THE CENTERS FOR DISEASE CONTROL AND PREVENTION

convenes the

PUBLIC MEETING OF THE

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

VOLUME I

The verbatim transcript of the Public Meeting of the Advisory Committee on Immunization Practices (ACIP) convened at 8:30 a.m. on Wednesday, June 25, 1997, at the Centers for Disease Control and Prevention, 1600 Clifton Road, N.E., Atlanta, Georgia.

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IMMUNIZATION REGISTRIES - PROGRESS IN DEVELOPMENT

VACCINATION OF BONE MARROW TRANSPLANT RECIPIENTS

COMMITTEE VOTES:

Legend of the transcript:

[sic]	Exactly as said
[phonetic]	Exact spelling unknown
--	Break in speech continuity

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

(By Group, in Alphabetical Order)

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Lousiville, Kentucky

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MONTESANO, RAUL
Mexican Health Ministry
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(Mexico's Health Secretariat)
Assistant Secretary for Disease Control and Prevention
Col. Juarez
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VEARUGHESE, PAUL (Acting)
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ZIMMERMAN, RICHARD, M.D.
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INVITED SPEAKERS/AUDIENCE

Anthony, B.F.
Blumen, Larry
Chen, Robert
Dykewicz, Clare
Grant, Chris
Hadler, Steve
Hinman, Alan
Katz, Samuel L.
Kilborne, Ed
Klein, David L.
Linkins, Rob
Malone, Kevin
Margolis, Harold
Mason, Dean
McHugh, Yvonne
Moon, Michael
Nichols, Bill
Plotkin, Stanley
Porges, Geoffrey
Seward, Jane
Snyder, Robert
Strebel, Peter
Vernon, Thomas M.
Wexler, Deborah
White, Jo

P R O C E E D I N G S

8:41 a.m.

DR. DAVIS: Time to start the moment. It's a little late, but I promise to get us past this phase and into the rest of our domain on time. Looking around, at this time of morning of the first day of ACIP there's actually not quite as large a group as usual, so it probably won't take us as long to introduce ourselves to one another.

So with that, I will immediately switch the mike over to Dixie, Dr. Dixie Snider, who will provide some important comments; and then I will return in just a moment.

DR. SNIDER: Thanks, Jeff.

First of all, I want to welcome several people. Dr. Walter Faggett, who I think will be sitting back there somewhere, has not arrived yet; but he is the liaison member from the National Medical Association.

Dr. David Trump, who is here, is our liaison from the Department of Defense. Dr. Trump is replacing Chip Patterson.

I also wanted to welcome Dr. Roberto Tapia Conyer, Secretary of Prevention and Control of Diseases. He is

located over here on my left. He is the liaison from Mexico and is attending his first ACIP meeting as a liaison.

I also want to recognize and welcome Dan Soland, who is acting liaison for PhARMA at this meeting in the absence of Gordon Douglas; and Dr. Paul Vearughese, again to my left, who is the acting liaison for the Canadian National Advisory Committee on Immunization.

Those members who have been given a green folder will find a travel voucher on the inside. Please sign this voucher and return it to Gloria Kovach so that you can get reimbursed for your expenses. Those members with a yellow folder must sign the enclosed waiver letter and return it to Gloria Kovach before you can participate in this meeting.

Gloria's thrown me a little curve ball here asking me a question, and it has to do with the plans of Dr. Steve Hadler and Dr. Walt Orenstein.

In fact, Steve Hadler has already left us, although I think he's going to join us for the meeting, and he is in Pakistan working on the global polio eradication program. And we all sent him off with a nice party, and several people are taking care of his

cats and plants and so forth while he's gone. He's scheduled to be gone two years.

Walt is -- well, since Walt is here, I'll let Walt tell you what his plans are.

DR. ORENSTEIN: I will be taking a six-month detail beginning the end of the summer to co-edit the textbook *Vaccines* with Stan Plotkin and with Ted Mortimer, and will be returning six months after that.

DR. SNIDER: Okay. As you can see, they're going to make it tough on us, the rest of us here left behind.

Although I'm going to say more about this later at dinner, I did want to take an opportunity in front of everyone to think first of all Dr. Jeff Davis for his hard work and dedication as Chair of the ACIP. Dr. Davis' term expires this coming Monday, June 30th. However, if a new member is not appointed by our October meeting -- you've heard this before -- we hope Jeff will return to Chair the Committee.

[Applause]

DR. SNIDER: We do have for Jeff at this particular point in time a letter from Dr. Satcher thanking you for your work with the Committee and a

copy of the book that I think many people are familiar with. It's a history of the CDC. It's entitled *Sentinel for Health* by Elizabeth Ethridge, and it's one of the prized possessions we have here we can to give to people who have contributed to CDC and service to the public in the way that you have. Thanks very much.

The other individual who may be leaving us, again with the same caveat, is Steve Schoenbaum. And I also have a certificate and *Sentinel for Health* for Steve, and wanted to think him very much for his tremendous contribution.

[Applause]

DR. SNIDER: We appreciate very much what both of these men have done on this Committee. According to Gloria's account, since appointment we've finalized 12 recommendations. Somehow it seems like it's even more that.

DR. DAVIS: Well, we've still got another meeting to go.

[Laughter]

DR. SNIDER: For those of you who are not familiar with the logistics of the Committee, the appointed Committee members and CDC employees who serve as

facilitators are seated at the rectangular shaped tables. The ex officio members and liaison members are seated at the tables on the perimeter.

Because it's important for us to hear all comments, we have set a microphone at each end of the Committee tables for members of the audience to use when they address the Committee. I want to make this especially an area of emphasis today because we have made a change in the way we are recording our meetings.

For reasons I won't go into, we have decided that we will not only have audio recordings, which we have been having all along, but that we will get typed transcripts of those recordings. Therefore it becomes very important that individuals identify themselves if they are not already introduced by the previous speaker so that the person doing the transcribing can attribute the comments to the appropriate individual.

Obviously we will be reviewing those transcripts to try to ensure accuracy, but your help in identifying yourself if you have not been introduced already will be greatly appreciated. And obviously that means the people in the audience who have a question will not be

caught on the audio tape unless they come up and use the microphones, so try to remember the come up to the microphone when you want to ask a question or make a comment.

For all of us, as usual, we need to speak into the microphones as clearly when we can so that our comments are picked up and transcribed appropriately.

Restrooms are located the next floor down. You go out the doors, turn to the right, go down the steps and keep heading up that little hall. There are some other restrooms in the Global Odyssey, the museum area, and other restrooms up near the main entrance to the building. It's to the left once you come through the main doors.

There may be because of a few new people who do not know where the cafeteria is located, it is located in the building directly behind me, the new building, Building 16. You go out the doors here, go around through the hall over to the museum, the Global Health Odyssey, make a right, and just keep walking down that hall and you will see the cafeteria.

Remember, for those of you who have visitors' badges, be sure and wear them at all times, at least

outside this room. There have been even recently instances in which there have been some security threats at Federal buildings including CDC buildings. And so our guards, although I think they're friendly enough, are on special alert because of the problems that we continue to have in the Federal Government with people making threats.

The snack bar is located down the hall in Building 1. If you were to come in the main entrance and make a right hand turn and then a left hand turn into the next hall and go down that hall, you will see the snack bar.

Dinner this evening is at The Country Place. Dining is casual. Dinner will be $30 which includes tax and gratuity. A cash bar is available. You should have the materials at your places on which you can circle the entree of your choice on the green menu in the notebook, and return it with the $30 to Gloria or to Felecia by noon today. If you need a menu, don't have one with your materials, see Gloria. We will be leaving from the lobby of the Emory Inn at 7:00 p.m.

And that's all I've been instructed to say. Your turn, Dr. Davis.

DR. DAVIS: All right. There's quite a few bits

of information for you, and I'll compound that a little bit but not by too much.

I too am pleased to welcome Dr. Faggett, Dr. Roberto Tapia Conyer, and Mr. Soland, Dr. Trump, and Dr. Paul Vearughese.

And I wanted the let you know we are working to finalize the minutes of the past two meetings. Our goal is to finalize both sets of minutes by September. So appreciate the patience that everyone has. We're moving quickly on it, actually, so hopefully you'll be getting the October minute from last year in the near future.

The next ACIP meeting will be October 22nd and 23rd in 1997. Please mark your calendars. The 1998 meeting schedule is in the Committee books, and you will find copies of the dates in the back of the room on the handout table. But what that will say is that the 1998 schedule is the February meeting will be on the 11th and 12th, the June meeting will be on the 24th and 25th, the October meeting will be on the 21st and 22nd.

This auditorium is scheduled for renovation in 1998, so you'll be notified regarding the appropriate

rooms. And if you really want to, an interesting way of finding out, just read the *Federal Register* and they'll tell you the room number. The ways of Federal Government, right?

Also in the back of your notebooks are copies of three recommendations published in the *MMWR* since our last meeting, which are the influenza statement, the pneumococcal statement, and the acellular pertussis statement. I'm very proud of those.

Members and people in the audience have commented that during the meeting speakers and Committee members are sometimes difficult to hear, so I request as Dixie did that everyone talk directly into the microphones when speaking. I also want to introduce Kim Newsom, who will be the reporter, and it's very important to speak into the microphone and announce who you are before you speak.

The meeting will be broadcast by Envision to the Parklawn Building in Washington D.C., and from time to time it may be necessary for me to repeat comments for the Washington audience. I always like to say hi to them.

I'd like to remind everyone that dinner tonight is

at The Country Place at Colony Square, and let Gloria know by the lunch break if you plan to attend.

So with that, we now move into a formal phase of our activities, the disclosure. ACIP members who have a potential conflict of interest should make it known at this time. All members, regardless of a conflict, may participate in discussions of all issues provided that full disclosure of potential conflict of interest has occurred. However, the persons with a direct conflict cannot vote on any issue related to the conflict. Only the members, the voting members, need to disclose. The ex officio and liaison members are not required to do so, but may do so if they choose.

As you can see, we have people not necessarily new to us sitting at the table. Chinh Le and Dave Fleming have participated actively in recently meetings. Dave, for some time, is the HICPAC representative to the Committee; and Chinh Le during sort of a transition time prior to his nomination being confirmed; and Dr. Mawle is here today as well, and I'm not sure exactly what your capacity will be.

DR. MAWLE: I'm here as Vaccine Coordinator for NCID.

DR. DAVIS: Okay, very good.

DR. SNIDER: Let me just say a quick word about that.

More and more I think you all realize that many of the vaccines that we're dealing with are vaccines in which the National Center for Infectious Disease has an important role, rotavirus and Lyme disease and so forth.

And in the future we anticipate that the National Center for HIV, STD and TB Prevention will be more engaged in vaccine issues. One that is on the table now coming up is, of course, the HIV vaccine. But there are other vaccines, human papilloma virus and so forth, that that Center will be terribly interested in.

And one of the reasons, of course, that this is not a National Immunization Program committee but a CDC committee is the fact that there are multiple centers that are involved in a variety of ways. And these three parts of CDC are really not the only parts of CDC that are involved, but they are three major CIOs that are involved.

And so we felt that it was important to not only

do this for symbolic reasons but for very real practical reasons, to have representatives from those CIOs at the table. And others are here at the meeting so that provides assistance to them, and I think also broadens the support the Committee will have, staff support and so forth, to carry out its functions in the future.

DR. DAVIS: Very good. Thank you, Dixie.

I want to welcome Drs. Fleming and Chinh Le, and I really appreciate your being here.

We'll start with our disclosure at this point.

I'm Dr. Jeff Davis. I'm Chief Medical Officer and State Epidemiologist for Communicable Diseases with the Wisconsin Division of Health, and I have no potential conflicts of interest.

DR. FLEMING: Good morning. I'm Dave Fleming. I'm the State Epidemiologist with the Oregon Health Division, and I also have no potential conflicts of interest.

DR. SCHOENBAUM: I'm Steve Schoenbaum. I'm the Medical Director of Herbert Pilgrim Health Care of New England, based in Providence, Rhode Island.

I believe my wife still owns stock in Angen

[phonetic], Bristol-Myers Squibb, Glaxo [phonetic] and Procter & Gamble. Our company runs courses in managed care for Pfizer, but I believe that I have no direct conflicts of interest with vaccine manufacturers.

DR. DAVIS: Thanks, Steve.

DR. LE: I'm Chinh Le. I'm the Chief of Infectious Disease for Northern California Kaiser Permanente.

And as an employee of that medical group I have to declare that we have four studies with various vaccine companies: Wyeth-Lederle for the conjugate pneumococcal vaccine in infants; Merck for post-marketing hepatitis A; SmithKline and North American Vaccine, and I'm not sure honestly what studies we're involved with them, because I'm only an employee of the group. I'm not the principal investigator, and I don't own any stocks in those.

DR. GRIFFIN: Marie Griffin, Department of Preventive Medical at Vanderbilt.

I consulted for Merck on a non-vaccine related issue in the past year.

DR. MODLIN: John Modlin from Dartmouth Medical School.

Either my wife or my children or myself own a small number of shares in stock in the following Companies: Merck, Angen, Chiron, and Glaxo-Welcome [phonetic]. I have also in the past year served as an advisory to both Merck and to Pasteur Méreiux Connaught and have participated in educational activities supported by both of those companies, and in the past three years have participated in studies supported by MedImmune.

DR. GLODE: I'm Mimi Glode from the University of Colorado, and at the present time I have no conflict of interest.

DR. GUERRA: Fernando Guerra, Director of Health for the City of San Antonio and for surrounding county.

My potential areas of possible conflict are one, I've served as principal investigator for a community-based field trial with a North American Vaccine product of acellular pertussis. That study has been completed. It was both a safety and efficacy study.

