 30 years ago by Bradford Hill and they've been modified over the course of the 30 years several times and most recently reviewed by Ken Rothman. I'm not going to review all

of these here, but just to point out that -- because they're widely available to anybody who wants them -- but no one criteria is sufficient to establish a causal relationship and no one criteria is essential to the establishment of a causal relationship. And there are strengths and weaknesses about each one of these issues.

We had a series of presentations by various individuals and groups, starting with concerns of parents of autistic children, followed by a review of autism, variety of aspects. One is the phenotypic variability and the particular phenotype that people are -- have raised a concern about is the regressive form of autism. Some review of the -- what's known about genetic predisposition to autism and various forms of autism, including related disorders such as Rhett syndrome, immunologic studies of children with autism and controls. There are a -- There are several different mild and subtle differences between children with autism and healthy controls with regard to immunologic parameters, the meaning of which really isn't known.

Some review of the -- what's known about pathogenesis of autism and the timing of the insults that have been

known to be associated with autism, most of which are in the first trimester of pregnancy. Some review of the risk factors that are -- have been identified for autism and some recent data that have been generated from MRI imaging of children with various forms of autism.

Followed by gastroenterologist reviewing what's known about gastrointestinal tract disorders in children with autism, and it's not as clean cut as many of would think. It's not a true inflammatory disease, but there's some discrepancies between gastroenterologists regarding what exactly is the pathogenesis of the GI disorders that is -- that have been observed. There have been several groups that have looked for viruses in the wall of the intestinal tract of people with inflammatory bowel disease and in autism and there are marked discrepancies between what they've found, from no evidence of any measles virus in several groups, some groups finding evidence of measles nuclear pepcid antigen, one investigator reporting complete viruses. I will come back to that in a moment in terms of what might be done to address these issues.

There was a review of animal models with viral infections that might predispose to autism,

particularly borna virus infections in rats infected in the neonatal period can create some lesions that may mimic some of the aspects of autism. Followed by review of measles, mumps, and rubella virus infections and the vaccines that are used to protect against those infections and the related CNS disorders from both the viruses and the vaccines. And a detailed review of the methods that have been used for documenting or ruling out causal associations between vaccines and adverse events and the epidemiologic studies that have been done to date of autism and possible associations with MMR, including the recent study that's been publicized widely from the United Kingdom, and Dr. Brent Taylor was there at the meeting to present those data.

We ended with critiques of the laboratory studies that have been done by an independent individual very knowledgeable in the laboratory methods, but having had no prior involvement in any of the controversy, and a review of how some of the conflicting data might be resolved based upon what's happened in other settings where there are conflicting data, laboratory study data, on possible other viral infections being associated with other disorders. And a critique of the epidemiologic studies that have been done and the

hypotheses that have been generated and whether or not some of them are testable hypotheses.

Followed by perspectives, and I think this is perhaps one of the more enlightening presentations for many of us who participated, is perspectives from two members of scientific advisory boards for autism societies. And there are many scientists, physicians and nurses who are parents of autistic children who have devoted a great deal of energy and effort and some of their scientific careers toward trying to find answers to the pathogenesis of autism. And I think they had a lot to offer each one of us over the process and the controversy that's been out there in the public for the last few years and some advice with regard to what's needed and what's needed to be done. And in addition, the somewhat -- it's not truly ironic, but the fact that controversy and the hypotheses themselves has helped bring to bear efforts to try to get to some of the answers that they have been seeking for so long, understanding of the pathogenesis and what's going on and why their children have autism. And so for them, some of the controversy has been very beneficial as there is an effort now to try to direct additional resources to answering their questions.

And then lastly, a review of the studies that are either in the planning phase or in progress by NIH and CDC, and there are others here who can talk more intelligently about those, but there are studies here in Atlanta trying to define the true prevalence of autism in the population. And there are a lot of variability in different areas, both of this country and elsewhere and there really needs to be some standardization of the methods in order for us to address the issue of whether or not there is a changing incidence or increasing prevalence of autism, as has been suspected by many individuals.

And NIH is planning, and I understand in conjunction with CDC, large-scale, multi-center trial looking at children with autism and appropriately matched controls. And CDC is putting some money into this to help address the issue of possible associations between MMR and autism and others here can talk more intelligently about those studies.

A writing panel has been formed to pull all of this information together and the panel has expertise in autism, neurology, infectious disease, epidemiology, general pediatrics and vaccine safety. The timetable for the review of this subject is that the panel has

requested supplemental information from several different presenters at the meeting and two key individuals were unable or unwilling to participate in the meeting and we will have follow-up interviews with them to collect supplemental information. And we plan to have a draft report submitted to the Academy by the end of the summer and the initial plan was to try to have it published by the end of the summer, but because of the need for supplemental information, the anticipation now is that the publication should appear in *Pediatrics* by the end of the year 2000.

Okay. That's it, John.

DR. MODLIN: Great. Thanks, Neal. That was a very concise summary.

Let me open this up to questions, if anybody has questions for Dr. Halsey or comments from the -- from the Chicago meeting. Chinh?

DR. LE: Neal, did what you learned from that meeting change anything that you wrote in the editorials earlier that you want to share with us, on a personal level?

DR. HALSEY: I'm trying to remember which editorial that you're referring to and which commentary, but I have written a few things on this. On personal level,

I learned a lot and I think that everybody who participated with individual expertise in one area learned a lot by bringing these people together.

A couple of the things that were shared is that there are new investigators who are looking hard for viruses in the wall of the intestinal tract, and we are seeing inconsistent data, but there are others who are finding evidence of measles nuclear antigen or other viruses and certainly, it's conceivable that some portion of the virus might persist. Whether or not that's causing any disease or that's part of the normal process is something that needs to be worked out.

I learned a lot, as I mentioned, by -- from the members of the autism scientific advisory boards over a perspective about what the information is, what's needed, and perhaps why this process has been allowed to get to where it is in terms of the hypotheses. And I learned a lot about the GI tract that I didn't know before and some about the genetics. So yes, I -- a very short answer is I did learn a lot. I'm not sure that's exactly the question you wanted to ask me.

DR. LE: Has it changed your mind about causality --

DR. HALSEY: A brief answer is, no, it hasn't changed my mind, but the process isn't complete yet in terms of

gathering all the information and so there's no final -- you know, no simple definitive black and white answer that's going to come out of this at this time. But I think that we will be able to provide a good summary of all of the evidence, where it stands and how it stands up to the testing for causal assessment. And I think that's what we can do.

In terms of recommendations or policy, that's not what this is about. Those are going to come back to you and to the members of the appropriate committees of the Academy who will make those.

DR. MODLIN: Yes, Larry, and then Rudy.

DR. PICKERING: I'd like to follow up a little bit on your question. I agree with Neal, I don't think it changed our minds -- didn't change my mind on the association or the lack of association between measles and autism, but I think what it did is three things. One is that the meeting really elevated the need to devote more funds and more research to the study, causes, prevention, and treatment of autism. Secondly, it's absolutely critical that we ensure that these funds are devoted to the appropriate -- to the -- in the appropriate direction so that they're not spent on areas or given to areas that are going to dead-end with

regard to answering the basic questions. And lastly, that -- something that Neal said I think was very important, is that we all need to enhance our communication with parents who have children with autism and with the autism groups so that we can more unify our goals to trying to solve the problems that are associated with this condition. And I think these three things were -- all of us who were at the meeting really benefitted and learned in these three areas.

DR. MODLIN: Thanks. Rudy?

DR. JACKSON: Briefly, Neal, could you share with us any comments at all about imaging studies or results of the same either in kids who did receive vaccine and had autism or those who might not in any form or fashion?

DR. HALSEY: I don't think that the --

DR. JACKSON: Was there any --

DR. HALSEY: -- study that you're referring to has been done. And the discrepancies between antigen and PCR and culture studies are so vast that it's going to require some very careful work. I think Ian Lipkin (phonetic) is the person who came to provide the external review and certainly provided us with a good perspective of what's been done in other settings, such as a carefully controlled collection of specimens that

are then handled by a totally independent group, split and sent out to various labs to try to get appropriate controlled evaluation under ideal circumstances. And that's what he proposed. I'm not sure what we will come out with here.

But I don't think there's an answer to your question at this time.

DR. MODLIN: Fernando?

DR. GUERRA: Neal, thank you for sharing that information with us. The academy has a wonderful web page that is certainly very popular with its constituency of pediatricians and also parents. How do you see this kind of information that is certainly complex and that has captured a lot of interest amongst the lay public -- Do you see a role for the academy to try to convey some of this in a way that will be reassuring or that will, you know, certainly keep the public involved in a way that allows us to continue to provide immunizations to children?

DR. HALSEY: Well, I think the academy sees that as part of their responsibility and exactly how the information will be disseminated is really an academy decision. That's beyond the panel and I can't speak for the academy with regard to that. A report will be

written, it will be reviewed by the board and it will be released. How that's going to be disseminated -- I mean, it's going to be written at the level for the physicians, which is our primary audience, and then how that may be summarized in an appropriate manner for the general public is something that the academy has done in the past and I anticipate will do with this.

DR. MODLIN: Further questions or comments? Dr. Severyn?

DR. SEVERYN: Dr. Severyn from Dayton, Ohio. Dr. Halsey, how many people attended this conference?

DR. HALSEY: I can't tell you the total number --

DR. SEVERYN: How about a ball park? Ball park.

DR. HALSEY: My recollection is it's about 100 altogether. It's -- Approximately.

DR. SEVERYN: Okay. You had also mentioned that the CDC helped fund this "in part," were your words. Who's the other part?