We have previously received a small grant from the Merck Vaccine Division to enhance our immunization registry and tracking system linking up an emergency

room of a children's hospital with a registry.

In the past we have also received support from SmithKline Beecham for my department to do a community-based hepatitis A vaccination program for populations of preschool and school-age children, and this was one of a number of grants that we received from -- SmithKline Beecham was the only pharmaceutical company, but it was a collaborative effort with funding from the City of San Antonio and also from the Vaccines for Children's program with the CDC.

I received one honorarium in the past year from SmithKline Beecham for some presentations that were given to a national organization of health and social service representatives. And then we're currently doing a MedImmune infusion study for a population of at-risk young infants.

DR. DAVIS: Thank you, Fernando.

I think what we'll do now is just go around the rest of the room and introduce ourselves. I think the CDC employees at the table can do that first. Start with Dr. Mawle.

DR. MAWLE: I'm Alison Mawle. I'm currently serving as Vaccine Coordinator for NCID.

DR. DAVIS: Thank you.

DR. LIVENGOOD: John Livengood, Acting Director, Epidemiology and Surveillance Division, National Immunization Program.

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

DR. HEYWARD: Bill Heyward, Vaccine Coordinator for the National Center for HIV, STDs, and TB Prevention.

DR. DAVIS: Thank you, Bill.

We'll go around here starting with Dr. Georges Peter.

DR. PETER: I'm Georges Peter from the Brown University School of Medical in Providence, Rhode Island. I'm a liaison member from the American Academy of Pediatrics.

DR. HALSEY: I'm Neal Halsey from Johns Hopkins University in Baltimore. I'm also liaison for the American Academy of Pediatrics and Chair of the Red Book Committee.

DR. MONTESANO: Raul Montesano from the Government Ministry in Mexico.

DR. IZURIETA: Hector Izurieta, just translating for Dr. Montesano.

DR. DAVIS: Could you speak into the microphone? Couldn't quite hear you.

DR. IZURIETA: Sorry. Dr. Hector Izurieta, National Immunization Program. I'm just helping him to understand English.

DR. DAVIS: Oh, very good. Thank you.

Paul.

DR. GLEZEN: Paul Glezen from Baylor College of Medical in Houston, representing the Infectious Disease Society of American.

DR. SOLAND: Dan Soland with SmithKline Beecham representing the PhARMA organization.

DR. CLOVER: Rich Clover from the University of Louisville representing the Association of Teachers of Preventive Medical.

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

DR. VEARUGHESE: Paul Vearughese from the National Advisory Committee on Immunization, Canada.

DR. SCHAFFNER: Bill Schaffner from Vanderbilt in Nashville representing the American Hospital Association.

DR. GARDNER: Pierce Gardner from the State University of New York at Stoneybrook representing the American College of Physicians.

DR. SIEGEL: Jane Siegel from the University of Texas Southwestern Medical Center in Dallas representing HICPAC.

MR. GRAYDON: Randy Graydon, ex officio member, representing the Health Care Financing Administration.

DR. GALL: Stan Gall, University of Louisville, representing ACOG.

DR. TRUMP: David Trump from the Office of the Assistant Secretary of Defense for Health Affairs representing DOD.

DR. HARDEGREE: Carolyn Hardegree from the Office of Vaccines in CBER at FDA as ex officio for FDA.

DR. BREIMAN: Rob Breiman from the National Vaccine Program Office.

DR. RABINOVICH: Regina Rabinovich from the National Institute of Allergy and Infectious Diseases,

NIH.

DR. EVANS: Geoffrey Evans from the Vaccine Injury Compensation Program.

DR. DAVIS: Thank you very much to our liaisons.

[Whereupon, audience members introduced themselves.]

DR. DAVIS: Thank you very much.

With that we'll begin with our updates. One will be the National Vaccine Program, Rob Breiman will provide that; and then following Rob's update Geoff Evans will give the Vaccine Injury Compensation Program update.

Rob.

DR. BREIMAN: Thanks, Jeff.

Good morning. The main things I wanted the update folks about were some recent comprehensive plans that the National Vaccine Program Office is working on. As you know, the NVPO coordinates the activities primarily of the Federal agencies, and there's a number of cross-cutting activities that are going on.

One that I've mentioned here at the last couple of meetings has to do with adult immunizations. The Department of HHS Adult Immunization Work Plan is at

sort of the completed stage now. It has come back from the agency heads.

The plan was developed by mid-level workers at all of the participating agencies and organizations, and then went back for clearance, sort of buy-in, at the upper levels. It has gone through that clearance and is now headed back to the Secretary, where we hope there will be approval and then a plan for action as stated by the Secretary.

I think it's a very exciting plan. It deals with a variety of issues very important for adult immunization including education and vaccine promotion. It also has research and development components, financing components, and we're hoping that it will have a real impact on coverage levels.

The other thing I wanted to mention to you is we are in the process now, in the early stages, of putting together again a department-wide vaccine safety action plan. As you may or may not know, there was a task force on safer childhood vaccines that actually was mandated initially as part of the statute that created the NVPO and the Vaccine Injury Compensation Program.

The process for actually putting together a report

began many years ago. Gina, to my left, knows a lot more about that than I, actually. But the report finally was completed in 1996 and signed by the Secretary in October.

Again, it's a very comprehensive report that deals with a variety, I think, of very important issues that include assessing and addressing concerns about risks and benefits of vaccines with an effort to enhance the education of both the public as well as health care professionals; also very importantly to strengthen the capability to conduct research and development, the type of research and development that would be needed to promote licensure of safer vaccines.

And also what we regard as extremely important, to strengthen the national capacity to conduct surveillance for vaccine-preventable diseases, to create the ability to not only know the magnitude of adverse events, and even more importantly get a better sense of causality attributable to risk. And basically the report talks long-term methods to do so rather than the relatively short-term methods that have been used up to this date.

So we are now in the process of taking that report

and turning it into a realistic action plan that would include specific action steps that are accountable that we can look at and see what sort of progress we've made, and that's something I'll be telling you a lot more about, I think, at upcoming meetings.

I also wanted to mention that, as I think that you're aware, there's a national vaccine plan that is sort of the Bible for the National Vaccine Program Office. Again, it deals with all facets of the Federal vaccine program, and we're in the process of updating that.

In fact, we will be meeting with our interagency group sometime in the fall and will be assessing our progress towards the objectives that are listed in the 1994 plan, and then reformatting, coming up with new priorities and setting timelines for accomplishing those things.

Because I think it's important to keep in mind the role of the NVAC, I thought I would mention some of the highlights of what the NVAC is now working on. There's been a year or two long process to develop a road map for partnership between manufacturing, the vaccine companies, and public health and academia in order to

produce efficiently safe and effective vaccines.

The first phase of that is basically a paper that describes the delicate fabric that exists in vaccine innovation, and that paper produced by the NVAC will be published sometime this winter in not the *Journal of Pediatrics,* but the journal called *Pediatrics.*

Another thing that I think is very relevant to this Committee, at the last NVAC meeting there was a proposal by both -- a resolution, actually -- that came from both the safety subcommittee as well as the coverage subcommittee to focus more intensively on the issue of vaccine registries, immunization registries, with the idea being that we've been talking about these registries for a long time.

There seems to be a number of important barriers that we must address if we're going to move these ahead. And the registries are very critical to a variety of issues related to ensuring optimal vaccine coverage as well as the potential for use in the process of surveillance for adverse events.

So there will be a workshop this fall, an NVAC-sponsored workshop. It will be coordinated by the National Immunization Program. It will bring together

a variety of people that can focus on a number of the different barriers that exist that include issues of confidentiality, there are issues of actual being able to facilitate such a vast network, there are all sorts of potential barriers; with the idea of seeing whether we can move this process more rapidly ahead, felt to be very important.

There are also two processes going on within our coverage subcommittees to look at strategies to sustain success in immunization coverage, and also to improve accountability for immunization across the board -- parents, providers, payers, public health people, and so forth.

Also, the NVAC is looking at the use of non-traditional -- that is, non-physician -- providers for immunization, particularly for adult immunizations. And we'll also be holding some sort of a workshop this fall to examine the role of pharmacists and other non-physicians providers in beefing up adult immunization coverage rates.

There is a big effort that the NVAC is taking charge of right now that I think is also relevant to what the ACIP is doing that has to do with combination

vaccines, the idea of aiming towards combination opportunity rather than what has been called combination chaos. There will be a series of items that the NVAC will be looking at, both in terms of what the government can do to improve, systematize the approach towards combination vaccines, as well as what can be done again in partnership with vaccine manufacturers.

There also is a very great interest in looking at the question of harmonization, harmonization of package insert information with the recommendations of advisory bodies. And that is something that we, Jeff, may want to consider in the future looking at in a joint way between NVAC and ACIP. I think there's great interest in at least examining why there are differences, making them clear, when possible streamlining.

So I think those are the highlights of what's going on with NVAC and NVPO.

DR. DAVIS: Very good, Rob.

That was some very, very important activities, and really appreciate that. I think clearly not only with this latter issue of harmonization, which has been of great interest to the Committee and to the FDA and

others in the past, but also I think the registry thing too, if ACIP recommendations are going to be used for the lexicon there may be issues regarding interpretation.

I think we're going to probably be getting into that somewhat later today. But very, very important initiatives that you all are involved with.

Any questions for Rob? Fernando.

DR. GUERRA: Rob, I'm interested in knowing a little bit more about the discussion around surveillance and what NVAC is suggesting.

DR. BREIMAN: Well, so far the NVAC has focused on broad issues, and has recommended in a resolution two meetings ago to the Secretary that methods be identified for finding long-term resources to support population-based surveillance for vaccine adverse events.

The NVAC is very firmly behind the concept of population-based surveillance. They've heard presentations about the vaccine safety data link. They're interested in long-term support for that as well as potentially expanding that.

And as I mentioned before, quickly alluded to, the

NVAC would like to consider whether one of the long-term solutions might be actually these registries, with the concept being that eventually they will be much like an automated computerized patient record that could in a more timely way and a more comprehensive way collect data that could then be integrated with vaccine vaccination information.

DR. DAVIS: Any other questions?

[No responses]

DR. DAVIS: Thanks, Rob.

Next is Geoff Evans, who will provide us with a Vaccine Injury Compensation Program update.

DR. EVANS: Good morning. As usual, I've shown up with a couple of handouts. You had sent to you the two-page summary of this 313 changes to the vaccine injury table, and also a copy of the current table aids to interpretation as well as a draft summary of table changes overall to the program. And I passed out before the meeting started a finished version of that, you also have the monthly summary sheet.

So far the program has received a total of 5,148 claims. And so in this fiscal year that averages out to about nine per month, 65 so far. And under

adjudications you'll see that a large percentage now have been adjudicated. Actually 85 percent of the pre-1988 claims have been closed by the program, a significant accomplishment, and 61 percent of the post claims have also been adjudicated.

We're up to payout of $777 million, and the post program, the money from the excise tax, the trust fund, is peaked out at $42 and is roughly in the $30 to $40 million range, and receipts in the trust fund now stand at a little over $1.1 billion.

I'd just like to briefly mention that the new final rule that was published in February and became effective on March 24th, I presented this to the Committee during the rule-making process, and also touched on it at the last meeting. Important parts are that it added three new vaccines -- hepatitis B, Hemophilus, and varicella vaccines -- to the program, and also made some other changes to the table and the aids to interpretation.

It should be noted, however, that the coverage for the new vaccines does not take place until Congress sets an excise tax, and it turns out also we have yet to receive any claims alleging injury from these

vaccines. My guess is that the lawyers that have educated themselves about the program realize the futility right now of filing a claim and awaiting to see what's going to happen with the legislature. Once Congress does set an excise tax and an effective date of that excise tax, then petitioners will be able to file claims for injuries going eight years retroactively, and will have two years in which to file a claim.

The one-page handout that shows the various iterations of the vaccine injury table really is an attempt to try to make sense of the three tables that are now in existence, even though the only effective table for claims filed today, of course, is the latest version.

I'd like to also talk about the excise tax which I've touched on. There are some further developments. And this is a Congress 101 lecture coming up. As you may remember, in July of 1995 we sent to the Congress, Secretary Shalala sent to the Congress, a proposal for the flat excise tax of 51 cents per disease covered for vaccines that were currently covered by the program as well as future vaccines that would come in that CDC

accepts as recommended for routine use in children.

There was also a provision to create an automatic 51 cent excise tax for any new vaccines to obviate the need for Congress to set an excise tax for each time the program's rule-making adds a new vaccine. So this is the important steps of that legislation.

There was very little progress in the interim, I kept reporting back to you, and this is because there was very little attention being given to this issue because we had not finished the rule-making process. And most of us felt that once that was done Congress would have the pressure to go ahead and deal with the excise tax, and that appears to be what's happened.

On June 13 the House Ways and Means Committee added to its tax bill its committee mark, and in doing so it actually changed the proposal from a flat rate of 51 cents to 84 cents, and it did this in order to keep the legislation deficit neutral. It felt that with the lower amount that it would actually increase the nation's deficit, and it did some calculations and thought the 84 cents would at least keep it budget neutral.

It also importantly did add the excise tax

coverage for the new vaccines, but did not include the automatic tax provision. We, of course, were disappointed by that.

There was also a provision based on the President's budget that was considered by the Committee that would have removed the need for the Federal Government to pay excise tax on vaccine purchases for one year, and that the Committee considered and also left out of its mark -- I'm sorry, that was left in initially and then taken out later on by the Senate Finance Committee.

A couple of weeks later the Senate Finance Committee considered all this, and the result was that the 84 cents stayed in; the automatic tax provision was not made part of it. It looked like the House mark all along, but there was an additional thing that was put in, and that is that the Department of Treasury was to report to Congress an analysis of the 84 cents and see what effect that would have on the program and the rate of expenditures and incoming monies.