DR. HALSEY: Well, from my understanding, as with many other of my own personal endeavors, they cost more than they initially plan to. CDC was the primary funder and it was intended to be the total funder, but certainly the academy donated a lot of administrative time and personnel to pull this off. I'm not in charge of the

budget, so I can't answer the question. There were no other sponsors, if that's what you're looking for. And there certainly were no corporate sponsors, if that's what you're looking for.

DR. SEVERYN: Thank you.

DR. MODLIN: Okay. Neal, thanks very much, again. I appreciate it very much.

Just a very quick introduction for the next item on the agenda. I think as many of you will recall -- Oh, I'm sorry, I beg your pardon. Frank. Oh, go -- I'm sorry. Go -- I beg your pardon. Frank, go right ahead.

DR. DESTEFANO: I guess I better make this quick.

DR. MODLIN: You bet. We were looking for you earlier.

DR. DESTEFANO: I think Neal has gone over how inflammatory bowel disease relates to autism and why this is being presented in this session. Here, I'd just like to present some results of a study we've done of this issue in the Vaccine Safety Datalink, and that's been presented a couple times at this meeting, so I think you'll be familiar with that. And I should note that the principal investigator on this study is Bob Davis from Group Health Cooperative in University of Washington at Seattle. Unfortunately, he couldn't make it to the meeting so I'll be doing the

presentation.

The possibility or suggestion that measles vaccination may be related to inflammatory bowel disease, particularly Crohn's disease and ulcerative colitis first surfaced in 1995 by a publication with Thompson as the first author in the United Kingdom, where they found that measles-containing vaccine recipients had a three-fold elevated risk for inflammatory bowel disease. This study was subsequently debated, had a lot of limitations to it, particularly that the cases and the controls were from different studies and ascertainment of vaccination was different in the two -- in the two studies.

There have been subsequent -- at least one subsequent better-done case control study in the UK that didn't find an association, and then the same group that Thompson works with more recently, last year, published in *Gastroenterology*. The main purpose of that study was looking at measles and mumps disease and risk of inflammatory bowel disease, but they didn't mention that they didn't find any association with measles vaccine in that study, so --

But that paper, I think, raises the issue that's kind of where the debate has shifted, where now, you know,

people are asking or wondering whether it would be safer to separate the three antigens in MMR. And I think the only kind of support I can see for that notion is that in this paper just published last year by Morris, Thompson, Wakefield, et al., there was a -- overall, there was no association with ulcerative colitis or Crohn's disease. But there was -- Like they had two or three cases that happened to have had measles disease and mumps disease within the same year. And even though it was a small number, there was a significant statistic, significant increased risk in that small subset.

I think it's been basically from that that the notion or this group has been promoting that it would be safer to separate out those three antigens. And certainly, that's had repercussions in the UK and even here, where at least, you know, one State has had legislation proposed that the three antigens should be separated. So it was sort of an issue that has -- you know, it's still controversial and still a lot of advocates for it.

Then in 1998, this was -- this issue was given new impetus because this same group in the UK reported on 12 children who were patients at this gastroenterology

clinic who had nonspecific colitis, iliolymphal hyperplasia, and developed mental disorders, many of which had autism. So as you heard Neal just present, the suggestion or the speculation was made that perhaps this bowel disorder was somehow related to the development of developmental disorders and autism and the ultimate or the primary cause of this was suggested to be possibly MMR vaccine.

Again, the only suggestion in this case series for that was that the parents usually, and sometimes the pediatrician, reported that they noted onset of the developmental problems within a short time following MMR vaccination. The only other -- The only epidemiologic study that's been done subsequently has been the one Neal Halsey mentioned, the one done by Taylor and reported last year, and that one that had comparisons, at least, with a population in northeast towns in London didn't find any association or increased risk with MMR vaccination and autism.

But our study, I think -- You know, our study was generated at the time when the debate was focused a lot on inflammatory bowel disease and MMR vaccine and basically I think the new -- what is new about the study we are doing is it's the first one that actually

looks at MMR vaccine. The other ones had been of single antigen measles vaccine.

So actually the study did have two questions. I'm just going to focus on the first one is this presentation, and that is, was the timing of vaccination or receipt of vaccination associated with an increased risk for Crohn's disease or ulcerative colitis later in life.

The data comes from the four HMO's that participate in the Vaccine Safety Datalink.

The study population -- In three of the HMO's, we're able to identify a study population that was born between 1958, this is when the membership files were first available at these HMO's, through 1989. One HMO had the membership files beginning in 1979. All four HMO's use hospital discharge databases to identify cases and three of the HMO's were also able to supplement the hospital discharges with outpatient urgent care and emergency department databases.

The population then were members who were continuous enrolled from birth or late as six months of age until onset of disease for cases. They were matched to a control and the control was assigned a reference date equal to the disease incidence date of the case. We matched approximately three controls per case.

Actually, in some instances, there were more than three controls per case. And the matching was on birth year and gender as well as HMO.

Exposure assessment was done by review of the medical records to ascertain all vaccinations from birth till disease onset or the reference date. We assessed all types of measles-containing vaccine, include MMR. In this one analysis, we didn't look at the -- we just focused on first-dose vaccination, we didn't look at the second vaccination at four to six or kind of the 12 years of age.

Then we conducted a medical record review to categorize cases in terms of certainty of the diagnosis. The first one was definite inflammatory bowel disease, that is, inflammatory bowel disease signs or symptoms were written in the chart and one diagnostic test confirming the result by a gastroenterologist at the HMO was present. A probable IBD had similar criteria except that the confirmatory testing could have been done by a gastroenterologist outside the HMO and the analysis was restricted to these two categories. These are the other, possible or questionable, but they didn't enter in the -- into the analysis. So I'm just going to skip over that.

We used a conditional logistic regression analysis, accounted for the matching criteria of HMO gender, birth year and enrollment, a total enrollment time from birth or six months up to the disenrollment from the HMO. We further adjusted for race. And again, as I mentioned, these were restricted to definite or probable cases.

For the question -- Just focus on the top bullet here. We'll just be focusing on is vaccination or timing of vaccination associated with risk for IBD and the relevant date for that was first disease diagnosis date. This is just some description of the -- We ended up identifying 155 cases for this analysis, and you can see that about half were Crohn's disease and the other half was ulcerative colitis. We only had two that we could not classify as either Crohn's or ulcerative colitis.

This is one of the gender and race breakdown of the cases and controls. And then the age at diagnosis, you can see the most -- most of the cases were diagnosed between 11 and 19 years of age. There were very few cases under five years of age or over 25 years of age at first diagnosis. And the controls have a similar distribution because of the age matching.

Okay. Here is the main result, in essence. And it looks at the risk of ever being vaccinated with either MMR vaccine or an MCV here would be other measles-containing vaccines, excluding MMR. Reading across here, you could see for MMR vaccine, which is a vaccine of primary interest, you can see that for Crohn's disease, there was actually suggestion of a decreased risk of .4, but it's not statistically significant, then no indication of an increased risk with ulcerative colitis, and for all inflammatory bowel disease, the relative risk is less than one, if anything, but again, not statistically significant. If you look at other measles-containing vaccines, again, all the relatives risks are right at or very near one and nothing is statistically significant.

I've gone ahead and kind of looked at this in a little more detail in terms of like age at vaccination. And you can see if MMR was given at less than 12 months of age, again, the relative risks are at or below one and the same thing with other measles-containing vaccines. There's a few cases here with very wide confidence intervals, but -- you know, most would be of in this 12 to 18 month range and again MMR in that range, no suggestion of an increased risk. Same thing with

measles-containing vaccine.

There's this -- The curious result that came out of this was actually a suggestion that if the first vaccination was at greater than 18 months, there may be actually a decreased risk.

And for all IBD combined, you see the relative risk is .16 and that's statistically significant, but you don't see that same thing for measles -- other measles-containing vaccines. These are like preliminary results and I don't think we figured out what's going on here, but certainly we see no indication of an increased for inflammatory bowel disease with either MMR or other measles-containing vaccines.

DR. MODLIN: Questions for Frank? Chinh?

DR. LE: I wonder why you chose not to look at kids with two-dose MMR, because if it were an autoimmune disease, then -- I may be naive about this, but wouldn't the first dose be the kind of a priming and the second dose is -- triggering the second exposure to the antigen is the triggering one. Maybe --

DR. MODLIN: It may be age of age of onset.

DR. DESTEFANO: Yeah.

DR. LE: And then the age of onset also --

DR. DESTEFANO: Right, right. That's a good point. I

guess we could probably look at that in another iteration and -- I mean, I can't -- you know, I can't give you a good reason why we haven't so far. This is the first -- you know, the first analysis, and I think that's a good point, I mean, something we should look at.

I mean, the only other reason if we're going to like link it -- I think kind of when we were doing this analysis was probably with the autism hypothesis in mind quite a bit and for the autism has -- has to have onset before three years of age, so -- And the -- And we're really trying to get at that issue of onset of symptoms inflammatory bowel disease and seeing if it was related.

This is a triggering hypothesis that I didn't present, primarily because I don't think we can have many cases, very few cases that had onset of symptoms around the time when they got MMR, just pretty much parallel of the disease onset. But I think that's a good suggestion if we look at the second dose to see if that made any difference.

DR. MODLIN: Other comments or questions? Fernando?

DR. GUERRA: Did anything come out in terms of either race or ethnic distribution, where we certainly know

that some of the inflammatory bowel diseases perhaps are more prevalent in some groups?

DR. DESTEFANO: Yeah, that may have, I'm just not that -- I'm not familiar with the data to know.

DR. MODLIN: It seems to me at least in this analysis they were controlling for race, Fernando, so that we wouldn't necessarily expect something to fall out.

Other questions or comments?

Frank, thanks very much.

DR. DESTEFANO: Thank you.

DR. MODLIN: I sure appreciate it, and again my apology for the slight.

Let's go on. And Bill, I understand you're going to introduce the next topic.

DR. EGAN: Thank you. I'm just going to take about two minutes for this topic.

At the last ACIP meeting, SmithKline Beecham Biologicals had presented some clinical data that related to a two-dose adolescent schedule for their hepatitis B vaccine. By way of additional background, just prior -- sometime prior to this, Merck had been approved for a two-dose adolescent schedule for their hepatitis B vaccine in a supplement submitted to FDA. And a recommendation for the two-dose adolescent

schedule for the SmithKline vaccine was to be considered at the advisory committee meeting, but following some discussions was tabled pending further discussions between FDA and CDC on whether this issue should be brought to the ACIP or not.

Now, since the time of that last ACIP meeting, there have been several meetings and discussions between CDC and the FDA. And from these discussions, we all agree -- we, CDC and FDA, agreed that as a process that SmithKline Beecham should be submitting their data to FDA for review for the two-dose adolescent schedule. And I think one of the issues that really brought this to the ACIP was a need for a harmonized schedule -- harmonized schedules between the two vaccines, between the manufacturers, for hepatitis B.

Also at those -- at these discussions that were held between CDC and FDA, and as we were needed, we discussed ways in which to improve communication between FDA and between the CDC and their associate advisory committees, this committee and FDA's Vaccines and Related Biologic Products Advisory Committee.

So that's where we stand, simply, on this particular issue.

DR. MODLIN: Bill, thanks. Any questions for Dr. Egan? We appreciate the update and the clarification. Barbara?

DR. HOWE: Is this on? Barbara Howe from SmithKline Beecham.

I just wanted to sort of remind the Committee as to the rationale for bringing the proposal really before the Committee. And there were a number of different reasons why we thought it appropriate to bring forward. You know, the first was that we felt the data were strong, and I believe that several of the Committee members agreed with that and actually used the term "compelling" when referring to the data. But I have to say -- Well, you would say if the data are compelling, then why not submit through the regulatory authorities and get the indication. And I think the main reason, or one of the compelling reasons why we wanted to bring it forward for recommendations was the time element, really, and the recognition that by the time the data were filed and allowing for the regulatory review process and licensure, that the cohort of previously unvaccinated 11- to 15-year-olds, which is currently shrinking now, would be possibly nonexistent by the time the product was licensed for this indication.

And then the third reason was the complexity confusion issue, which we did not discuss very much at the last meeting, but we really felt it was important that the two licensed hepatitis B products be -- it would be helpful for them to be viewed as being able to be used in a like manner. And since that time, we have learned from several States, actually, that there is a lot of confusion and that based on a lot of concern about confusion, that they're refusing to use the new adolescent two-dose schedule.

So I actually understood that this meeting that was taking place was for the purpose of maybe the more generic policy issue around off-label recommendations and under what circumstances that might be appropriate and I had hoped that this was not closing the door to further discussions if there was actually a public health need for allowing for this recommendation. So I don't know if you have a comment on that.

DR. EGAN: Well, we did actually have some discussions on off-label use in general and, you know, did recognize that some of them, some of those recommendations would need to be made by ACIP, you know, such as the recommendations that were made at that same meeting regarding DTaP vaccines. What we

couldn't come up with was, you know, a precise algorithm to utilize to determine whether or not any particular issue, you know, would be better to go one way or another and that we needed to have better discussions of this, you know, between the two agencies, between the agencies and the -- their advisory committees and working groups.

DR. MODLIN: Fernando?

DR. GUERRA: I guess the sooner that this can be resolved, the better it will be out in the field, because that is such a critical age for us to be immunizing, and certainly anything we can do to facilitate it with trying to harmonize the schedules -- I guess this may also be one of the vaccine schedules that might be visited by the group that's looking at the optimization of the schedule and trying to fine tune that. So, hopefully, that's a good point.

DR. MODLIN: Thanks. Anyone else on the Committee would like to make a comment about this? Okay. Dixie Snider?

DR. SNIDER: I might just say that we will include some additional language in a new iteration of the policies and procedures, some of the things that we agreed that -- with FDA that we would do to try to facilitate the

communications between FDA and CDC and the ACIP so that we can all hopefully be on the same page as we decide how to deal with these issues. Because as Bill said, it was hard to try to come up with some general statement that said well, this class of issues would always be appropriate, you know, for ACIP to deal with and this other group, that we could define in some generic way.

It appeared to us that at this point in time, we're really going to have to do this on a case-by-case basis, which means that we have to have some strong mechanisms for communication with FDA, including FDA representatives in the working groups on a regular basis to facilitate those kinds of communications and they in turn bringing, you know, proprietary information and you folks who are in working groups signing the usual things that you will not reveal proprietary information.

So we'll outline, lay out, all this kind of stuff that -- I think that's quite -- the discussions were quite productive in terms of the generic issues that were being referred to. And with regard to the specific issue, there actually was a unanimous agreement after discussion among CDC and FDA staff that this was one

that should go the FDA direction.

DR. MODLIN: Chinh?

DR. LE: I don't want to sound cynical about this, but if there were a public-health crisis in term of vaccine shortage or if there is a advantage to society that having two manufacturers competing for the same market and decreasing the price, I think we would think a little bit differently. But if it were a marketing crisis for a company without a public-health crisis, I'm not sure whether we should break the process.

DR. MODLIN: Thanks, Chinh. Further comments? Let's go on to the next item on the agenda, which will be an introduction for the Committee for a novel vaccine that I think few of us or any of us have had any experience with or knowledge of for a unique indication. And is it Dr. Fridkin, will lead the discussion?

DR. FRIDKIN: Thank you very much for giving us the chance to update you on the status of this vaccine. This is an effort that started 12 years ago in John Robbins' Lab and continues at NABI. It relates to a development of a novel vaccine, *Staph aureus* -- against *Staph aureus*.

And as we see in the United States, about 55 million

people are hospitalized each year, and in spite of the prophylactic use of antibiotics, five to seven millions will contract -- are at risk for nosocomial infections. *Staph aureus* is second most common cause of nosocomial infection, comprising 20 to 25 percent of all infections. *Staph epi* is number one.

And *Staph aureus* infection associated with high mortality and morbidity almost doubled the length of stay in the hospital and cost lots of money to treat cases of staph. And with the emergence of antibiotic resistance, including the vancomycin, the looking for alternative therapies, such as immunotherapies, is clearly warranted.

To approach this kind of pathogen, if you will examine the bacterial pathogen, the bacteria that cause disease in humans, you will found out there is -- they share some general properties. They all have capsulated polysaccharide or surface polysaccharides. Those polysaccharides are antiphagocytic and you need specific antibodies in order to kill those organisms. The opsonophagocytic activity is a good correlate for in vivo protection in many cases and its proven for pneumococcus and (inaudible).

It was until 1982, when Walter Karakawa came down from

Penn State University to the NIH, working with Willie Vann and John Robbins to develop the vaccine for *Staph aureus* and look at serology. What they discovered is that the *Staph aureus* has eight different capsules and those capsules are polysaccharide and cell-associated polysaccharides. Now we know about 11 different capsules.

The major issue, the major thing that was discovered, is that all clinical isolate could be listed under two major types, type 5 and type 8. So type 5 and type 8 in our hands, too. It's about 88 percent of all clinical isolates from bacteremia from -- and pneumonia.

The type 5 and type 8 are strictly (inaudible) activity and there are four type 5 will mediate opsonophagocytosis of type 5 and type 8 will mediate opsonophagocytosis of type 8 and there is no cross-reactivity between the two. This is an in vitro opsonophagocytosis that contains PMNs and complements. The structure, the polysaccharides were purified and the structure was elucidated by Willie Vann and John Michelle (phonetic) in his lab. And what we found out, that the two polysaccharides are actually identical in the composition of their repeat units because that

means (inaudible) acid. The only difference between the two is the bond between the two (inaudible) acid and the site of the (inaudible). These two small differences actually render the two polysaccharide serologically distinct and no cross-reactivity whatsoever.

In addition to that, the polysaccharide is very small and, therefore, compared to other vaccines, like pneumococcus, so to -- we would expect that these polysaccharides will not really be immunogenic in humans if you would like to use it as a vaccine, and therefore, we went into the production of conjugate vaccines. We utilized the (inaudible) group on the polysaccharide with the spacer and we conjugated the recombinant DPA. This is an exotoxin from Susan Wallace, the organizer, that the glutamic acid number 553 was deleted and, therefore, this protein is identical to exotoxin but lacks the enzymatic activity and therefore is not toxic anymore.

So we utilized that and produced the vaccine, a conjugate vaccine, from these two entities. And this is the immunogenicity in animals and here, just giving you the Type 5 and exactly the same thing from Type 8, that the polysaccharide alone is not immunogenic in

animals and the -- when you inject the conjugate, the first injection is actually priming. Second injection, you get the booster response. If you prime the animals and then you inject one injection of the vaccine, you get effect one injection of the vaccine is giving you amounts which are equivalent to second injection with the vaccine. Those two properties, a booster response and carrier priming is indicative of the T-cell dependency of this vaccine and especially that the BSA prime which none are related did not give you any effect.