So as things stand now, both the Senate Finance Committee and the House Ways and Means Committee bills have left committee and are now on the floor, and we

expect and it's hoped that there's going to be action before the July 4th recess. And ultimately hope that this will all be decided in conference before the final break in August, so we may be able to get a tax bill reported out.

I should add parenthetically that as we begin to talk to people that are working in Washington and are familiar with the manufacturers, et cetera, the Vaccine Compensation Program is really just a small issue on the whole scale of the tax issues that are before the Committees, and it's hard to draw a lot of attention to the importance of maintaining what was already considered to be an appropriate level.

But I think that this certainly indicates progress, and I'll let you know what's going on. I think I'll stop at this point and see if there's any questions.

DR. DAVIS: Are there questions for Dr. Evans? Dr. Orenstein, and then Dr. Katz, and then Dr. Halsey.

DR. ORENSTEIN: I'm intrigued in looking at your table, Geoff, with what appears to be for '96 a substantial drop in petitions filed. And while we only have eight months of '97, that still would project out

to less than 100 claims files. Is there any reason for what looks like this drop, that you're aware of?

DR. EVANS: We don't know of any. We can speculate. We've only received one DTaP claim, for example, and we certainly are going toward that as the predominant vaccine that's being given, so that may be one reason. The blip that you see in fiscal year 1995, of course, represented the move by 75 petitioners to get claims in ahead of time before the table changes.

So I think we need a couple of more years' experience to really see if this is real, but certainly it's encouraging.

DR. DAVIS: Sam.

DR. KATZ: Geoff, in the table for your new Section 313, for immunodeficient individuals with both measles vaccine and with vaccine-associated paralytic polio, you have a limit of six months from the time of receipt of vaccine.

Since the only case with human immunodeficiency virus in which giant cell pneumonia developed was 12 months after receipt of vaccine, and since most of the children with severe combined immune deficiency who develop vaccine-associated paralytic polio have

developed their disease 10 and 12 months after receipt of vaccine, why do you limit it to six months?

In an era when you have unomic [phonetic] analysis so that you can study measles virus or polio virus and show that it's vaccine virus, it seems inconsistent that you put a six-month limitation. It doesn't fit with the actual cases that have been studied.

DR. DAVIS: Sam, I think that's an excellent point. I guess as we went along the public comment and the scientific comment didn't really point us in that direction. That's certainly something that we would consider. We just continued the original table guidelines that were placed into effect.

I would also add, though, in terms of pragmatics that anyone that would file a claim and show laboratory evidence of causation, they would certainly be compensated assuming legal requirements are satisfied. So that's not a problem or an obstacle at all, but it's a good point.

DR. EVANS: Neal Halsey.

DR. HALSEY: Two points, Geoff.

One on new vaccines, if they're not going to be automatically added to the table if the new bill passes

as you've described it, maybe you could just reiterate a point I think you've made before, that new combination products of existing antigens will be covered because that's the way that it's designed.

The second question was on varicella vaccine, and you don't have any compensable events on the table at this time. Can you outline what the plans are for establishing those events and how soon we might except to see something there?

DR. EVANS: As far as the first question goes, we've been giving Hib vaccine now for several years, and of course anyone that would receive Hib along with other antigens could always file a claim and have done, I think in some cases, or at least considered it, claiming one of the covered vaccines, for example.

So it was de facto coverage, but there is coverage by the fact that it's on the table; and that's not a practical problem at all. And once, of course, it's added, then you have the eight years of retroactive coverage. It's just there would be a delay if they were going to be alleging vaccines that are not covered, but we don't think there's any problem in terms of the delay that's happening now in terms of the

taxation.

DR. HALSEY: My point was, I just didn't want there to be concern about new combination products when they're introduced. There might be some apprehension on the part of providers not to use a new product if they thought it might not be covered.

My understanding is that all those are covered because they're the antigens that are covered, and I didn't want there to be a negative perception that they shouldn't use a new product because it's a combination product that might not be covered.

DR. EVANS: We have emphasized that point. Of course, we can't say without -- it's all likelihood it's going to be covered eventually, and that message is brought home. But it's something that we can't say with 100 percent that you are definitely covered the day you give it, but in all likelihood you are. And that confidence is transmitted.

As far as your other point of varicella, the only thing that we can turn to is the experience that the program has had with rubella vaccine. And here the court, after the 1991 Institution of Medical report, had a grouping of cases that alleged rubella vaccine

associated arthropathy and arthritis.

And the court along with the program began looking at that and considering the possibility of making that a compensable injury, and indeed the court went on and provided guidelines, and we eventually made that a table injury in 1995.

My guess at this point will be that for both hepatitis B and varicella vaccine, if we begin to see some kind of pattern of cases that are coming in, that we will have to bring on experts and provide some kind of guidance to the court and determine whether there's strong enough evidence for causation, and if so through rule-making later on we will add that as an injury to the vaccine injury table so there can be a legal presumption of causation.

DR. DAVIS: Georges Peter.

DR. PETER: One suggestion, Geoff, is once the final legislation is approved by the President, if a brief summary could be sent by your office to the members of the Committee it would be very helpful because these matters are fairly complex. They change depending on which committee, indeed certain items might be deleted. And I think to have them in advance

of the October meeting would be helpful for us in distributing them to our organizations.

DR. EVANS: So my Congress 101 lecture was a little fuzzy?

DR. PETER: No, you haven't signed the legislation yet.

DR. DAVIS: Well, it wasn't 101, maybe 201.

Well, thank you for providing that, and it's very useful. And I concur that we'll certainly want to get more information in writing so that we're real accurate on these issues.

But thanks very much, Geoff.

I think what we'll do now is move on to the next agenda item, which is the ACIP procedures and policies work group progress. And you received a draft of the statement that's evolving as a result of this process as a part of your packets. It's actually, I think, a very exciting process.

The need for an ACIP policies and procedures to govern the development of ACIP recommendations seem to be somewhat of an insidious phenomenon. Gloria would requests from Federal agencies regarding what are the ACIP policies for developing recommendations not only

for our scientific recommendations, but in particular with regard to the Vaccines for Children program.

And I think in our discussions during the Committee meetings increasingly there would be awareness among ACIP members and others regarding inconsistencies in our process in developing recommendations. We might take a somewhat different approach for one vaccine or one prevention program than for others.

The need for ACIP policies and procedures seemed to come to a crescendo during our Committee activities in revising the statement on polio myelitis prevention, I think a rather compelling crescendo at that. And then following open discussions during a full ACIP meeting, the process was somewhat formally germinated, as some of you may recall.

Joel Ward and Steve Schoenbaum presented their thoughts regarding the utility of different approaches and different issues to be framed in the process of our developing our recommendations. And this led to the formation of a working group to recommend an explicit set of principles which would guide the process of developing recommendations and specific criteria to

follow during the development process.

Members of the working group were myself and Drs. John Modlin, Steve Schoenbaum, Jessie Sherrod, Dave Fleming, Dr. Georges Peter, Rick Zimmerman, Steve Hadler, and Dixie Snider. We had an initial conference call on August 14th, 1996, and the group identified problems with the present process which was used to establish ACIP recommendations.

And rather than belabor or discuss specifically what we discussed at that time, I'll just summarize it by saying that there were ten key problems that were identified which impacted on the development of recommendations, and about nine general recommendations were generated to improve the process of developing ACIP recommendations, and these were then further refined. The reason why I didn't want to belabor this is because all of these items are included in the draft which people have had an opportunity to look at.

The process then involved expanding the list of problems of the working group members. We solicited the thoughts regarding the process from all ACIP members and liaisons and ex-officios and anyone else, for that matter, who wanted to provide some comment.

All of that input then resulted into the generation of a straw document which was drafted by Dixie Snider for detailed discussion during our working group conference call on January 8th, 1997. And I believe that all of the comments people have provided and the input through our working group discussion process was quite thoughtfully incorporated.

And that was then followed by another round of correspondence, which has now resulted in the draft policies and procedures for development of recommendations for vaccine use and for Vaccines for Children by the ACIP. The current draft is dated June 19th, 1997. This has been circulated for comment and discussion. And Dixie will provide the critical kernels from this draft.

Thank you.

DR. SNIDER: Thank you, Jeff.

What I'm going to do is just give you an overview of this document and then highlight some of the issues I think that still need to be discussed.

First of all, I just want to point out that there are two major sections. We felt it was important to, in addition to having procedures and practices or

policies and procedures for developing our recommendations routinely. As you know, the Vaccines For Children program involves some change in the way we ordinarily do recommendations, and so we have that separate section just to point that out to you.

Again, why develop written policies and procedures? I'm sure there are more reasons than I've listed here, but some of the things that were important to us is, first of all, to make what we do more explicit to the outside world so that people know better how we arrived at the conclusions that we did.

Second, to have some standardization in our approach, rather than for each recommendation come up with a different approach. And that obviously leads to hopefully consistency in the process, at least, of how the Committee would operate.

I think this argument also has tremendous value is helping orient new members, and some of the things we've included in there have purposely been included because we think new members will be able to read that and come on board and be more productive more rapidly as a result of having a written document.

Overall, we think that this has the potential to

improve the quality of the recommendations of ACIP, and that that in turn will lead to an increased acceptance of the recommendations of the ACIP. Admittedly those are conjectural but reasonable conclusions to draw, I think.

With regard to the purpose of the Committee, we've made a number of statements.

First of all, I want to point out that we will be modifying the charter, but we have said that the purpose is to provide advice and guidance to the Secretary, Assistant Secretary for Health, the Director of CDC on the most effective means for preventing vaccine-preventable diseases, which takes us away from just concentrating on vaccines but allows us to talk about other interventions as well.

So we acknowledge the broader scope of the Committee; make it clear -- as we went through the polio recommendations it became clear -- that these recommendations of the Committee are subject to the approval of the Director of CDC.

We do point out that ACIP has a unique role in the Federal Government, at least, with regard to making recommendations. There is no agency, there is no other

constituted group that serves the function that ACIP does, and so we've made that very clear; and identified for the ACIP our overall goals, which are obviously to reduce the incidence of vaccine-preventable diseases and improve and increase the safety of vaccines.

One of the things that has been done recently is to modify the charter. At Dr. Satcher's request we're going from ten to twelve members, and one of the reasons for that is that he feels that we should have more representation from people with clinical practice expertise, preventive medicine expertise, but yet not lose the kind of expertise we already have on the Committee. And so we'll be increasing to twelve members.

Obviously there are diversity issues which are addressed in the document. We have pointed out in the document how we currently solicit nominations. One of the things we did not include -- which I will come back to later, one of the areas for comment and discussion -- is whether we should routinely, as the National Vaccine Advisory Committee does, solicit nominations through the *Federal Register* notice.

We point out in the document how we select

candidates, and we point out in the document the role of the regular members and ex-officio members and liaison members; also, that everybody understands our perception of who they're speaking for -- for example, a liaison is speaking for that organization that they represent; an ex-officio is speaking for the agency that they represent.

Selection of topics: We have an appendix in the document that you have, an information sheet that we provide to people inside of CDC and outside, that we use to try to inform us about the topic they're proposing and make rational suggestions about whether it ought to be included on the agenda, the criteria we use for selection of topics for the agenda.

We establish a policy of reconsidering all of our recommendations at least once every five years. There have been suggestions of making minor revisions by short *MMWR* notices and by posting things on the Internet. I think there's some pro's and con's to that, and those are some areas where we probably need to have some comments from folks and ultimately some discussion.

The process of developing recommendations we've

tried to make much more explicit, identify what working groups are, what they're supposed to do, the fact that they are to review labeling.

We have identified cost-effectiveness analysis as something that should be done. I have a question mark here, though, because I think the question at least in my mind is whether we want to say to all the programs that this should routinely be done for every recommendation that we make, or whether this would kick in only when ACIP requests a cost-effectiveness analysis; and obviously this has resource implications, et cetera.

Some of the other things on here are rather obvious. Specific rules of evidence, the question mark there is not whether we have specific rules of evidence but which set. There are several different sets that can be used: U.S. Preventive Services Task Force; HICPAC has used one; the folks who put together the recommendations for prevention of opportunistic infections in immunocompromised persons have another set. And so as a fallback we've gone and we've said the U.S. Preventive Services Task Force, but the Committee may feel some modification of that or some

other model of rules of evidence would be better.

Evidence tables have been suggested as being needed in every guideline, but several people have raised the question about whether that should be done, so I again put a question mark about it.

Meta-analysis is suggested to be done whenever it's requested by ACIP. Again, the reason for the question mark is whether that should be routine or whether it should be upon request, not whether it should ever be done.

In the interest of time let me move along.

I think Dr. Sherrod was a primary mover behind our putting in the section on policy analysis. It's not so much that the scientific method and the approach we use doesn't lend itself to doing policy analyses as well as evaluating scientific data, but I think appropriately there is a need for us to, when we think about public policy, to have a process that's explicit.

And what we've done is to actually borrow from a textbook which I have with me the approach, and I've just put very briefly the steps here that we would follow in doing a policy analysis. This is a rather standard thing that's taught in policy analysis

courses, so there's nothing really amazing about what is on that overhead; only the fact that the ACIP would start to use such a process, which we don't right now.

In drafting the recommendations, again we talk about working groups and how they function, what their role is as opposed to the full Committee, about the opportunities there are for public comment, about Committee comments and how they are incorporated, who makes the decisions. And in fact the bottom line is, in terms of a recommendation coming to the full Committee, is the chair of the working group makes the call about what version and what the version that comes to the full Committee will say to clear up that piece of confusion.