We looked at the opsonophagocytosis picture and correlation between opsonic activity and the antibodies that we are generating. We found out that we have very nice linear relationship between the two, indicating that this vaccine and the conjugate that we are producing is generating antibodies that totally -- or most of it, if not all of it, is functional, so there is no indication or generation of antibodies to a nonfunctional epitomes on these -- on this polysaccharide.

We evaluated the antibodies for protection in animals and, in this case, those are animals that were actively immunized three times with the vaccine and then

challenged with the bacteria one week after the last injection. And what you see here is that the animals that were immunized with the type 5 conjugate were protected about 50 percent protection, compared to the animals immunized with phosphate-buffered saline, only four of 30 survived the challenge. So this is the first time that antibodies to the capsular polysaccharide are showing protective efficacy in vivo. We tried to correlate between the survival and the antibodies. Those are titers -- the titers of antibodies before the challenge and those in all animals. So those are the 12 animals that did not survive the challenge and of the 33 animals that survived the challenge. And you see the difference between the antibody titers. This is geometric mean between the groups and it was statistically significant. So for the first time, we're also showing that there is some correlation between protective activity and titers of antibodies.

We were able to receive the viso strain from -- that was isolated from New Jersey. This is a type 5 and we evaluated that again in active immunization. And you see here these are the animals immunized with type 5 recombinant EPA and challenged with the viso strain

from New Jersey. And these are the animals that were chall- -- were immunized with a carrier. As you see, it's zero out of 15 dead or 100 percent protection versus 50 percent in the carrier, which means that regardless of the antibody profile, if you're challenged, if the capsule is there, antibodies will protect against these organisms.

We evaluated the -- this vaccine in phase I as a monovalent vaccine. And the point that we're presenting clinical data at this point of time is just to indicate a few things. First, all of us have antibodies in all our systems against *Staph aureus* capsular polysaccharide, whether type 5 or type 8. Secondly, one injection, in two weeks you are almost raising the antibodies about 30-fold and second injection at six weeks did not really change the amount of antibodies generated, which means that there is no booster response, which is we've seen with all the conjugate vaccines in adults, because the first injection is actually a booster injection.

Now, we looked -- We went back to the NIH -- This was done at the NIH -- went back four years later and obtained blood samples from those volunteers that were still in the government service. And as we see here,

we have many of those, eight of 23 in this group and eight out of 35 this group. If you look at what's -- I mean the amount of antibodies is still there, four years later. It's about 50 percent of the maximum values that you obtain at six -- at six weeks. And that indicates that actually the vaccine not only elicit high levels of antibody, but those levels will stay for a long time in the system.

The human antibodies and opsonophygacitosis exactly the same like (inaudible). You have very nice correlation between the two and also the human antibodies, which are almost totally functional.

We evaluated the immunoglobulins that gave -- that were elicited in human normal donors, plasma donors, and this is the immunoglobulin that was generated from their plasma and this is the standard IVIG. What you see is the animals were immunized subcutaneously and were challenged IP. And you look at the survival. You see here the same story that you've seen before, passive immunization with the hyperimmune IVIG is giving you about 80 percent protection in the animals while standard IVIG is not giving you much protection. So the antibodies that we are generating in humans also protected in the animal models.

We looked into some other animal models. In this case, we looked at the endocarditis model. This is a model where the heart has been damaged by -- the valve is damaged by inserting a catheter and then you challenge the animals. And this is the -- You look for number of rats with endocarditis. This is the normal IgG versus immune IgG, seven out of nine versus one out of nine, and you look at the column before in the kidneys, the abscesses, ten to the seven versus ten to the two. And all these differences are significant. So the antibodies from the vaccine, reduced??? antibodies, are protective in several animal models rather than in one. We all remember this statement in 1965, which actually closed down the whole subject of immunotherapy for staphylococcus. And if you -- In '65, Dr. Rogers was one of the prominent staphylococcologists (sic) in that era. That statement that he said in that meeting, that closed the whole field for 25 years.

So the question was, and this is really reasonable, if we have antibodies, as we see in ourselves, if we have eight micrograms to ten micrograms, why we get infected with *Staph aureus* on top of those antibodies. And this is a legitimate question. We tried to look into that and see if there is any explanation why. And we went

back and took some standard IVIG. These are IVIGs in the market from Bialpha (phonetic) and Bivaxer (phonetic) and so. Those contains about 50 to 70 micrograms per ml. of the specific antibodies, and we looked at the IVIG that we generated from vaccinated. This is an assay for affinity, and what you look here is the amount of sodium thiocyanate needed to disassociate that immunocomplexes and the higher the affinity, the more thiocyanate you need. Look at the 80 percent, when you talking about vaccine-induced antibodies, you are talking about two molars versus nonvaccine-induced. So naturally occurred antibody, you're talking about .2, .3. So by vaccinating or by using the vaccine, you are generating a high affinity antibodies that will bind very strongly to the antigen while the natural antibodies are not of a good quality or good affinity and that would may affect the functionality of those antibodies.

If we double up the assay when we looked at the ability of the immunocomplex to fix complement or to bind C3B -- complement C3B, you see this is the hyperimmune and this is the standard IVIG and this is a correlation with the micrograms per ml. antipolysaccharide. So you add the little bit antibodies, you have very nice

binding of complement on the vaccine-induced antibodies while (inaudible) antibodies actually drag and drag the whole thing and the ability of the immunocomplexes to bind complement is really almost nothing.

So that's an indication that the antibodies, because of low affinity, the efficacy is not available for fixing complement on the immunocomplexes and, therefore, it's not functional and we need the C3B binding in order to get the optional fibrocytosis to work, which is the only mechanism for grand positives.

So that can explain why in the early days we had the antibodies but we could not really protect or we were getting infected on top of the antibody there.

To summarize this pre-clinical data, it is that the *Staph aureus* is capsular polysaccharide, it's antifibrocytic. A bivalent vaccine is required. We need to bind valent 5 and 8 in order to cover the majority of the isolates. Antibodies (inaudible) type specific fibrocytosis with linear correlation and conjugates are immunogenic and reduce high-affinity functional antibodies. Conjugate vaccine is protective in several animal models representing different infection modalities. And the antibiotic resistance, including vancomycin and the mediate strains did not

affect the protective efficacy of the vaccine.
Infections in humans superimposed on the presence of antibodies in the blood may have been a result of low affinity and functionality of the natural wild antibodies and the safety and the immunogenicity and the functionality warranted the clinical development of the vaccine.

And I'll turn over to Dr. Horwith to continue into the clinical development of this vaccine.

DR. HORWITH: Okay. Following on with what Dr. Fridkin just presented on pre-clinical information, we'll just touch on some of the clinical information primarily because what we want to do is to enable the ACIP to start to see some of the study designs at least, so that when we eventually come through with some data, that will be a basis for us starting to have some discussions.

As Dr. Fridkin said, the initial clinical trials started back in 1991 and then were brought to Univax, which subsequently became Nabi, in 1993. So we performed phase I and phase II clinical trials between '93 and '97. Then in 1998, we initiated a pivotal phase III study that, for all practical purposes, kind of stayed underneath the radar screen for most

individuals.

This is just a representation of the antibody response in normal individuals following the bivalent vaccine at a dose of 25 micrograms of each capsular polysaccharide. As one can see, in the normal individuals, which is depicted here as a yellow and red triangle, there was a brisk antibody response and quite durable, as was described for the people who were studied at the NIH.

The end-stage renal disease patients we studied in order to be able to use them as a population where we could find clinical endpoint was somewhat less robust than that found in all individuals. In addition to that, as Dr. Fridkin described, in terms of a booster response among normal individuals, we performed a study to look for a booster response in end-stage renal disease patients and likewise found no booster response.

This is just a summary of the geometric mean titers that were observed following different doses of the vaccine: 25 micrograms, 75, and 118 for the type 5; 25, 55, and 83 for type 8. And one can see that the peak antibody response had -- which we measured at day 42, it followed a nice dose response curve.

In terms of adverse events associated with the vaccine, this is a summary, if you will, of the phase I/phase II data. The adverse event profile is pretty typical of what you would expect with an intramuscular injection. There was some muscle pain, some headache, nausea, malaise, and some erythema, a little bit of induration and pain at the injection site, which lasted about 24 to 48 hours.

Based upon the phase I/phase II data, we initiated the pivotal phase III study. This is double-blinded multicenter study in dialysis centers throughout northern and southern California. The study was run predominately at Kaiser-Permanente and Gambrell and TRC Dialysis Units. The population used were end-stage renal dialysis patients, which we have previously identified in a prospective study that indicated that their -- the infection rate among this population is about 0.4 -- 0.04 to 0.05 *Staph aureus* infections per patient year. So we could use that as a basis for trying to define our power.

We did note initially, of course, that the elderly and the end-stage renal dialysis patient population had a somewhat blunted response to the vaccine and the dose of vaccine that was used, therefore, was 100 micrograms

of each capsular polysaccharide. Individuals were randomized one to one to either receive the vaccine or a placebo. They were also stratified by nasal culture at the time that they were enrolled in the study, those who were *Staph aureus* nasal culture positive or negative, as well as by the type of dialysis access, that being either fistula or a heterologous graft.

The primary endpoint of this study is the bacteremia events during a period between two and 54 weeks following vaccination. And as one might imagine, there were multiple secondary endpoints that we will be looking at.

In order to be enrolled in the study, individuals had to be over 18 years of age. They had to be on hemodialysis for at least eight weeks prior to entering the study. Naturally, they had to have either fistula or graft. They could not have an active infection within two weeks of vaccination and they could not be on any immunosuppressive agents.

The study was designed to have 80 percent power to detect a 60 percent decrease in the rate of *Staph aureus* bacteremias. That required 810 individuals per group and would have required approximately 44 bacteremias overall, for a P value of 0.042. The

somewhat lower P value than the conventional 0.05 is due to an interim analysis that was done. So that's the hit we took on that. That blinded interim for a futility analysis was to be performed in order to determine for us, as a sponsor, whether or not it would be futile or not to continue with the study. And the design was to collect 12 months of data on each subject.

This is a cartoon, if you will, of the randomization and stratification. I put in just a little bit of the demographic data. The database has not been closed yet. So this is subject to a little bit of change, but it's essentially very accurate. Among the group who had a fistula and were nasal-carriage positive, that represented seven percent of the population. And you can look at the other numbers. The largest group, of course, were those who had a heterologous graft or synthetic graft and were nasal-carriage negative. That constitutes 55 percent of the population.

In total, we enrolled 1,903 subjects. Of those, 1,808 were actually vaccinated or received placebo. The last subject was vaccinated in August of last year. A little bit of demographic information for you: the median age was 59.5 and the mean, 58 years; the eldest

individual is the study was 90 years; the male/female ratios with regard to graft and fistula were really quite different. As you can see here, the male/female ratio for those who had grafts was one, equal distribution, whereas those had fistulas were predominately males. And there was a fairly equal distribution across the ethnicity.

We performed two interim safety analyses that were done by an independent drug safety monitoring board, when we had 20 percent and 60 percent enrollment. Of course, the drug safety and monitoring board now found no issues to warrant stopping the study. At the time that we did the futility analysis, in August of 1999, we had 31 bacteremias that had occurred between two and 54 weeks following the vaccination and the denominator was 1,774 subjects who were included. That futility analysis indicated to us that we should continue to the end of the study.

The trial was actually completed as of the 30th of April, and at this point, we're in the process of resolving data resolutions to the database. What follows here is a curve of the first 190 or so individuals who we guess, because it's -- it's still blinded, we guess these are the individuals who were

vaccinated as opposed to receiving a placebo. And one can see that we had some pretty brisk antibody responses with geometric mean titers at peak of about 200, 220 micrograms per ml., and then at about a year, it had waned to about 70 or 60, thereabouts. Actually, the record, one individual so far seems to have generated about six milligrams of antibody at their peak response.

So, in summary, then, we feel that the Staph VAX, following the analysis of the pivotal trial, will be indicated for individuals at high risk of *Staph aureus* infection. Obviously, that includes the end-state renal disease patient population. We also plan to conduct some immunogenicity studies in other high-risk patient populations where the infection rate is not sufficient to obtain clinical endpoints, but we will obtain immunogenicity endpoints. Those would be individuals who are going to have elective high-risk surgery, individuals in nursing homes.

So, in summary, then, as a second part, we feel that at this point we've demonstrated both through our pre-clinical and our clinical data that we have a novel approach to tackling a serious infection. Problem? This clearly is at least novel in terms of *Staph aureus*

infections. The vaccine clearly has a unique mechanism of action compared to what we've been doing with *Staph aureus* so far. We feel that we probably will be able to reduce the morbidity and mortality of *Staph aureus* infections and possibly even impact on the spread of antibiotic resistance.

Okay. Any questions?

DR. MODLIN: Dr. Horwith, thank you. I'm sure there are. Fernando?

DR. GUERRA: That certainly was very informative. I noticed that on the distribution by race and ethnicity for number of conditions, there's a fairly significant number of hispanics, and I guess many of those had end-stage renal disease.

DR. HORWITH: Uh-huh (affirmative). These are all end-stage.

DR. GUERRA: Did they have diabetes as a co-morbidity?

DR. HORWITH: Oh, yes, a large number of individuals have diabetes as co-morbidities. Diabetes, hypertension, the usual sort of mix that you would expect and in the PSRD patient population.

DR. MODLIN: Which potentially could be another group of patients that could --

DR. HORWITH: Yes.

DR. MODLIN: -- could benefit before they lapse into end-stage renal disease.

DR. HORWITH: Absolutely.

DR. MODLIN: Have you looked at such a group in any of the studies?

DR. HORWITH: Not as a separate study, no.

DR. MODLIN: Paul?

DR. OFFIT: Yeah, actually, I had two quick questions for Dr. Fridkin, the first speaker.

You said, if I understood you correctly, in your animal model, with your immunization, you used adjuvant; is that true?

DR. FRIDKIN: No, the --

DR. OFFIT: It's a --

DR. FRIDKIN: All the immunization in the animals and the humans are in BBS --

DR. OFFIT: So when you said -- Well, didn't something there say plus adjuvant, or did I misunderstand?

DR. FRIDKIN: That study, we used another polysaccharide --

DR. OFFIT: I see.

DR. FRIDKIN: -- added to that.

DR. OFFIT: Second quick question -- in your challenge model, which was a lethal challenge model, what did the

animals die of? Was it sepsis, pneumonia, what?

DR. FRIDKIN: No, it's bacteremia. We looked at the bacteria counts in the blood and when you inject the bacteria intraperitoneal, you will get a ten to the five to ten to the six bacteremia and then the animals just lose weight and just die within 48 hours. So it's a bacteremial sepsis kind of problem.

DR. MODLIN: Chinh?

DR. LE: I think certainly it's a very exciting vaccine. I have one question and some comments.
One of the last few slides you have is the antibody curve, the peak and then the decay. Could you remind us again what is the protective level, meaning like by 52 weeks? Is that still the protective level or not?

DR. FRIDKIN: We wish that we had the answer for that question. That will solve many of our problems. Since this is the first time that the vaccine for *Staph aureus* is introduced, the -- defining the protective level is going to be one of the tests for future studies.

DR. LE: I thought you had some animal data to tell you a little about what that would be.

DR. FRIDKIN: Yeah, well, animal data was -- goes to animals and the animals' bacteremias tend to survive

until you kill a mouse and in the humans, the bacteremias tend to mature to ten to (inaudible). So the amount of antibodies in the humans and the animals are not really equivalent.

DR. LE: Yeah. The other comment I have is, you know, renal patients, notoriously, historically, has a relatively large turnover of antibodies, whatever you say, you know, like --

DR. FRIDKIN: Yes.

DR. LE: -- nephrotic syndrome, kids, you know, lose the antibody titer in pneumococcal vaccine fast. The hepatitis B vaccine in dialyzed patient -- hemodialysis patient also doesn't last as long as well. And my feeling is you also should study another group which is at high risk for staph bacteremia carditis, which is basically IV drug abuser. They're a younger population. Their antibody dynamics are probably a little different. And I would expect that if one would have to have booster doses eventually, there will be probably a population difference in one -- dialysis versus endocarditis in drug addicts and so on.

DR. MODLIN: Yes, Larry?

DR. PICKERING: I also have two questions. One is, in individuals who were not immunized and who developed

bacteremia due to *Staph aureus*, what are their antibody concentrations compared to those induced by your vaccine?

DR. FRIDKIN: Well --

DR. PICKERING: And secondly is -- You want me to ask now or do you have a good memory?

DR. FRIDKIN: Let me just answer that question. We followed the shock trauma patients at University of Maryland. We looked at the amount of antibodies at admission and at infection for those who got bacteremia and at discharge. The amount of antibodies was the same. It was about five to ten micrograms per ml. At infection, there is kind of a removal from almost all the antibodies going down almost to zero, which means that the bacteremia is a high enough or large enough number of bacteria taking out all the antibodies, and then you have back to almost the same value. So the convalescence -- or antibodies from convalescence is not really much higher.

DR. PICKERING: The second question is, you stated that you had 31 cases of bacteremia out of 1,774 --

DR. HORWITH: Yeah, that was at the interim analysis, or the futility analysis. We actually have approximately 56 bacteremias now at the end of the

study.

DR. PICKERING: But did -- But you didn't say because it was an interim which group they're in?

DR. HORWITH: No.

DR. PICKERING: And yet you still feel comfortable saying Staph VAX is indicated for high-risk groups without knowing which group these bacteremias --

DR. HORWITH: Well, this is assuming that the efficacy analysis will demonstrate that the vaccine was efficacious. At this point, the study is still blinded so we have no way of knowing.

DR. MODLIN: David?

DR. FETSON: David Fetson, Aventis Pasteur MSD. Do you have any plans to do any studies of this vaccine in health care workers to see what effect it might have on nasopharyngeal colonizations?

DR. HORWITH: Those would be some very nice studies to do, yes. If we demonstrate efficacy, we've got plans for a number of different types of studies.

DR. FETSON: Well, but efficacy in preventing bacteremia is one thing. Efficacy in preventing nasopharyngeal colonization might be a different outcome and yet it might have enormous potential for disease prevention in intensive care units and it would

define another market for the vaccine, namely health care workers.

DR. HORWITH: Uh-huh (affirmative).

DR. FETSON: OSHA might be interested.

DR. MODLIN: Stan?

DR. PLOTKIN: I just wanted to be clear. In your animal models, can you prevent localized staphylococcal disease or is it only bacteremia?

DR. FRIDKIN: We did several animal models. Here, just presented the lethal model or the sepsis model. If you do bacteremia, you see that the *Staph aureus* have some kind of affinity to the kidneys and it's established kidney abscesses. So you can see that the animals, if you prevent bacteremia, protect the animals, and you look at the kidneys, there is no abscess in those animals. While the animals that did not have the antibodies, there were very severe kidney abscesses. So you are impacting the different modalities of the infections.