I think everybody knows that the *MMWR Recommendations and Reports* is our primary vehicle, but there's been a question about format for our recommendations; and in another appendix in the document you have there is a suggested format for all of our recommendations that we also would appreciate your comments on. And this just goes on with the format, but you can look at that in your handout.

A couple of other things that are dealt with in

policies and procedures:

It's been our recommendation that the ACIP not be responsible for developing implementation plans once recommendations are in the process of being developed, but that it's the program's responsibility; however, it's the program's responsibility to tell the ACIP how it plans to implement and keep ACIP informed about any implementation problems. So again, trying to clearly delineate who's responsible for what.

Finally, for other things that are not covered in our document, we fall back on the CDC publication *CDC Guidelines: Improving the Quality*.

For VFC -- I won't go over this in great detail -- but there are some additional considerations beyond what I've already mentioned. When we talk about VFC we start thinking about programmatic feasibility and implementation strategies, vaccine supplies, and cost-effectiveness in more detail, I think.

Also, we obviously have to have written resolutions; and we have voting, as you know, and *Federal Register* publication as required for VFC. So there's some differences from our routine development of recommendations.

A couple of questions here related to VFC, we don't have -- actually, perhaps, beyond VFC -- we've not put in our policies and procedures, it occurred to me as I was putting this together, anything about conflict of interest. And I wondered if we shouldn't include something along those lines in this document.

And also in looking at what Steve Hadler, our Pakistani representative who just came in, had put together for our VFC resolutions for this meeting, I wondered as I started looking at it if there weren't some elements in there that perhaps shouldn't be incorporated into the next draft.

So let me just stop with that. I know we're running overtime, and I don't know how much discussion you want to have.

One option would be to have some rather brief discussion of some of the major topics that people feel strongly about here, and then get written comments from the Committee and come up with another version that we could look at and perhaps discuss more extensively at the October meeting; because given the time we have on the agenda I'm not optimistic that we could do a lot with that.

DR. DAVIS: I think we could address some questions now. We've cut a little bit into our break. I think a half hour wouldn't -- whether we had a lot of time or a little, we've only got a half hour -- it wasn't going to be enough time for all of this.

But I personally want to think Dixie for his efforts in generating this draft and really listening to everyone. I think we had a very good process as a working group. And we feel it's real important to get this draft out there for you all to comment on at this point in time, and look at real carefully and provide us with appropriate feedback.

Let's take a few questions.

Neal Halsey.

DR. HALSEY: Dixie, I think of all the things you talked about, the one substantive change that might impact on the manner in which the recommendations develop is the insertion of rules of evidence. Doesn't matter which one you use, but whether or not one is inserted. And I wondered if you have any strong opinion one way or the other.

My concern would be that there may be -- if somebody feels that the evidence is in a somewhat lower

category than the absolute highest category, it gives more ammunition to people who don't want to follow the guideline. And I think we do establish guidelines, and we hope that everybody does follow them; and we try to implement them through a variety of mechanisms.

I wonder, based upon the experience of other groups that have used these, whether you have any feedback or suggestions because we have not done that here. We have not done that at the Academy of Pediatrics. We have contemplated it but rejected it to date.

DR. SNIDER: I'd be interested in other people's opinions.

I guess I've been involved with this kind of thing for a number of years, and to me it almost becomes an ethical issue in terms of making recommendations. I have a lot of difficulty, personally, in not sharing with people the basis on which I'm making a recommendation.

I do not think that there is anything wrong with making a strong recommendation that's based on clinical judgment, so I don't see that there necessarily has to be a weakening of a recommendation just because of what

the basis of the recommendation is. I personally feel it's terribly important to be very explicit on whether there are controlled trials, case-control studies, case series, or expert opinion.

And I think what you say is true, that there is the potential for people not following a recommendation if they feel that there are no controlled trials, and that may be what we have to live with. But as I said earlier, I think one could still say that the ACIP strongly recommends doing X, Y, or Z, and that doesn't necessarily have to be related to the fact that there is not a clinical trial.

There's some things in this world you're never going to get a clinical trial for, and yet I think you can get a pretty fair consensus that it's the right thing to do. There's all kinds of circumstantial evidence that it ought to work, that it ought to result in tremendous benefits for society with relatively minimal risk or nil risk of harm; and so you make a strong recommendation.

DR. DAVIS: Pierce Gardner, and then John Modlin.

DR. GARDNER: I think the document looks spectacular. I congratulate you for doing this, and

those who stimulated its occurrence.

My concern as you speak, Dixie, regards to the length of these documents. And when you get into the conflicts of interest and go around the table and learn who owns stock in this and that, I guess what I see happening here is a process that's going to result in a very large document; but that what we publish in the *MMWR* is going to have to be some boiled-down version that allows it to still be user-friendly.

Most people are eager to get to the bottom line and want to know what this Committee does. There may be another subgroup that wants to know exactly every jot as to how this thing happened. But we don't want to get away from this as being a user-friendly document, and these things are going to be 100 pages long pretty soon if we include everything on your list.

DR. SNIDER: Well, hopefully we can be relatively succinct. I agree with your point. I'm not sure we're not already there, in terms of having documents that for the average general practitioner or general internist really doesn't want to read through the whole thing.

And it seems to me that is another issue that we

ought to be concerned about, and whether there should be some shortened version of our recommendations; but I don't think it's an argument not to go through this process.

DR. MODLIN: That was exactly the point I was going to make. It seems it bears on the question also of the previous topic we were just talking about, which is whether or not we should be inserting some indication of what the strength or the nature of the evidence supporting the recommendation is.

It seems to me if we follow what other groups have done, you wind up basically distilling the strength of the recommendation down to a letter, an A or a B or a C, perhaps with some sort of sub-designation as well, that inevitably, seems to me, is a -- the only reason for doing that is to give -- well, it's for someone who doesn't want to read the entire document.

It seems to me like most of the statements are already well written enough that we really do take great pains to indicate what the nature and the basis of the recommendation is in the body of the document. And for those readers who do read it that information is there; the strength of the recommendation is there.

I'm not sure it's necessary, and I think maybe we do need to discuss whether or not we should have a lengthy document and an executive summary version. And it may be that the executive summary version might include a letter, an A or a B or a C, saying that this is based on two well-designed, controlled prospective clinical trials or not.

But I think I agree with Neal in the sense that I think this really does deserve a closer and wider look before we adopt this as policy for our Committee.

DR. SNIDER: In my own look, John, I think our problem is not that we don't have some documents that are exactly as you describe, where for the major recommendations we say there are clinical trials, there are case-control studies, or it's expert opinion and so forth. It's not that we don't have things like that, but we do not have consistency.

In looking back, if you look back at the recommendations that we've issued, I think they're pretty spotty in terms of some of them have it, some of them don't. And so I think it's this inconsistency of having that information in there that is a problem that

needs to be solved. But how we put it in there, how you want to do it, I think we need to talk about.

But I don't hear anybody saying we shouldn't really be saying what the evidence is, and in many cases we do. But we don't consistently do it, and I think the point we're trying to make is we need to consistently do it.

DR. DAVIS: Thank you.

Fernando Guerra, then Rick Zimmerman, and then Chinh Le; and then I think we'll break off our discussion for our break.

DR. GUERRA: Dixie, was it within the scope of the work of the Committee in developing these recommendations and guidelines to include in that a way that this information can be communicated to the general public, rather than just obviously those that are listed within the Federal administrative structure?

DR. SNIDER: We did not have that as part of our charge. Our major concern was how do we go about developing recommendations, how did we get to the point where we even have a set of recommendations?

So I think the bridge is what was mentioned earlier, about how we're going to then effectively

communicate our recommendations to our various constituencies. And to me that's another issue -- a very important issue, but not one we were focusing on -- because a lot of our concerns were that we didn't even have a process in place that would help us assure the consistency, standardization, and quality that we want out of this Committee.

DR. GUERRA: Is it possible at this point, though, to perhaps consider another section that would deal with the recommendations for communicating to the general public?

DR. SNIDER: Yeah, I leave that up to Jeff to mull over, about whether we want this Committee to do that or we want another committee to do it. But it seems to me that it is a very important issue.

I do want to remind the Committee that when the CDC Practice Guidelines book was put out, and there's a CD-rom with it, those are shortened versions of your recommendations. Some people here at CDC edited those down, worked with the programs to have shorter versions of our recommendations. So there is a precedent for coming up with shorter versions for consumption by clinicians.

And the Public Health Practice Program Office, with assistance from the various CIOs, plans to continue that activity. So it may not be exactly what we want, but we can bring to you some examples of how the longer guidelines -- which document for the public the process we went through, everything we considered, what data were available and so forth -- and show you how that then was boiled down to a set of guidelines for clinicians that are much shorter than the *MMWR.*

DR. DAVIS: Did you have something that you wanted to add to what Dixie was saying?

MR. MOON: Yes. My name is Michael Moon, and I just wanted to comment on the use of the Internet as a tool to disseminate the information.

I believe that it would be a great idea to actually have the Internet as a tool for that. And at that point each individual organization -- I know at NIP we have a section on our web page for ACIP recommendations -- and at that point we can use that section of the web site to view the executive summary to go with the recommendation. That's part of my job there, is to update and maintain the web site, and that's something that I would be interested in.

DR. SNIDER: Well, the CDC guidelines are on the web site. I don't think we have the shortened version on the web site, but we do have all the CDC guidelines -- ACIP and others -- on our web site.

I think what we were particularly concerned with here, though, has to do again with the development of recommendations. Let's say we have a recommendation for which we have to make a minor change, one paragraph for the whole document. Are we going to go through the whole process of coming up with another recommendation, or could we put a notice in the *MMWR* and make a change on the Internet without having to go through the whole process of printing up a whole new set of recommendations?

I think there's some pro's and con's to that, but it's something that needs to be further discussed.

DR. DAVIS: Thanks.

Let's just have two very quick comments, hopefully very quick.

Rick, then Chinh Le.

DR. ZIMMERMAN: I support the movement to the explicit outcomes-based approach. I think that's important. It goes along with what's happening, I

think, in a number of other organizations. When they're creating guidelines they're giving an explicit approach, and they're saying what their strength of evidence is and the basis for those recommendations.

And I think that's the trend in guideline development, is to move towards an explicit process. It's being done by a number of professional organizations. And in terms of acceptability of ACIP's recommendations to other groups, this makes it much more acceptable.

The American Academy of Family Physicians' evaluation for policy specifically looks at the type of evidence and is it laid out, and it critiques. Does the policy tell you the type and strength of the evidence? And if you sit at this table or you read the whole document and are aware of what that literature is, then you can do that perhaps the way it's done.

But I agree with Dixie's comment. It's been spotty how it's applied in the past, and someone who spends a modest amount of time with the documents cannot tell the strength of the evidence upon which it's based. And I think it will make the ACIP recommendations much more acceptable to the broad

practicing community if they are explicit.

DR. DAVIS: Thanks.

Chinh Le.

DR. LE: Rick, I was just going to say exactly the same thing. And even beyond that, I think when clinicians look at ACIP or AAP guidelines we do really want to see how we are going to practice medicine.

I think the strength of the recommendation is absolutely very important, because truly if we adhere to the title of this Committee it is an advisory committee; and I think the strength of advice is dependent on the strength of the evidence. And I think we should always remind ourselves there's a sore thumb somewhere that needs to be looked at again and again.

So I entirely agree with the two of you.

DR. ZIMMERMAN: If the Committee would like, I can probably get AAFP's forms if you're interested in seeing the evaluation that's done by some of the outside groups of different policy recommendations, from whatever group it comes from.

DR. DAVIS: I think what I'd like at this point would be for everyone to provide your comments, and certainly if you have other items you want to submit

for consideration it would be fine to do that. But let's have comments on this draft, and have them submitted by a month from now.

I think we have to be a bit reflective and look at this and what the intent is. We certainly would appreciate that. I think this is an evolving process, but we'll revisit this during the next ACIP meeting.

Dixie, thanks very much; and thanks, everyone, for the discussion.

I know it's break time, and technically it's almost over, but what we'll do is come back in 15 minutes. Let's just take a 15-minute break. It's basically ten after now. We'll start at about 25 after.

[Whereupon, a brief recess was taken from approximately 10:11 a.m. until 10:31 a.m.]

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DR. DAVIS: We're now going to embark on the next discussion. We're running about 15 minutes behind schedule at this point.

We'll be discussing an update on acellular pertussis vaccines, and Peter Strebel will lead this. He will tell you what will be discussed this morning.

There's one topic that was listed on the agenda that won't be, so he'll explain what will be done.

Peter.

DR. STREBEL: Thank you, Jeff.

The update this morning on acellular pertussis vaccine is really a session for discussion only. There are no action points, and it should be an interesting session.

The main purpose is to inform members of increased use of DTaP vaccines and also report the results of the Stockholm Trial II. These results were announced in May in Stockholm. And I'll start out by providing you with some of the vaccine purchase and distribution information regarding acellular pertussis vaccines, and then Dr. David Klein from the NIH will present the results of the second trial in Sweden using acellular vaccines.

The third item on your agenda, which was going to be an update on combined DTaP use for infants, has been withdrawn because the manufacturers are under discussion with FDA in finalizing licensure for that product.

Okay, let's take a look at what's happened to

vaccine purchase and distribution under the CDC contract mechanism. This graph shows the total number of doses purchased and distributed under the CDC contract from January 1996 through 17th of June of 1997.

On the X axis are the number of doses in thousands, and the color code, as you see in the red bar or maroon bar at the bottom is whole-cell DTP; in the purple is DTP-Hib. In the light blue is DTaP; in the light yellow is DTaP-Hib; and in the sort of lightest bar is DT only.

And the main points to take from this is to notice that back in the beginning of 1996 approximately half of the doses purchases and distributed were whole-cell DTP; this was stocked as of September 1996. And DTP-Hib combined was about half of the doses purchased and distributed during 1996, and that's declined to about a quarter.