DR. PLOTKIN: But if you challenge with a local injection of staphylococci, in other words, can you prevent abscesses by preimmunization?

DR. FRIDKIN: We did not do exactly that kind of animal model or wound infection of localized, but we have some

indication from mastitis. We are evaluating the vaccine in mastitis with challenging and that's modalities kind of mucosal attachment, mucosal pathogenesis, and we are seeing that this vaccine can prevent mastitis in cows. And in some cases, we can also cure some cows from mastitis.

DR. MODLIN: I think Dr. -- I don't want to prolong this, but Dr. Plotkin is asking if you just simply inject some staph underneath the skin in an immunized animal, what happens?

DR. FRIDKIN: We didn't do that experiment.

DR. MODLIN: Okay. Dr. Tompkins?

DR. TOMPKINS: My concern was whether your mouse model really would translate into the real world of human infections and some of my questions were the same as Dr. Plotkin's, whether you had used a cutaneous model of infection or a pyelonephritis model, for instance, not just the bacteremia model in the mouse, and had you done it in other animals as well.

DR. FRIDKIN: Well, I presented the data from the rat endocarditis model, which everybody Is accepting that resembles human infections. I don't know. But we tried to get some information from some animal models. What will definitely be the outcome of this study at

Kaiser hemodialysis is going to be the ultimate answer. If we get efficacy in humans, than I think that will be our best bet at this point. But, you know, there are so many animal models that you can work with. The question is, can you -- what -- where you can go, it was actually -- The purpose of these studies was to prove the principle that antibodies to the capsule can protect animals. Right now, we're talking about bacteremia and maybe pneumonia and endocarditis or secondary infections, but we did not really go to each and every indications like wound infections, catheter-related, along those animal models.

DR. TOMPKINS: Right. But most or many of our bacteremias start out as wound infections, so the pathogenesis is -- you know, is related to cutaneous infection and/or catheter-related infection. And so it might be helpful to look at some other models of infection with this -- to see whether antibody really truly protects in those instances.

DR. MODLIN: That's a good point.

Thank you. We certainly do appreciate you bringing us this very interesting information and we look forward to an update at the not-too-distant future.

So that people can catch their planes, let's go on and

deal with the last item on the agenda, which will be updates from the various PHS services, and we'll start with the National Center for Infectious Diseases. Dr. Mawle?

DR. MAWLE: I just wanted to very briefly update the Committee on the outbreak of W-135, meningococcal disease, following the Haj this year. I think as you're probably aware, NCID is one of the WHO collaborating centers for meningococcal disease. So I wanted to just let you know what we've been doing and where we're likely to be going with it.

Saudi Arabia has a policy in place requiring Haj pilgrims to be vaccinated with meningococcal vaccine following outbreaks of sero group A meningococcal disease, going back as far as 1987. And the vaccines that are used are either the bivalent AC vaccine; or in this country, we have the quadrivalent vaccine, that covers A, C, Y, and W-135.

Following the Haj this year, there have been cases described in about 13 different countries, obviously including Saudi Arabia, of W-135 disease, including four cases within the U.S. Two of these cases were in pilgrims and presumably represent vaccine failures. They were vaccinated. One had close -- who was a close

contact of other pilgrims and one who possibly had contacts with pilgrims returning from the Haj, though that has not been completely traced.

I think I might say I took this from the WHO web page and they've been tracking this outbreak, and we're looking at just over 300 cases -- This is dated the 12th of May -- at this point from about 13 different countries.

Now, our lab has been looking at the isolates that we've had. W-135 disease is a very small percentage of the meningococcal disease identified in this country, about three or four percent. And it has not up to this point been identified with an outbreak. It's usually sporadic cases. So I've been looking, using four different techniques, at the U.S. isolates and then subsequently isolates that they've had from both Saudi and from other countries. And by these four different methods, the enzyme electrophoreses, which is a standard tracking method for mening, serotyping, sequencing of the 4-A gene and also sequencing of the (inaudible) 16SR and A. By all four of these techniques, this is clearly one identifiable all around the world. Not only that, it's been identified prior to this outbreak. This is not a new identified W-135.

It's just never been identified in an outbreak before. It also has some fairly unique characteristics, which they're exploring, and at the moment they're in the process of doing a study of 50 Haj-associated strains against 50 unrelated strains to more closely characterize what's going on with this particular strain. We have been invited to go to Saudi. We will be looking at what's happening over there. I do want to mention that the mening in Saudi Arabia was also serovalent meningococcal disease. So it wasn't just the 135.

But obviously, this has implications for vaccine in the future. Most of the world does not use the W-135 in their vaccine and clearly, that's something that the Saudis are going to be looking at closer.

DR. MODLIN: Lucy?

DR. TOMPKINS: Allison, I just wanted to ask one question. How many different strain types are there of W-135? It's not monoclonal, is it?

DR. MAWLE: It's not monoclonal, no, not at all. In fact, this one -- I can't tell you how many they've actually looked at. There are not a whole lot of isolates of 135 that have been looked at in this amount of detail, which is one of the reasons they're doing

this study of the 50 and 50 collected from around the world.

This apparently is -- Although it's been described before, prior to this year, in different countries, it's -- it looks quite a lot different from a lot of other isolates, and it has some interesting characteristics, which they're still working on.

DR. MODLIN: Georges?

DR. PETER: You mentioned that these cases -- You mentioned these cases were vaccine failures. You mean the two pilgrims --

DR. MAWLE: They're presumed vaccine failures, yes --

DR. PETER: I see.

DR. MAWLE: -- because they were vaccinated with the quadrivalent vaccine.

DR. PETER: But you don't whether they actually were failures to respond or were true vaccine failures?

DR. MAWLE: Correct.

DR. MODLIN: What do we know about the efficacy of the --

DR. MAWLE: Of the quadrivalent vaccine?

DR. MODLIN: Exactly, or the W component of the quadrivalent vaccine.

DR. MAWLE: Of the -- actually the W-135 --

DR. MODLIN: Yes.

DR. MAWLE: -- it's not known. I mean, the -- because it's such a --

DR. MODLIN: Because it's a small number. That's why I asked the question --

DR. MAWLE: The vaccine itself is supposed to be 80 to 100 percent efficacious, but that's basically . . .

DR. MODLIN: All right. Thanks, Allison.

Walt?

DR. ORENSTEIN: I wanted to talk about two things, and I would like to publicly thank Nicole Smith, who prepared some of my information on the IOM, and Mark Paponya (phonetic) on measles elimination in the United States.

A year and a half ago, the Senate asked the Institute of Medicine to help in review of what the federal role in immunization should be. We worked with the Institute of Medicine and a committee was developed on immunization finance and policies and practices. It was chaired by Dr. Bernie Guyer (phonetic) of Johns Hopkins University. Rosemary Chalk (phonetic) was the permanent project officer at IOM. The Congress asked the following: assess the overall spending during the 1990's. For those of you who don't remember with the

Childhood Immunization Initiative and actually the measles resurgence, there was a major increase in funding for states for infrastructure and then that gradually was -- not so gradually was cut quite dramatically over the next years.

The second was to identify state spending patterns; to recommend current and future funding requirements; to recommend a methods for distributing federal funds; identify how to target funds for high-risk populations; and finally, we added a role, is what is the role of the CDC in supporting state adult vaccination efforts. And the primary focus of this effort was the 317 Grant Program, which is the discretionary grant program managed by CDC.

A copy of the executive summary, I think, has been handed out. I know it was at my desk. I think I'd like to call your attention to what is said in the preface, "The U.S. immunization system is a national treasure that is too often taken for granted." And we would agree with that. The report is available through this web site at www.nap.edu, and I believe the executive summary may also refer you to this web site. And I can come back to that at the end if you haven't copied it down.

The IOM, I think, has probably done the best job, in my opinion, of trying to say that an immunization program is not solely vaccine purchase and that there are a variety of functions that successful immunization programs must do. They developed a puzzle, actually, and it's in the executive summary, but there are five -- six parts to the puzzle, four of them surround the control and prevention of infectious diseases and at the base of it is the resource issue.

Assuring vaccine purchase is obvious. Assuring access to vaccines is really capacity clinics, doctors, nurses, et cetera. Control and prevention of infectious diseases includes surveillance, outbreak control and the like. Surveillance of coverage and actually in safety, this is coverage measurements. Sustaining and improving coverage levels relates to the intervention, such as reminder and recall systems or linkages with the WIC program, et cetera. And using primary care and public health resources efficiently is basically the financing aspects of the whole system.

The report had the following conclusions. That there are real problems with an ebb and flow of funding, that there needed to be some stability and that instability was having substantial adverse impact on our

immunization programs. Second, that the immunization policy needed to be national in scope, all the recommendations that you've made, but to be flexible to allow them to be incorporated into many different health care systems within the 50 states. In essence, we really don't have a national immunization program, but at least 50 state and local immunization programs. We have also stated quite emphatically that there is -- federal and state governments have important roles, both in vaccine purchase and infrastructure and that one -- neither one nor the other was sufficient. It did say that the federal government in essence was the senior finance partner but that the state and local governments had a major role. And it said that the private health care has the capacity to do more and specifically talked about insurance coverage of vaccines.

Now, when we spoke with the IOM, pneumococcal vaccine was not licensed and we said the major issue was dealing with infrastructure, and that's where the IOM report is focused. Nevertheless, in their recommendations, they said that current vaccine purchase budget must be adequate and there's a footnote that says that this recommendation was made prior to

pneumococcal vaccine, but that only highlights the need to having funds for persons that are not covered through the Vaccines for Children Program nor private insurance.