And the main message, I guess, is that based on ACIP recommendations and obviously licensure of acellular vaccines, the first one which was in July of last year, there's been increasing purchase and distribute of DTaP in the public sector.

Are there any questions about that? Otherwise we can move on.

DR. PETER: Do you have any information from the manufacturers with respect to a similar trend in the private sector? In other words, are private physicians who do not obtain their vaccines through VFC giving DTaP as frequently as this data would suggest?

DR. STREBEL: I don't have that with me. Bob Snyder actually provided these numbers to me; may be able to speak to that.

Bob, the question is do we have information from the private sector in the same sort of format as this?

DR. SNYDER: We're seeing a similar trend using the biological surveillance data. I only have that through about March of '97 at this point, but DTP is virtually non-existent. DTaP is continuing to increase. DTP is approximately a quarter to a third of the market, with DTaP continuing to rise as a proportion.

DR. ORENSTEIN: I think there are some changes, though. I think if anything the proportion of the acellular pertussis market is higher in the public sector than in the private sector, which is implying

that uptake is substantially faster in the public sector than it is in the private sector.

In other words, if I remember the numbers correctly, in 1996 public purchase account is for about three-quarters of acellular pertussis vaccine purchased, while overall DTP-containing vaccines were about 60 percent, implying a much slower uptake in the private sector.

DR. PETER: And is a good deal of the use of the DTP-containing vaccine the DTP-Hib combinations? Does that account --

DR. ORENSTEIN: That's what we believe, is most of that is DTP-Hib.

DR. STREBEL: Okay. Let's move on.

By way of background to David Klein's presentation on the results from Stockholm II, I just wanted to pose two questions before David starts his presentation. And the first one relates to what new information do we learn about vaccine efficacy of acellular pertussis vaccines from this trial; specifically, down at the bottom of the overhead, does protection against milder illness increase with the addition of more components in the acellular vaccine?

And the importance of this is if milder illness is more effectively prevented by a multi-component vaccine, one might anticipate that this would have a greater impact on infection and herd immunity and basically increase protection of young, unvaccinated infants who, as you know, are the group at highest risk of disease and death. So look out in David's presentation regarding the impact of the number of components on vaccine efficacy.

And just by way of introduction, the 1986 to '87 Swedish clinical trial raised this question. When they looked in the randomized clinical trial for vaccine efficacy for a case definition of 30 days of cough plus culture positivity, the single component PT-containing vaccine had an efficacy of 80 percent and a two-component PT-FHA had an efficacy of 79 percent, so very similar protection against classical disease.

Whereas when they looked at cough of any duration plus culture positivity, there appears to be some decrease in protection for the single component at 54 percent, the point estimate, and the two component at 69. However, this difference was not statistically significant; but the question was raised, do more

components protect better against milder illness?

The second issue that the Stockholm II trial may help us with relates to vaccine safety. And I've just put up to remind members of the frequency of adverse reactions associated with whole cell, and this goes back to the publication by Cody, Baraff, and Cherry published in 1981.

And here the frequency of reactions within 48 hours after DTP are listed from most frequent to least frequent, and you'll see that we have on the right good evidence to show substantial reduction, a statistically significant reduction, in pain, redness, swelling at the site of injection, fever greater than 38 degrees, drowsiness, persistent crying, and high fever have all been previously shown to be less frequent following acellular vaccine; where the data has been not that convincing due to the rarity of these events, HHE and seizures, which you may recall in this study were reported at a frequency of 1 in 1,750 doses.

Now the Sweden Trial II, Stockholm II had, I think, about 80,000 children enrolled, approximately 20,000 in each vaccine arm. So clearly for a frequency of 1 in about 2,000 doses, we may get important

information to help distinguish if there's actually a lower frequency of reactions.

So question two here is, are DTaP vaccines associated with fewer moderate to severe adverse reactions when compared to DT whole-cell vaccines? And look out specifically for the HHE and seizure results.

David, over to you.

DR. KLEIN: Thank you, Peter.

As Peter indicated, my charge this morning is to basically provide you with some overview of the results that occurred in Trial II in Sweden. As Peter mentioned earlier, the data was first disclosed in May of this year in Gotland, and I guess this is the first real formal presentation of that information to a U.S. audience.

This just gives you the objectives. I guess I should say up front before I even begin my discussion that the results of the two trials, essentially when I'm done you'll realize that the overall efficacy results were very similar to what we're seeing in Trial I, and I think that's something we all hoped for, expected; but I just wanted to make sure that's clear up front.

The Trial II objectives were to estimate the relative efficacy of acellular pertussis vaccines against typical pertussis, and again pertussis infection as compared to the whole-cell vaccine. And as indicated, the trial was conducted between 1993 and 1996. The investigators on this trial are listed here, and I think they do deserve a lot of recognition because it certainly was a painstaking effort on the part of many to conduct this trial.

And of course, this trial was basically an extension of Trial I, which began about a year earlier. And the idea of Trial II was to provide information at least to the Swedes using their schedule of 3, 5, and 12, which was quite different from what was originally used in the initial trial, Trial I, which uses schedule 2, 4, 6.

The design is shown here. It was double-blinded, randomized, multi-centered, whole-cell pertussis controlled trial; and approximately 83,000 Swedish children at 37 child health centers located throughout the country. The only center that wasn't really involved in the study was the Göteborg area, and that was because the AMVEX [phonetic] group was conducting a

trial in that location.

The schedules, and I indicated, are 3, 5, 12; and there were approximately 72,698 in that schedule; and a 2, 4, 6 schedule was also included to provide some bridging information, and that had approximately 10,194. Surveillance was both passive and active.

The case definition, there were basically two case definitions. The primary definition was similar to the one used in the study in Trial I, and that is to look at culture-confirmed pertussis with 21 days of paroxysmal cough; that's standard WHO case definition. They also looked at culture-confirmed pertussis with or without cough simply to examine looking at the colonization and infection as well, the impact on colonization and infection.

The vaccines used in this trial were again also an extension of the vaccines used in Trial I with one exception -- with two exceptiones, actually. The SKB vaccine was the same vaccine used in Trial I. The Chiron vaccine was added. That was not a part of Trial I, but it's the same Chiron vaccine that was used in the Italian efficacy trial three-component vaccine.

The CLL vaccine was the Connaught Pasteur Méreiux

five-component vaccine with the components as listed here. And the other change was the whole-cell vaccine, which in Trial I was the Connaught, Inc. vaccine that came out of Swiftwater [phonetic]. In this case we used the Evans Medical vaccine, which is the vaccine that's now used commonly in Great Britain.

The vaccine contents are shown here, just to give everybody some idea that there are differences. This table is rather incomplete because there are many other differences that aren't even indicated, such as the preservative and the adjuvant that's been used.

But overall you'll see that -- I don't want to go into any great detail -- you'll see that there are differences in the way that the vaccines are inactivated as well. And also in the amount of diphtheria and tetanus toxoid, the concentrations used for diphtheria and tetanus were slightly higher than that used in Trial I.

Otherwise the only other difference between these vaccines is that in Trial I the DTaP-5 vaccine had lesser amounts of PT and FHA than used in Trial II. The amount of PT-FHA used in Trial I and Trial II for the two-component SKB vaccine were identical.

I think the first thing I'd like to do is talk about the immunogenicity data, and this slide just gives you a quick overview of what kind of schedule was used. Essentially there were four key times at which blood was taken.

You had a pre-bleed, then your first bleed was after dose two for the 3, 5, 12-month schedule. Your next important bleed was one month post dose three for both the 3, 5, 12 and the 2, 4, 6-month schedule. And the final bleed that was of importance was the seven-month bleed post third dose. So for the 2, 4, 6 we're talking about at 13 months; and for the 3, 5, 12, at 19 months.

I tried to break down the tremendous amount of data that had been accumulated for immunogenicity. There were just reams of tables. I thought it would be simplest just to show the reverse cumulative distribution curves. I think it basically provides a good overview of all the information without going into a lot of great detail.

This is for the distribution of IgG anti-PT antibody levels for the four vaccines. And as indicated, the vaccine that provided that greatest

amount of anti-PT antibody was the three-component recombinant Chiron vaccine.

I should also mention that for those who are unfamiliar with this type of reverse cumulative distribution curve, the 50-percent level, basically a 50-percentile level which is equivalent to the median dose, and it's very similar to the GMT. It's not identical, but it's similar. So if you just go across and look at the 50-percent level, that will give you basically your GMT for each of these vaccines, and you can see how there are some differences for each.

I should indicate also that there weren't really any significant differences seen between the 2, 4, 6 and the 3, 5, 12 schedules, which is rather interesting because the 12-month dose is basically considered a boost, at least by the Swedish scientists, and I think we have to agree that that type of schedule, that the third dose at the 3, 5, 12 schedule is actually a boost. So the fact that there were no differences was rather striking.

I should also indicate that there were good antibody differences after two doses, not as high, but they were definitely there. And as you can see, there

was a low antibody for the whole cell compared to the other vaccines. And this is a trend that we see constantly throughout all the trials that we've completed when comparing whole cell with acellular vaccines.

Just quickly, I'm going to run through these next slides because they basically show the same thing. This is just a reverse cumulative distribution curve for FHA. Again you'll see that there are some differences for each of the vaccines. In this case the two-component vaccine provided the best anti-FHA antibody levels.

The next one is for the data for the pertactin, and -- I should indicate that it's interesting that the antibody for the FHA, there were some differences in 3, 5, 12 versus 2, 4, 6. For some reason the 3, 5, 12 antibody data was much better.

For the pertactin, you can see that there's hardly anything to mention for the two component, and this was expected. However, the other three vaccines -- whole cell, DTaP-5, and the three-component DTaP vaccine -- were almost identical as far as their antibody content.

For the fimbriae, again the only two vaccines that

had fimbriae were the whole cell and the DTaP-5 vaccine from Pasteur Méreiux Connaught, and there was some slight difference between the antibody content between these two vaccines. The whole cell obviously had slightly more antibody than the DTaP-5. But the levels were quite high, as you can see. If you look at the 50 percent you're talking about levels around 700 micrograms for the acellular, very high.

The next one is for the diphtheria. I think it's important to realize that we also measured antibody to diphtheria and tetanus. Here the whole cell gave a much better response to the anti-diphtheria antibody than the acellular, and I think that again was expected due to the adjuvanting effect with the whole-cell vaccine. I should also indicate that comparing the 3, 5, 12 schedule to the 2, 4, 6-month schedule, 3, 5, 12 schedule gave a much better antibody, significantly higher antibody response than the 2, 4, 6 schedule for diphtheria.

If you look at the response -- this is the last reverse cumulative distribution curve I'm going to show you -- if you look at it for tetanus, you'll see that the levels were basically very similar for all four

vaccines.

And they were quite high overall, and I think the reason for that is one has to remember that in this trial the Swedes provided not only acellular pertussis or whole-cell pertussis, but IPV and tetanus-conjugated HIV vaccine. They weren't combined; they were given a separate injections. But they were provided, and I think because of the fact that you're giving the tetanus one would expect that you'd get higher levels of tetanus antibody overall when you measure post third dose responses.

I should mention also that there's evidence of waning immunity after -- I mentioned they took a blood seven months post their dose, and there's definite evidence of waning immunity at that time. I don't have a slide to show that, but the levels were still present. They just were not anywhere near as high. If you looked at antibody levels one year out, the levels at that point were almost equivalent to background levels. They drop precipitously for all the components for each of the vaccines.

So in conclusion for the immunogenicity data, as I mentioned, I think the results parallel those results

seen in Trial I. All three acellular vaccines had serologic responses proportional to their antigen content. We saw that in Trial I as well. And all three acellular vaccines showed antibody responses after two doses that were lower than after three doses. I think that's kind of an interesting point because it demonstrates that the individuals do respond as early as the second dose, and these vaccines are quite potent.

And of course, as with the case with the first trial, at this time there is no serological correlate of protection, although there is work ongoing to try to demonstration some relationship between CMI responses correlate to protection.

The next group of slides I will show you will basically emphasize the efficacy analyses. And this slide might somewhat confusing, although believe me, if you saw the original slide it was ten times more difficult to interpret.

Essentially I'm just showing you here the relative risk estimates for the two primary case definitions, again the WHO case definition of 21 days of paroxysmal cough and the definition looking at less disease. And

this shows you the number of cases for each of the two definitions, for each of the vaccines on the top row here; and the relative risk is demonstrated below.

I should indicate that the objective of this trial was to test the null hypothesis where the relative risk of pertussis is greater or equal to 1.5 against the alternative hypothesis that the true relative risk is greater than 1.5 compared to whole cell.

So in this case if you look at the DTaP-5, the relative risk for that vaccine is similar and close to what was seen with the whole cell vaccine, and that's looking at the more severe case definition of 21 days; whereas if you look at the DTaP-3 vaccine compared to the whole cell it was somewhat less effective. If you look at the WHO data for with or without cough or for less severe definition, again the relative risk for DTaP-5 is closer to the whole cell than was observed with the DTaP-3.

The next overhead shows the intent to treat analysis, and again this is for the 3, 5, 12 schedule following up after dose one. Essentially, again, if you look at the DTaP-5, the risk for pertussis for that vaccine was very similar to whole cell. The relative

risk was 1.25 versus 1 for whole cell, whereas with the DTaP-3 vaccine the relative risk was a little bit higher than whole cell.

And if you look at the results for secondary analysis results -- that is, in this case comparing what happened when you looked at the relative efficacy after dose two but before dose three using the 3, 5, 12 schedule; and I bring this up because again there was some interest as to what kind of data one would observe just using two doses based on the 3, 5, 12 schedule -- here again you'll see that all three vaccines -- and let me just make one other point here.

I guess in this case what happened was that because in Trial I the efficacy for the DTaP-2 vaccine was low, around 59 percent, the Swedes felt that it was necessary to discontinue the use of that product and subsequently immunize the entire population with one of the acellular vaccines, in this case with the five component. So the Swedes felt it was an opportunity to actually look at the DTaP-2 vaccine as a placebo group type vaccine and use it as a standard.

So now they're comparing the two acellular vaccines, the five component and three component from

Chiron, along with the whole-cell vaccine to the two component. And so these next couple of slides will show you how these two acellular vaccines -- this is the five component, and this is the three component -- how it compares to the whole cell. And you see essentially that after two doses they all provided good relative risk.

The scale is at the top. It should be 1.0, .75, .5, .25, and the bottom line should be zero. But the relative risk numbers are .13, .18, and .4. -- .13 is for the whole cell; .18 is the five component; and .4 is the three component Chiron vaccine. That's for severe disease. That's 21 days of paroxysmal cough.

If you look at the less severe, same thing. After dose two, in this case there are some differences. Again, the five component and the whole cell are quite similar. They show that the relative risk for pertussis is similar for both vaccines. It's a little bit higher for the three-component vaccine, again it's 5.2. The scale here again is 1.0, .75, .5, .25, zero.

So the bottom line is that there is definition evidence that after two doses one can demonstrate efficacy with all vaccines that are tested in this

trial.

The next overhead shows the non-randomized comparison of the 2, 4, 6 schedule versus the 3, 5, 12 schedule. I think this is something that a lot of people were interested in looking at. There are different ways one can look at this, and I think one has to be very careful about interpreting the data. What I did here was just to simply look at an intent to treat analysis.

What happened after dose one? And essentially what you're seeing here is that after dose one the relative risk for all three vaccines -- that is, the whole cell, the five component, the three component -- were very similar overall.

And I think that if one took and examined the information, the data, after three doses, one would then notice that the 3, 5, 12 schedule was more effective than the 2, 4, 6 simply because, again, I think you're talking about the results following that third dose at 12 months, one has to consider that a true booster effect. And I think that would account for the differences between the two schedules. But looking at it after dose one, which I think is a more

fair comparison, I don't believe there's really any differences between these vaccines as far as relative risk is concerned.

So in conclusion, my conclusions for relative efficacy are that the whole cell, the WHO case definition, using that definition, all vaccines gave similar protection. As far as for mild disease, the three-component vaccine gave somewhat less protection than the whole cell vaccine; and the results for the two-component confirmed the low efficacy that was observed in Trial I. And as I indicated, this arm was unblinded and all children were vaccinated.

This goes on. Between dose two and dose three using the 3, 5, 12 schedule, all protected after two doses against both mild disease and severe disease; and that comparing the two schedules using a non-randomized comparison, which I think has to be emphasized here because there were regions allocated to receive 2, 4, 6, and there were other regions that received a 3, 5, 12, so I think that's a very critical point to consider when evaluating that data. Also, one has to interpret data again very carefully because there were lower numbers used in the 2, 4, 6 and the higher background

incidence in the 3, 5, 12 schedule.

The last area of interest was the safety, and again the methods used for the safety analysis were both passive and active. Passive included linkage to children's medical records and hospital records, and the active surveillance for hospitalization looking at specific serious adverse events that occurred with the hospitals throughout the country.

There were no adverse events contraindicating further doses for the following within 72 hours -- and that's critical, within 72 hours: There was no severe neurological symptoms, there were no deaths, there were no general allergic reactions, there were no invasive bacterial infections, and there was one infantile spasm reported.

If you look at the adverse events contraindicating further doses within 72 hours -- this is a little more complicated slide, but I thought it was important to put this information on here -- it shows you the three vaccines, it shows you the total number of individuals involved, it shows the reactions for the temperature greater than 40.5 degrees Centigrade or around 105 degrees Fahrenheit following dose one, dose two, and

dose three.

You can see there are 36 events after dose one, 24 after dose two, 14 after dose three, for a total of 74. Overall there was a significant difference between the rate of temperatures greater than 40.5 for acellular vaccines versus the whole cell vaccine, at .001.

For HHE events there were a total of 101 events, broken down as indicated on the slide. The significant difference between the whole cell and the acellular was marginal at .06. For convulsions, however, there were 25 total events and there was a significant difference between whole cell and the acellular vaccines at a .02 level.

The next slide will examine the number of deaths during the trial, and it indicates that there were 30 recorded deaths. The timing was 14 after dose one, 14 after dose two, and two after dose three; and the diagnoses are indicated here. They run the gamut. I should indicate that there were 13 SIDS deaths. And I should have mentioned in the earlier slide for HHE events of the 101 that were indicated, approximately 57 of those were actually hospitalized.

DR. CLOVER: And these occurred at any time during

the trial?

DR. KLEIN: These occurred at any time, up to the time where the study was terminated.

I'm sorry; I was corrected. Thirty-three hospitalized, but I think that --

UNIDENTIFIED: Fifty-seven sought health professionals --

DR. KLEIN: Okay. It was 57 that sought health professional care, and 33 actually hospitalized for HHE events. Thank you.

I just want to show you a couple more slides here. This shows you the incidence of hypotonic/hyporesponsive episodes for Trial I and Trial II for the five component, the DT vaccine, the whole cell, and the two-component vaccine. And it basically shows that the -- a couple of things can be said about this.

First of all, the overall incidence was approximately 1 to 1,200 or so for both trials, so there really wasn't any difference between the incidence for Trial I and Trial II. The numbers in Trial I, even though there were more in the whole-cell vaccine -- it's hard to say anything much about this

data because the numbers were so low, but obviously there were greater numbers for whole cell than acellular -- however, in Trial II there was an indication of a larger number of HHE events.

Of course, the cohort was larger, or denominator. But they were spread throughout all vaccines, even though there was some indication that the whole-cell vaccine had more than the others. Again, there was no significant difference. But there was still, as I mentioned earlier, the rates were very similar.

And if you look at seizures for Trial I and Trial II, one will see that for Trial I there wasn't any difference between the rate of seizures in Trial I. However, in Trial II there was a significant difference in the rate of seizures between the whole-cell vaccines and the acellular vaccines.

And the last slide will just give you quick conclusions of the data, and that is that the acellular vaccines were documented to be very safe. The Trial II did not emphasize or look at the less severe diseases as Trial I did so I didn't present that data, but overall there was fewer incidences of pain at the site of injection and local erythema in duration. Seizures

and fevers in Trial II were greater than 40.5, were more frequent in the whole cell group. Within 72 hours an HHE was reported for all groups.

I think that pretty well summarizes the data. Any questions?

DR. DAVIS: Thanks, David.

John Modlin, then Pierce Gardner.

DR. MODLIN: If you look at the immunogenicity data it looks like the titers of PT antibody that are induced are higher with the three-component vaccine compared to the five-component vaccine, yet the efficacy of the five-component vaccine, if anything, appears to be slightly superior to the three-component.

If you look at individual cases of study participants that had end points, was there any evidence that there was a relationship between immunogenicity and efficacy in this trial, or has that been looked at yet?

DR. KLEIN: No. There was no indication, no correlation of protection based on immunogenicity.

It's intriguing that the two-component vaccine, which basically in Trial I has the worst efficacy -- 59

percent versus 85 percent for the five-component Connaught vaccine -- that particular vaccine had a much more significant antibody levels for antipertussis, that is, than the five component; and certainly there was a marked discrepancy between that data and the efficacy outcomes.

So there is absolutely at this time no correlation between immunogenicity and efficacy.

DR. MODLIN: Just one other quick question. With respect to the SIDS events, the cases that occurred during the trial, was there any evidence that there was any temporal relationship whatsoever to any of the three doses of vaccine, and again has that been looked at yet?

DR. KLEIN: It hasn't been carefully looked at, but I believe that there were not any temporal relationship --

DR. RABINOVICH: None of them occurred within 72 hours. And I think that they will be presenting different types of analyses for the publication that in terms of they were spread out then over different intervals, time periods.

DR. KLEIN: I should indicate that also there's

continuing evaluation of the individuals that had HHE events. They're being looked at for cognitive responses, motor responses, et cetera. And this is an ongoing effort on the part of the Swedes. They're also looking at other children who also suffer from seizures as well.

DR. DAVIS: I think Pierce Gardner had his hand up first, and then I'll call on Neal, and then Geoff Evans, and then Stan Plotkin.

DR. GARDNER: Toward the end of your discussion of the tetanus antibody, you mentioned that the antibody levels went down after a year. I assume you were talking about the pertussis.

DR. KLEIN: I'm sorry. Exactly; that's correct.

DR. GARDNER: But I wanted to focus on that, what you said -- and I hadn't heard of a previous discussion of this -- is that after a year out from the third dose the levels were back to background --

DR. KLEIN: Close to background, slightly higher. But they do fall.

DR. GARDNER: And I guess my question is are there data about the clinical consequences of that, and are we looking at a more aggressive immunization schedule

during later childhood. It seems to me that has some policy implications, and I guess I'd ask you to speculate on the consequence. And if you'd fill me in, it's the same poor response even to whole cell after a year as it is for the acellular?

DR. KLEIN: Whole cell is --

DR. GARDNER: Same?

DR. KLEIN: Yes. And --

DR. RABINOVICH: David, can you comment on efficacy? Because we've already shown there's no serologic correlate to immunogenicity.

DR. KLEIN: Well, what I'm going to say is that, in response to your question, the antibody levels fall. The efficacy data three years out shows that there is no waning -- there's no indication that there's any waning protection.

I should emphasize that perhaps the antibody is not the critical element to consider here. Perhaps we should be looking at cell mediate responses, because if one does look at that there is indication that the cell mediated responses two years out have not declined considerably. So there still seem to be sustained.

DR. GARDNER: Thank you.

DR. DAVIS: I can't remember what the order was, but you know who I called on. Neal, you can go ahead, and then I know Stan Plotkin had his hand up, and Geoff Evans.

DR. HALSEY: David, you mentioned that there was efficacy after two doses, and you also mentioned that the overall efficacy after the 3, 5, 12 appeared to be somewhat higher than after the 2, 4, 6 schedule.

My concern would be over the actual rate of disease and relative rates of disease in children under 12 months of age when we see the most severe pertussis. I'm concerned that people might think we could move to a 3, 5, 12 schedule in the United States. We still have a significant problem with children under six months of age and under nine months of age getting pertussis and getting very severe disease, and that's where almost all of our deaths occur.

So I was wondering if you could comment further on the relative efficacy between those two schedules in children under 12 months of age.

DR. KLEIN: Well, I could repeat what I said earlier, and that is between the two schedules there were several large tables provided by the Swedes to

examine the issue of 3, 5, 12 versus 2, 4, 6.

And depending on how you look at the data -- and these are secondary analyses, again -- depending on if you look at the data following the first dose, or four months after the first dose when a large portion of the overall number of children receive perhaps two doses, or after nine months when the majority had received three doses, between four and nine months, at least the majority had received three doses for the 2, 4, 6, but not for the 3, 5, 12, or after nine months when everyone received three. Depending on where you cut these off you're going to get different results in relative efficacy.

I feel that you're right, perhaps there may be a period of time where there's a lack of protection for the 3, 5, 12 schedule between the second and the third dose, even though the antibody levels seem to look good. There was indication that the relative efficacy looked adequate as well.

But I think it just depends on when you examine the data. If you look at it after one dose, there wasn't any difference between the 3, 5, 12 and the 2, 4, 6 schedules. They essentially had the same relative

efficacy. But after three doses the 3, 5, 12 was better.

DR. HALSEY: But again, the point is what proportion of the disease is prevented at under 12 months of age, and what is the difference between two doses in the 3, 5 and three doses in the 2, 4, 6? And I suspect there is an improvement in the efficacy with the 2, 4, 6 during that time interval when most of the severe disease occurs.

DR. KLEIN: I don't have that data in front of me. It might be true, though.

DR. DAVIS: That certainly appears to be a key question, really, in terms of severe morbidity.

DR. SNIDER: But you have to start with kids at birth, really, to do it properly and observe them for the period of time from birth on, because you have to collect the data for the first two months and first three months into groups and add that into you calculations.

You would have to start at birth looking at these cohorts to get your full body of information you need to make that kind of an assessment. You can't look at one group from the third month of life onward and

another at the second month of life onward to get information that's relevant to the public policy issue of how many cases are going to occur in the two groups at less than 12 months of age, unless you do it from birth.

DR. KLEIN: I'm trying to recall some of the data from the tables, and I believe that after four months, between four and nine months, that the relative efficacy for the 2, 4, 6 schedule is better than the 3, 5, 12 schedule.

DR. DAVIS: Thank you. Stan.

DR. PLOTKIN: Yes. I'd like to make three points.

First, in regard to the question of the addition of components, attachment factors, it is tempting -- and I think it's biologically plausible -- that attachment factors would prevent colonization and infection and mild disease. However, I would point out that it's difficult to discern which factors are important owing to the way the trials were organized.

The five-component vaccine which has agglutinogens in addition to FHA and pertactin also had twice the level of PT and FHA of the vaccine used in the first part of the Swedish trial. The result is that in

comparing with the three-component vaccine there was ten times the amount of FHA in the Connaught five-component vaccine as in the biasing vaccine.

So just to point out that although it's tempting to say that the difference is the agglutinogens, it may be that each of the attachment factors may provide efficacy against mild infection. And of course, that may depend on the concentration as well.

The second point in relation to three doses versus two doses is that my recollection is that the absolute rate of pertussis expressed in person years, rate per person years, is higher after two doses than after three. In other words, if the third dose does add something, the inference would be, as Neal suggested, that those infants who were immunized according to 2, 4, 6 would have a better chance of avoiding pertussis in the second part of the first year of life distinct from the Swedish schedule, and that of course has bearing on our own policy.