The second recommendation is that adults and adolescents with high-risk conditions are falling through the cracks and that there is a public sector role. And it recommended that the 317 vaccine purchase budget be increased by 50 million to cover vaccines such as hepatitis B for high-risk groups and that the states ante up $11 million as their share in trying to cover adults between 18 and 64 years of age who are not covered by Medicare.

They also recommended that there needed to be increased spending for infrastructure and recommended that the federal government increase its annual appropriations for infrastructure by $75 million and that the states increase their spending for infrastructure by $100 million over what they're spending now to show that, in fact, this is a partnership and not one sector or another.

They also recommended that federal funding for immunization for states be made more transparent through a formula. At this point, it's discretionary

and the feeling was a formula would make it more fair. Terms of the formula needed to take into account need, a la low-coverage areas perhaps needed -- probably needed more money, capacity and wealth are a key, that wealthy areas perhaps needed less money, the states ought to be putting more in. And finally, there ought to be some incentive rewards.

The other concern was that the states needed to take ownership of immunization and they recommended that there be a match program for federal funding. They didn't define that match, but they clearly felt that states needed to visibly demonstrate that they're taking more of a role in immunization, that this is not solely a federal government role.

And the last recommendation was to develop consistent and comparable measures, such as harmonizing the National Immunization Survey and HEDIS so that we could all be talking from the same page when we're talking about immunization coverage.

The next thing I wanted to talk about very briefly was in March, we held the consultation to look at progress towards measles elimination in the United States. John Modlin was there. I think several other people in the room were there at this point -- at that point. To put

in perspective what has happened with measles, is that we've had about 100 cases reported for each of the last two years in this country. This compares with over 27,000 cases that were reported in 1990 alone. We are now substantially below one case per million in this country of measles.

The other thing that I wanted to point out is we're seeing more and more cases -- a proportion of our cases that are documented to be due to importations. This does not include the import-linked cases and so, in essence, we are seeing very few cases that cannot in some way be linked to an importation. And so we asked each of the individual consultants what their opinion was and all of the consultants said that measles is no longer an endemic disease in the United States. But what was of interest is that this state is exceedingly tenuous, that we are perpetually being challenged by importations and that any drop in immunization coverage (inaudible) indigenous circulation.

I think the other thing that was interesting is that we can expect cases and outbreaks of measles and still not have an endemic disease. And nobody was going to define an elimination, because it becomes difficult to give a precise definition, but I think people in

general had a concept of continuous circulation. We still may have blips in measles with an introduction and some spread, but the likelihood is that if we can maintain our levels, we will not have reestablishment of continuous circulation in the U.S.

And I think the third point is that the best way of maintaining or elimination is not only a good defense, but a good offense, and that

meant -- means going and working with countries around the world to decrease their measles burdens, which would help their own populations as well as decrease the risk of importations into the United States.

DR. MODLIN: Walt, thanks. Any quick questions for Walt? Thanks very much.

Dr. Egan?

DR. EGAN: Thank you. I just have a few comments for my update.

I'd like to mention that we have a recent Vaccines and Related Biological Products Advisory Committee in May and at that meeting, there were two topics I'd like to bring to your attention. One was that we had a generic discussion of potential future rotavirus vaccines and there was a unanimous -- it was the unanimous opinion of the Committee that there was -- that we should go

forward with appropriate candidate vaccines for rotavirus.

Then we also had a discussion of the use -- related to cell substraits for the production of viral vaccines and, in particular, the use of continuous cell lines and tumorigenic cell lines for use in the production of viral vaccines and what CBER's approach towards treating these cell substraits were. Previously, or until now and still, there are no live viral vaccines that are produced in continuous cell lines and there are no viral vaccines at all that are produced in tumor cell lines. Yet, some vaccines may require tumor cell lines for the future, for example, some of the HIV vaccines.

So that was the highlights out of the VERPAK meeting in May. I should say that over the past year that vaccine safety issues remain at forefront of everybody's attention and our attention and that among those vaccine safety concerns, certainly thimerosal and mercury in vaccines is one of the leading issues. And we heard much about that yesterday, so I don't think there's any need for much update in that regard, except to say that in March of 2000, in March this year, that SmithKline Beecham Biologics, their supplement for a

thimerosal-reduced hepatitis B vaccine was approved.

Now, I just want to turn to the future, towards -- to next month and to let people know that we're going to be having a special advisory committee meeting on the 27th of July. And this is going to be a joint meeting between our Vaccines and Related Biologic Products Advisory Committee and the TSE Advisory Committee, the Transmissible Spongiform Encephalopathy Advisory Committee. And at this meeting, we're going to be discussing principally two issues.

One is the use or the past use of fetal calf serum and calf serum that was sourced from the United Kingdom in the derivation of cell banks and viral seed banks that are used for vaccine -- that have been used for -- are used for vaccine production. And also the -- to discuss the use of European-sourced, although not UK-sourced, bovine components that are used in bacterial fermentation, that is in the preparation of some bacterial vaccines.

The reason for this meeting is our finding that some of the vaccines that are used do use European-source bovine materials. This is not in accord with our previous recommendations that such materials not be used. And it got prompted by the changing list of

countries that is on the USDA list relative to countries that they consider BSE-free or not. And the -- And again, the

previous -- the prior use of calf serum or fetal calf serum from the UK that had been used in cell banks and viral seed banks. And that will be on the 27th of July.

DR. MODLIN: Bill, thanks. And we will have an update on that meeting at the October

meeting --

DR. EGAN: Definitely.

DR. MODLIN: -- and a report.

DR. EGAN: Definitely.

DR. MODLIN: Terrific. Any questions for Dr. Egan? Bill, thanks, very much.

Dr. Geoffrey Evans.

DR. EVANS: I'm going to be attempting to use the advanced technology.

Good afternoon. I'm going to just cover several main points that have been covered in previous meetings but just kind of a quick update. You should have in front of you the monthly statistics that were passed out. And just to highlight a couple of points, we're still getting about 12 claims per month and if you look back,

just a reminder, the huge increase we had in fiscal year '99 was due to the bolus of hepatitis B claims because the deadline for filing older ones ended in August of '99. And we're just beginning to review those, to some extent, as you'll see that of 285 that we received, we only have medical records in about 68 of them. And various medical conditions have been alleged in these and the court, as recently as the last commission meeting, came and advised the commission that it would probably be a process of four or five years or more before these cases would be adjudicated. The science surrounding adverse events in hepatitis B vaccine is still pretty new and there'll be some more studies' results coming in the next year or so. But it's -- This is a -- This is a vaccine that's going to be looked at carefully and these claims will be adjudicated under a causation-fact basis, meaning that the various injuries that are being alleged, if they're not on the vaccine injury table, and the only injury that's on the table is anaphylaxis, will have to be done almost on a case-by-case basis, although it is our hope that the court, as it did with chronic rubella and -- chronic arthritis and rubellacin vaccine, will go ahead and group certain kinds of vaccines and approach

it that way.
So it's still in the early stages and we're beginning to get depositions, but this is something that we'll watch progress. I should tell you that France has a compensation program and they have told us that of the last dozen claims that they've looked at, they have now compensated multiple sclerosis in about half of them. So what impact this will have in terms of our program remains to be seen. Obviously, much of it is independent processes, but this will be something that will proceed from publicity over time.
As far as other newly-added vaccines, we have three Hib and two -- and eight varicella. These are vaccines that were added in 1997. Of course, DTaP is -- has always been covered on the program and interestingly, we have only 12 to date.
Under the adjudications, we have just about 60 of the older pre-88 claims remaining. And this just gives you a breakdown overall of the kinds
of -- of the percentages of those that have been compensated or been dismissed. Of course, the older claims sometimes lack medical records and were -- where there was a whole series that came in at one time and not as quite sufficient as the newer claims for more --

for more recently administered vaccines.

And the program, as you can see, has paid out about a 1.1 billion to date, with 1.5 billion in the trust fund. And the excess tax is $.75 on each dose of covered vaccine. And we take in about $126 million annually, which has been a controversial point, which I will get to.

Many of you have heard me talk about this legislation pending in Congress to reduce the amount of excise tax. Nothing has happened to that this year, largely because of the attention that the program has received and the controversy surrounding the amount of excess money in the trust fund and the reasons that it is that high. So we're not very optimistic that this will receive any action this year.

As you may remember, we did have some legislation pass at the end of last year which placed an excess tax on pneumococcal vaccine and that was licensed, of course, this past February. And not getting into semantics, but it's not officially covered until CDC goes ahead and publishes the ACIP recommendation. But for all intents and purposes, coverage will start or has started as of December 17th of '99, when the excise tax was applied. And that will be the coverage that will -- any

retrospective coverage from that point will be from that date.

So, in other words, if someone was injured during the clinical trials, for example, they would be covered because it predated the date of the excise tax being applied. So it will officially be covered once it's published, but it really is being covered -- the effective date is really when the excise tax was on board.

There also was some legislation introduced for coverage of hepatitis A vaccine, and it's still not clear to me if that actually was included in the child health legislation that's currently being considered by Congress. But it -- this is the first time that legislation to include hep A was introduced. And there is a reasonable argument to be made, even though it is not designated by -- for CDC for routine administration to children that once the excise tax is applied, that it will be a vaccine that will be covered under the program, because it is being routinely administered in some states.