Finally, I think it's comforting to note in the Swedish data that the rate of SIDS was eight times higher in children who refused or whose parents refused inclusion in the trial than in those who were

vaccinated, suggesting, of course -- I don't think that vaccination prevents SIDS, and obviously the are societal differences between the two groups -- but that certainly doesn't add any fuel to the suggestion that SIDS is related to pertussis vaccination.

DR. KLEIN: In fact, Stan, the rate of serious adverse events for all the non-randomized groups, for all serious adverse events except HHE were higher in the non-randomized than in the randomized.

DR. DAVIS: Interesting.

Okay, I think we had Geoff Evans, and then we had Rick Zimmerman, and Jo White. But we're going to need to cut this off right after that.

DR. EVANS: A couple of things.

HHE has been of interest in our program. It is part of our original table, and it is not a very well understood condition. We've actually had a very small number of claims that have been filed that we would view as having true HHE, or at least clinically would be consistent with it, and even in those cases there was nothing you could see in the weeks afterwards that would point to anything that had changed as far as development, et cetera.

The condition has now been removed from the table, and this is something that we thought would probably ride off into the sunset once we went over to acellular pertussis vaccine. And that doesn't seem to have happened.

The results of the Stockholm II study were noteworthy, and taking into account the fact you also have a health system that is a little different than ours, and some of these children that showed up to the hospital were asymptomatic by the time they were admitted and were simply kept for observation. So I'm not sure that the 33 children that were hospitalized has the dramatic meaning that it might necessarily have in our country.

We have since started a project internally that needs funding that is going to consider the possibility of using some of our surveillance data to do some long-term follow-up studies of HHE, and of course I'm looking forward to any further data that will come out of the Stockholm II trial, which is actually a nice opportunity.

DR. DAVIS: Thank you.

Rick Zimmerman, then Jo White, then we'll be done

with this discussion.

DR. ZIMMERMAN: In addition to the point that's been brought up about the difference in terms of the schedule in terms of protection in the second half of the first year of life, there's also the month difference between the second 2, 4, 6 and the 3, 5 month two, which is also a time when pertussis disease can be significantly severe.

Another thing, I wonder if we need to reconsider the precautions to acellular pertussis vaccine based on the data and the comments you've made. Should high-grade fever and seizures be a precaution any longer? And I guess I wonder. Certainly HHE will have to stay, but I wonder if we should have them as precautions any longer, given the data you presented.

DR. KLEIN: You're saying precaution for the acellular vaccines?

DR. ZIMMERMAN: Yeah.

DR. KLEIN: Based on the data, I think that the data shows that yes, there's incidences of high fever and seizures, but compared to whole cell those two are significantly less.

Now I'm not sure if I'm understanding your

question, what you're trying to --

DR. ZIMMERMAN: I thought you also made a point, though, that not only is it less than whole cell but it actually is less than the background rate for the group that was non-randomized.

DR. KLEIN: Oh, yeah. The non-randomized group, that's correct, had higher incidence of fever greater than 40.5 and seizures. But again, that was a non-randomized group. I'm not sure what the size was. But it's just a piece of information that was provided that I threw out there. I thought it was interesting. I'm not sure if it's --

DR. RABINOVICH: Just to clarify the HHE, it's something, again with our colleagues in the PHS, we continue to examine. And I remember David telling me that 13 of the children with reported HHE did receive acellular pertussis vaccine again with no bad experiences.

It's difficult to make national policy recommendation based on that, but we'll be having to look at a number of different kinds of databases and information to try to learn from those experiences and what the implication really is for child health.

DR. DAVIS: Thank you, Gina.

I think we'll get to Jo White's comment now, and then -- yeah, is it pursuant to this? I'm trying to bring this to a close here.

DR. PETER: The only point I was going to make was I think that perhaps the review of the adverse events and contraindications is reasonable, but the most important point are those that pertain to children with underlying neurological disease. Because indeed, first of all we don't believe that whole cell vaccine aggravates severe neurological disease, but we do have precautions and contraindications that are really developed from whole cell, and those may not be applicable in the case of acellular now that we have this kind of data.

In other words, I would rather see a child with underlying previous seizure receive acellular vaccine and be protected against a subsequent vaccination than might have been the case with whole cell where the precaution was really based upon concern the you would not be able to differentiate the underlying cause of further neurological deterioration.

But I think this is a point that warrants

discussion in the future, not today.

DR. DAVIS: Thank you, Georges.

DR. WHITE: Jo White, North American Vaccine.

I just had some new data that I wanted to share with the Committee about an ongoing mass vaccination project that's going on in Göteborg. That's why that wasn't included in this Stockholm II Trial.

And in this study they're actually vaccinating the entire birth cohort 3, 5, 12 months of age, and also preschool children who have not received pertussis vaccination. It's actually a phase four cellular look at the epidemiology of disease. It is a monocomponent vaccine.

We're also looking for safety. And I think it's pertinent to this discussion. The end points are positive cultures. There's a central avenue to look for positive cultures for pertussis, and I'll show that in one second, and also hospitalizations in children under six months of age.

Both the culture positivity and the number of cases hospitalized less than six months of age have gone down dramatically. And there also have been, interestingly enough, in the Swedish population no

reports of HHE. And since this report is conducted as a phase four study, we'd mostly be looking at hospitalizations due to HHE, and we haven't seen those.

I just reviewed the data last week. So just to show you this one slide, which I think is sort of interesting -- and it will be presented, I believe, at ICAAC -- these are the positive cultures by month. You can see the year on the bottom. The top says Pertussis Bacterial Lab in Göteborg, and on the Y-axis is the number of positive cultures per month. You can see the year here, and you can see this is the efficacy study where they had a huge outbreak in pertussis.

And then in June of 1995 the mass vaccination program started in Göteborg. It's the only pertussis vaccine being used in Göteborg at this time. You can see that the incidence of pertussis has decreased dramatically. So it's encouraging, and the nurses were very happy that they don't have to advise parents on how to take care of pertussis, and they can do other things.

DR. KLEIN: To add to that, I should indicate that the Swedes have been immunizing their entire population

since 1995 in addition to what's happened in Göteborg. I don't believe that they've seen any indication since they've had this mass inoculation of the entire country of any cases of HHE that's been reported, from my understanding. So it's kind of significant because we're talking about hundreds of thousands of doses.

DR. DAVIS: I appreciate that, thank you very much.

If there's no further discussion -- Peter Strebel, did you have anything else that you wanted to include?

DR. STREBEL: [Negative response]

DR. DAVIS: Okay. I want to thank David for taking the time to share all of this information with all of us, and Jo for adding that little bit of information as well.

I think clearly some of the information we'll want to look at down the road is what the impact of these vaccines are on long-term colonization, because that will have what our end points should be in terms of our prevention and control of pertussis. We should consider not only the issue of severe disease in young children but also what the impact might be on colonization and transmission of Bordetella pertussis.

With that I think we'll switch over now to the next topic. This is on combination vaccines. As you know, the ACIP has generated, an ACIP working group has generated a statement. It's clearly in draft form and still needs a lot of impact.

Bob Chen will introduce this topic, and Bob Chen and John Livengood will be presenting information to us.

DR. CHEN: Thank you.

The working group first met in January, as many of you know, with Mimi Glode being the Chair and Bruce Renniger [phonetic] was the Secretary. Most of this work really has been done by Bruce, who's on vacation. So in February we had the first draft statement, and comments were received from ten persons.

The major comments were to shorten our initial draft and consider a separate journal publication for some of the more extensive material that was presented. There was consensus that there should be a focus on general principles for dealing with combination vaccines rather than getting into nitty-gritty specific vaccine recommendations.

And then there was also a feeling that the

vocabulary that was needed to discuss some of these new situations that we're running into should overall try to enhance communications, and so there was a feeling that certain words like extra vaccinations and mnemonic formulary we should try to draw upon words that may already be existent.

So here in the current next 60 minutes, what we wanted to do was to try to go over the key ideas that were discussed in the introduction and then six general principles or recommendations that we tried to gather from the previous version, and we wanted to make sure that we successfully capture the major intents of your comments, and then try to discuss what the next steps are.

Due to the lack of time, what I'll try to do is -- what I've done is tried to make each of the major sections into bullets of what the major ideas are. I think all of you have the actual full text versions in the handouts, on the back table for those in the audience, so that you have a better flavor of what the discussion talks about.

So I think in order to not waste the time, I will just actually not go over the bullets, and just leave

it up there and go to the group to see if in general there are major themes that we have missed in the introduction that you would want to add.

In terms of some of the difficulties that are introduced by combination vaccines, I've already received a couple of potential additions from the FDA folks. They have highlighted that trying to regulate combination vaccines is a very difficult endeavor; and then when you're combining additional vaccines you in a sense increases the risk a little bit because that whole batch, something goes wrong with that, you're actually having to destroy potentially a lot more vaccine. So those are a couple of the additional risks.

But let me just stop there and see if there are additional major themes that we would want to introduce. I should mention that we highlighted the fact that the current situation is more or less an intermediate problem, that in the long term hopefully there may be additional solutions that may get us out of some of the current difficulties so that that will give a sense as to the evolutionary process that we are in.

DR. DAVIS: Any input here? Any additional things that need to be in the introduction?

[No responses]

DR. DAVIS: If not, you obviously can provide some comments down the road as well.

I think we can move on to the next thing.

DR. CHEN: Okay. The next one is a general purpose for combination vaccines, that they should be used instead of separately to get the components in order to minimize the number of injections.

And then we discussed what the potential advantages are, what the impact of resistance to multiple injections in terms of its impact on coverage, that's been documented in the literature; on the other hand, some of the additional problems that may be introduced by having to deal with some of these combination vaccines, and that in the future hopefully additional antigens may be combined into a new product.

Any comments on this?

DR. DAVIS: Comments on this?

[No responses]

DR. DAVIS: If something comes up a little later feel free, but go ahead.

DR. CHEN: Okay. Under changeability, I think we went ahead and separated this into two arenas, vaccines with serological correlates of immunity and vaccines without.

Clearly in the first situation with serologic correlates it's a bit more straightforward. In the ones without, for example with pertussis, the preference would be for the same manufacturer's brand. The question comes up when the provider does not know or does not have the same brand available. We have polled the Committee, and the sense was that it would be okay to use any of the licensed products to complete the series.

So again, additional discussions in your document about formulation, interchangeability, manufacturer interchangeability, the availability or the lack of availability on those individual points.

DR. DAVIS: Comments?

[No responses]

DR. DAVIS: There's one term called monovalent. The issue of valency, do we have to consider just valency according to the name of the vaccine, or valency according to the number of antigens delivered?

Sam certainly has been making a point with inactivated polio vaccine, that's really a three-valent vaccine because there's three different polio antigens that are being delivered. So we should really be consistent. If we use the term valency, we have to decide what it's going to mean.

DR. CHEN: Should we had some discussion on that question? I guess for the average practitioner out there, their focus may be more on the antigen level than necessarily the valency level or the disease level.

DR. HALSEY: I think Jeff is right. I think you would be redefining something by using the term valent to refer to a three-component polio vaccine, and so I think you would be creating confusion if you didn't go along with the already existing definitions that are there.

DR. DAVIS: Maybe using a term like stand-alone vaccine, where you're actually using an individual product, that might be a better term.

DR. CHEN: Okay.

DR. DAVIS: Other comments?

[No responses]

DR. CHEN: Okay, next one. I guess there was some confusion that was caused by not putting in the term individual in front of -- on the overhead I've included that. And this deals with the issue of which vaccine formularies would any particular provider wish to try to stock given that there are potentially many, many permutations possible, and to try to give some guidance on this issue.

So we go through what some of the advantages are, give them some examples of what are certain backbones and certain complimentary vaccines that they would wish to stock, and if they choose a specific product as their backbone. And then how do you deal with low turnover vaccines; the whole issue of acellular pertussis vaccine, whether the formulary should be limited on that; and then developing tools for selection.

I know there was some question about what the basis for manipulating the formulary for acellular pertussis vaccine is. At the working group meeting, and then I think at the last meeting, what we did was formulated nine questions to ask the members, and then

I asked them to check yes or no in terms of their standing. So this was incorporated into the question, vaccines without serological immunity, for example, like DTaP.

And unfortunately I don't have this overhead, but just to read you the wording: Whenever feasible, the same brand of vaccine containing acellular pertussis antigens should be used through the entire vaccination series in a child. Clinics which elect to reduce polypharmacy -- that was our old term -- however, need not stock more than one brand of acellular pertussis vaccine, even if they occasionally immunize patients who have previously received brands other than the one routinely stocked in the clinic.

Plus situations will arise in which the vaccine provider does not know or have available the same brand of acellular pertussis vaccine with which the child had been vaccinated. Under these circumstances, to avoid missing opportunity to immunize, any of licensed acellular pertussis vaccines may be used to complete the pertussis vaccination series.

This is somewhat related to the previous recommendation, and the responses that we received were

all affirmative in terms of saying that this was okay.

DR. DAVIS: Comments on this? John Livengood, and then Dan Soland.

DR. LIVENGOOD: Yes. We're going to be taking a look at this section because we've received a couple of comments that clearly indicate that somehow or other we've introduced confusion.

We're not recommending necessarily that states or clinics or individual practitioners limited their formulary to one DTaP. We're trying to allow that those people who do choose either in their HMO or in their individual office to select some number less than the full range of all possible combinations, that we've covered the position that by doing so they're not necessarily creating a problem just because they don't have the individual brand that the person had received previously with DTaP. And we're doing this fully in the knowledge that we have no data to support interchangeability, which was one of the previous items as well.