Okay, I think most of you know this information about rotavirus vaccine. The key points are that the program covered it as of October '98, when the excise tax was

applied, and that we have now -- I'm going to fast forward -- we have now received two claims to date, both injuries, both required surgical intervention. And currently, even though intussusception is not a table injury, there's certainly very solid scientific information on which to think that there is a causal association and we are in the process, as you can see, of developing a notice of proposed rule-making that will indeed add intussusception to the vaccine injury table under rotavirus vaccine with an interval onset of 30 days. I would suspect that if someone were to present a case 32, 35 days, that that would still probably receive some favorable consideration, but it -- but the presumption will go up to 30 days out.

But there is a -- there's a caveat here, and the caveat is that under the law -- and this is something that the Secretary can't change by rule making, but can only be changed by Congress, that anyone that is -- receives compensation has to show six months of continued effects. And as we know, most intussusception cases, other than the one very unfortunate death, fully resolve either with medical or surgical intervention. So this is a problem in terms of some of these cases being covered under the program.

The Senate, in anticipating this earlier last year -- or later -- at the end of last year, passed on their side changes to the statute which would allow anyone who had inpatient hospitalization and surgical intervention to be eligible and thus removed the six months of continued effects. So even though there's none, just the fact that surgery was necessary would qualify you.

But this is -- And this is language that has now been included, as I understand, in the House bill, but there's been no definitive action. It has to go to conference and it's not clear that this will make it out this year. But if not this year, we're hopeful that it will next year. And once that's done, then a family who has unreimbursed expenses, who did -- whose child did require surgery, will be eligible for -- you know, for -- to be entitled for compensation under the program.

Interesting year and a half. The program was up in front of a subcommittee this past September. I think I -- I reviewed that with you. There has also been two GAO reports. The first, I talked about the last time I was here, looking at the claims processing, how long it takes to get through, the extent to which the table

changes have been favorable or unfavorable to petitioners, and again, the trust fund.

And out of this first report, there was only one recommendation and that there be a clear methodology in terms of why we remove and add, as well, injuries to the vaccine injury table. And the -- we responded -- The Department, that is, responded that it was impossible, in our opinion, to produce a clear flow chart and methodology to say how we would approach every single case. I mean, there are -- science is not that exact and we felt very comfortable with the explanations that were provided in the Federal Registers during both vaccine injury table changes in '95 and '97 that that explained the reasoning behind the changes.

But there has been a growing attention on the trust fund, both within and outside government. In fact, there's people in NIP that would like to use our money for certain safety activities. But as you can see, it's now 1.5 and there -- you can -- If you're a vaccine company, you would like to have it reduced in price, at least some of them would. If you're a parent group, you think that the excess funds in the trust fund are indicative of a very restricted vaccine injury

table and process and that that should be changed. And if you're -- Again, there's the need for some kind of a dependable source of vaccine safety funding.

So the GO was asked to actually do a second report concentrating on the trust fund, and they found that yeah, there's a lot of money and that the two vaccines which account for a good deal of the trust fund payments are now being phased out of use in the U.S., which is an interesting circumstance in terms of timing. And if you -- The payments are higher if you have a vaccine-injury table injury and non-table injuries are awarded less compensation and approximately about half as often, so clearly, there's an advantage of having a table injury.

And again, they talked about options, but they did not come up with any recommendation, which I think is quite interesting given the fact that that was one of the real expectations of them taking the time to do this. They discovered that there are no easy answers and if you are going to take money out of the trust fund, for example, to fund vaccine safety, that money has to come from somewhere else.

So it is politically charged. There are also certain restrictions within the legislative language of

Congress. So it's something that certainly needs a lot more discussion, but there are no easy answers.

And I -- In terms of the next year, I look for more attention on the program in terms of the decision making and eligibility criteria. I think the vaccine-injury table has become less of a focus in terms of decision making because the science is only coming into being for some of the newer vaccines that are licensed or being used. So we don't have enough information to determine adverse events they put on the table, so claims will proceed -- the receipt of this kind of additional epidemiological information, so these claims will be judged on causation and what scientific evidence there is on causation, so there are arguments being raised today that perhaps the -- in law, that the criteria for judging causation needs to be loosened so that the program will be more favorable towards petitioners that come forward. And I think this is something that we will be working with the academy and others and looking at critically.

I believe that's it. Any questions?

DR. MODLIN: Thanks, Geoff. Any questions for Dr. Evans?

Dr. Myers?

DR. MYERS: Being last, I'm pressed to the hard core. I'll also try to be mercifully short.

NVPO's charge is to facilitate and coordinate policy relating to vaccine across the agencies and with its external partners. And it operates primarily through the interagency vaccine group that you referenced a lot of times. So it'll be fairly obvious to everybody who's here, we've

had -- we've been very busy recently on issues.

Roger had to leave, and on the back table is the joint statement concerning the -- of the American Academy of Family Physicians, the American Academy of Pediatrics Advisory Committee on Immunization Practices and the United States Public Health Service, which I think when we next see Roger, we ought to extend our appreciation to him for having him. I told him I would announce that.

The other advisory committee on vaccine is the National Vaccine Advisory Committee, which advises the Assistant Secretary of Health on vaccine policy issues. Georges Peter is the Chair of that and he may want to add a couple of comments at the end, also. John Modlin has just joined as the ACIP liaison to that advisory committee.

There are a number of issues I'd like to mention.
First, Walt mentioned the IOM report for Congress and it heavily includes many of the issues from the NVAC's sustaining success in childhood immunizations. With the NIP, there's
a -- the NVAC has developed a vaccine registries report, which will be published shortly in the MMWR, including a separate publication on specific issues on privacy and confidentiality relating to registries.
There was also an IOM report commissioned by the NIAID on vaccines for the 21st century, developing an economic model looking at benefit and risk assessments for vaccines for future development. And I don't know if Stan Plotkin is still here, but he chairs our Futures Subcommittee of the NVAC and with them, he helped coauthor and critique an overview looking at an assessment of the economic model and which we plan to publish on our web site, we hope later this year.
And we generated a work list with the NVPO and for NVAC from that. That work list will come next fall in the workshop on barriers to the development of acellular meglo virus vaccine intended for prevention of perinatal disease -- perinatal-acquired disease, for example, and NVAC is planning several of the Futures'

subcommittee -- several sessions on understanding the complexities of trying to develop vaccines to prevent chronic diseases from autoimmune diseases such as diabetes. One of the things we've learned is -- in the vaccine group, we don't keep up quite as well in some of the other areas.

As we explored some of that, we've also found that the people who hold very exciting new research endeavors potential for vaccine don't have a lot of understanding about the process of developing vaccines. So we're going to do -- we hope later in the year, we're sponsoring a workshop, also, on developing -- development of a vaccine for prevention of chronic autoimmune diseases.

With the FDA, we'll be co-sponsoring a meeting that was discussed at the last ACIP, the suggestion that we needed to take on the issue asking the question about how many patients -- how many people should be evaluated from a vaccine safety perspective in the pre-licensure and then post-licensure phase. And that is tentatively scheduled for November 14th and 15th with the NIH.

We're going to have a benefit risk communication workshop in November, we're going to sponsor on

November 5th and November 6th, with the intent of trying to explore mechanisms that have meaningful dialogue with interested parties on issues relating to vaccine safety and complex issues. We want to learn how to have -- to understand issues from other people's perspective. So we'll have that workshop which ought to prove to be very, very, very interesting.

And in parallel with that, we have a working group that Georges and I are just in the process of organizing to request the VAXCO (phonetic) to consider the issues of establishing guidelines that states might utilize for implementing mandates. And John, I think you're going to

get a -- like a liaison member from the ACIP --

DR. MODLIN: I understand Bill Schaffner has agreed to do so.

DR. MYERS: Bill, great.

We mentioned -- Somebody mentioned earlier in the meeting about polio eradication. One of the issues relating to polio eradication is laboratory containment of wild-type polio viruses and we will shortly be asked by the World Health

Organization -- we, the United States, will be asked to take on the issue of establishing inventories and then

destruction of inventories or collections of wild-type polio viruses. We're just in the process of forming a working group to advise the Department on a process for developing such an inventory and developing a process for the elimination of wild-type viruses.

Two other points. We're in the process, with the NIP and NVAC in drafting revisions to the Pediatric Immunization Standards, and we also have a draft of the Adult Immunization Standards, which NVAC has been developing and which we hope we'll have input from ACIP on.

Georges, did I cover it?

DR. PETER: Well, I would only add that I hope that we get comments from the work group on adult immunizations on these adult standards. Now Rick has left and I forgot to mention to him, but this is a document that has basically been developed by NVAC in conjunction with the National Coalition for Adult Immunizations, and it needs a lot of review. NIP will be involved and, ultimately, we will need to have partner organizations. So that I hope we could foster their comments sooner rather than later.

DR. MODLIN: This has been passed on to Rick and I'll follow up with him --

DR. PETER: All right.

DR. MODLIN: -- on part of that post-meeting follow-up with others.

Terrific. Is that it, Marty?

DR. MYERS: That's it.

DR. MODLIN: Any other questions for Marty?

DR. PETER: And I have nothing further to add, because I think if I did, two things might happen. One is I'd be talking to myself. Number two, I'd be missing my plane.

DR. MODLIN: We'll see you all in October.

DR. PETER: Thanks everyone.

[Whereupon, the meeting was adjourned at approximately 4:33 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 25TH DAY OF JULY, 2000, IN ALPHARETTA, FULTON COUNTY, GEORGIA.

PAMELA T. LENNARD, CCR, CVR
CERTIFICATE NUMBER B-1797
(CCR SEAL - NOTARY SEAL)