So we're not really recommending it, and we at the Federal level are committed to having contracts for all available DTaP products at the states and the VFC

providers could order from. So if they choose they can have multiple of these, but if they choose only to have one or some number less than all possible options, that we would still be supportive of that general choice.

DR. DAVIS: Thank you, John. Dan?

DR. SOLAND: Yes, just a comment that the vaccine manufacturers in general support an open formulary, and that we support provider choice.

And historically when there's been wording that could be confusing -- and I appreciate John's comments -- pertaining to comments about limiting formulary, that oftentimes it can be misinterpreted out in the field. And we appreciate an opportunity to work with Steve and others in order to limit the confusion and to make sure that we do not suggest that we're supporting a limited formulary for vaccines.

DR. DAVIS: Thank you. Yes?

DR. GRANT: My name is Chris Grant. I'm Vice President of Public Policy at Pasteur Méreiux Connaught.

And just to reinforce what Dan said -- we obviously don't have time to go into this today, and we'd welcome an opportunity to sit down -- there's a

bit of a process and substance issue here. Process-wise, the PhARMA members really haven't had a chance to reaction. There's some new words in this newer version as it relates to limited formulary, and we particularly would have concerns with the section which takes a particular example, such as acellular pertussis.

So I just want the full ACIP Committee -- this is a fairly big deal. And when we get involved in talking about the substance, we would be bringing up issues such as the limited formulary approach.

Fortunately the ACIP has been relatively sheltered from the seven years of discussion in the world of Medicaid rebates, but there is a whole history of seven years' discussion and balancing of maintaining relatively open formularies in return for which very significant cost concessions are made. And our concern substantively is obviously we're sort of drifting into this issue in the vaccine area and need to hit it head on with much more discussion.

So I won't go into any further substance today, but to say this is a big deal, and certainly as a thought piece offers a lot for reflection. But were it

to become policy of ACIP, I would second what Dan said, that our experience is that this will have a very high likelihood of being misread, misinterpreted, and create a chain of activities which would probably go far beyond what you intend as a guidance document.

Thank you.

DR. DAVIS: Thank you, Chris. Chinh Le.

DR. LE: I guess on the issue, coming from an HMO I see the parallel between stocking seven different cephalosporin or one or two which are cost effective. And I guess the law required the providers to vaccinate a child again a disease, and with the recommendation of whatever is the best antigen but not necessarily that HMOs will have to stock an array of me too vaccines either. So I guess there's the balance between the two.

I think many of the managed health care plans will say I will use this vaccine because I got a good contract for this year, and next year they're going to change. And there's a tremendous amount of confusion every year about which vaccine we're going to stock. So it's a very big issue. But I'm not sure that -- I do agree that we don't want to limit the number of

different vaccines; on the other hand, the market will dictate that some will.

Thank you.

DR. DAVIS: Mimi Glode.

DR. GLODE: Just a question for the Committee to respond to would be that in this section, getting back to the evidence-based medical issue. And we have the additional problem of not having the evidence about interchangeability, so we say that in once sentence no doubt exists.

Is that sufficient, and is therefore, then, the recommendation too strong that says that if you don't know what someone received previously, sort of in the interest of public health go ahead and mix and match in the absence of data, with one sentence saying there are no data, and then this other issue?

From the public health point of view I'd just be interested in the response of Committee members about is it clearly stated in here, the basis on which the recommendation is made, when the vaccine provider does not know or have available the same brand of DTaP any of the licensed DTaP vaccines may be used to complete the immunization series? Do you agree with that

recommendation?

DR. DAVIS: How do people feel about that? Fernando, and then Neal Halsey.

DR. GUERRA: I think, as Mimi was suggesting, it's certainly clearly stated here for a group that is accustomed to dealing with these kind of issues.

But how we take this information to the hands-on administrators of the vaccine -- the nurses, the staff that work in clinics and physicians' offices -- is not going to be so easy. And I think we have to think that through very carefully because it's already very confusing as it is, when we're changing schedules every other year and we are introducing any number of new products; and then to add another dimension to a decision-making process is going to be very confusing for them.

DR. DAVIS: That's certainly true. Neal, and then Walt Orenstein.

DR. HALSEY: With regard to the evidence to support the interchangeability with the pertussis vaccines, I think that's covered in more detail in the pertussis statement, as Georges was pointing out to me.

But also the evidence that David Klein presented this morning, that two doses of any one product really provides -- I should say any one product, but of several products that have been evaluated -- provides protection. And so if you're getting involved in a change situation in the middle of a 2, 4, 6-month schedule, it's highly likely that the infant would receive at least two doses of the same product, and that's part of the rationale for allowing for interchangeability.

One could add that evidence to this statement if you wanted to, but I think it's also covered in the pertussis statement which you will be referring to.

DR. DAVIS: Certainly provide a good example of what the intent of the statement in this particular document is attempting to achieve.

Walt.

DR. ORENSTEIN: Neal had made the same point. I was just going to pull out the Committee's prior recommendations on this issue. Neal made the same point that I was going to make.

DR. DAVIS: Okay, thank you.

Georges Peter.

DR. PETER: Well, along that same line is under the section of vaccines with serological correlates of immunity.

I agree with the recommendation, but it is not consistent with the current ACIP nor the Red Book statement. I think the time has come to change the Haemophilus influenzae recommendations to the sense that any three vaccines, any three doses completes the primary schedule.

But this schedule, this establishes a new policy. And I think it's correct; but I think it should be stated that it is a change. I think Walt is not correct if you look at the Haemophilus statement. And I think in the Red Book we should have done so, and I wish we had.

DR. CHEN: I just know that in terms of our last recommendation for additional research priorities, number one on there is pre- and post-licensure data on the interchangeability of vaccine antigens produced by different manufacturers. So that is there.

Moving forward, the administration of extra antigens -- or perhaps maybe the term is extra vaccines, and again we could decide what the best term

is -- given the mobility of children and the fact that different buyers may change their formularies from year to year, there will be situations for both inadvertent as well as intentional extra vaccination. And so we describe the situation that may occur and then the criteria.

Some discussion about whether this may impact on reimbursement policies. I think the comments back from the Committee has been more divided on this issue as to whether we should venture into that arena or not.

DR. DAVIS: Comments? Any?

Yes, Carolyn Hardegree.

DR. HARDEGREE: In making statements like this which may imply that there might not be any safety issues involved, at this stage of the timing of these drafts are any studies under way that would address some of these issues in research way to look at those products that we even have available, much less those that may be coming, with multiple antigens in them?

I think the document really has not included a fair amount of discussion on safety issues that might need to be considered.

DR. DAVIS: Thank you, Carolyn.

Any comment there, Bob, on that?

DR. CHEN: Well, I guess we -- the wording is that the data currently do not suggest an increased risk.

I think it's a difficult issue. We clearly will continue to monitor in VAERS as well as in the VSD project. I don't know to what extent either phase four type or mix-and-match studies are planned in the NIH [inaudible].

And I think perhaps you're getting at a larger question, is should we perhaps think through and come up with a research plan of at least the most common reactions and the most likely -- most common vaccine combinations, the most likely situations in which some antigens will be given an extra dose.

DR. DAVIS: I think that's a good point.

Yes, Bud Anthony, and then Deb Wexler.

DR. ANTHONY: I wanted to mention the safety issue, too, Bob. And maybe I'm missing the point here, but I just want to remind you -- and everyone here knows this -- that the more we see with these acellular vaccines, the more reactions we see with later doses.

And so I think suggesting that the little extra vaccine is not unsafe, I think we have data suggesting

that additional doses of many of the acellulars are going to give you increasing local and systemic reactions that we are accustomed to seeing, but they're real.

DR. DAVIS: Thank you, Bud.

Deb Wexler.

DR. WEXLER: I just want to follow up on that. There's a tenet out there for practicing public health departments and physicians that you don't give over six doses of DTP by the sixth birthday, I think -- by seven? -- at some age.

So I think this doesn't agree with that statement that we follow when we're out providing immunization services in the community, the line about, and the data currently do not suggest an increased risk of adverse events will result from the administration of extra antigens for most patients.

DR. CHEN: I think the point is well taken. And we tried to make this document short, and perhaps we made it too short.

Some of the comments that we received back last round was to try to make a distinction between viral vaccines and kill back vaccines, in that in general

with live viral vaccines our experience has been to date that in general additional doses have not been a problem; but with the kill vaccines that, as both Bud and you pointed out, the additional doses do seem to have a cumulative effect.

And I think some of the comments from the other Committee members was that we should try to discourage this per se, and make it permissive only in the sense where there was no other options available. So that was some of the other possibilities. And given the tenuous nature of the data on this arena, perhaps we could expand this section a bit more if that is the intent.

DR. DAVIS: I think that certainly would be worth considering doing very carefully.

Georges Peter.

DR. PETER: I think the question about the maximum number of doses of pertussis vaccine before either the fourth or sixth birthday is a very practical question, because you have parents who have not wanted their children to get whole-cell vaccine have gotten adequately immunized with DT, and then indeed decided they want to be immunized against acellular pertussis.

And then you get into complex questions.

So I think this issue needs to be addressed and needs to be flexible, because the fact of the matter is that we don't know what the maximum number of doses is before we begin to have difficulties. And a lot of the recommendation is based upon concern of excessive immunization against tetanus. So I think and urge further consideration.

DR. DAVIS: I think that's an important point.

Why don't we cut it off on this item now and move on to the next one so we can complete our discussion on this.

DR. CHEN: The next recommendation is something on vaccine history information. One of the things that we have been experiencing with both VAERS and the VSD project as we have watched the evolution into the unique first generation of combination vaccines is recognition that there's a lot of inaccuracies in recording the vaccine exposure as to which specific vaccine was actually received by the child.

And just to illustrate, this is just focusing on lot numbers as a first cut given, as you know, a lot number's a non-logical mix of alpha and numerics. Any

of you who have done vaccine studies will know the type of errors that could creep into trying to record this, and then trying to retrieve it later. But in any case in one study, one project, only about 83 percent of the lot numbers of what probably, in our best guess, were very intent, were recorded accurately; and in one other study it was only about 93 percent.

In any study of vaccine coverage, efficacy, or safety without being able to track the exposure information accurately, basically you introduce a lot of misclassification which reduces your ability to be able to assess the effect accurately.

So in any case, it's just to point out that there are certain legal requirements right now in how we may work together with industry to come up with some way to track this more accurately over time, among which are issues related to standard vaccination records, registries, and perhaps would include the way we currently use our vaccine identifiers, be it lot numbers and et cetera.

DR. DAVIS: Thank you.

Any discussion on that?

[No responses]

DR. DAVIS: Clearly a complex issue.

Let's go onto the next issue, then -- Neal, did you have something you wanted to say?

DR. HALSEY: Well, this is someplace where the pharmaceutical manufacturers could assist us in helping standardize, and I wondered if we could have a comment from them whether or not that's even going to be feasible.

It would make life a lot simpler if we had a standard method of recording the numbers, and we didn't have interchangeabilty of letters and numbers at the same place. I wonder if Dr. Soland would maybe comment about the feasibility from their standpoint.

DR. SOLAND: I think the question was on standardization of lot numbers to reflect what's contained, and I know that there is -- we've had discussion with the CDC, but we've not had discussion amongst ourselves concerning this.

I think there's a general feeling, at least from SmithKline Beecham's standpoint, that we would like to assist in this area.

DR. CHEN: At the National Immunization Conference I spoke with, I think, three or four separate

manufacturers directly on this issue, and I think all of them said that they were very interested in working together. So I think the next step, in fact, is for us to organize a specific meeting to talk about different options along those lines.

DR. HALSEY: I don't know whether it would help or not to have a recommendation from this Committee that it be done. That might carry weight to those manufacturers that might be reluctant to carry the burden of the cost that might be incurred.

DR. CHEN: Well, our hope is to use something that is currently -- for example, lot numbers that are already being used by all the manufacturers, and somehow re-engineer the information content of that in a way that's more efficient and user-friendly. But that's just one of multiple options, and it is currently a recommendation of this set of combination vaccine recommendations.

DR. HALSEY: Could we just add onto that the ability to scan the information, not just numerically but also a scanning device, which is something that some people in the American Academy of Pediatrics have been promoting? That's not yet any policy or anything,

but it would simplify the transfer of information to electronic files if somebody could just scan a vial and then put it into a record, and it's only going to be possible if we have a uniform system of recording it. And that's what's happened with regard to grocery store sales and so forth, and it's certainly simplified checkout, as an example of what can be done.

DR. DAVIS: You know, I think there's some really good opportunities there, using a standardized form that everyone would agree upon, and then using standardized codes and equipment to enter data in a consistent and relatively error- free way.

Last comment on this -- or two more, Rick and --

DR. ZIMMERMAN: While this is certainly a problem with childhood vaccines, this is also a problem with adult vaccines. So I would urge an inclusion of that as an issue instead of somewhat limiting it to child vaccines, as the document does in this section.

DR. DAVIS: Right.

MR. GRAYDON: If I can add just one other facet to this, and that would be to include CPT codes -- for example, differentiate a DPT-1 from a DPT-3. If as part of this work group that could be done, that would

be tremendously helpful in registry development to sort out what particular DPT has been given.

DR. DAVIS: Thank you.

DR. CHEN: Then just identifying a number of research priorities that we have identified, but there may be others that we have overlooked.

DR. DAVIS: Okay.

Any discussion? Any other research priorities that anyone wants to entertain? I think probably the most prudent thing to do would be to write them out and submit them. It appears as though we're moving forward with a statement on combination vaccines, but there's a good bit of work to do before we would be anywhere near finalizing this.

Clearly, there's some areas in here that are going to require some careful input, and we're sensitive to the issues raised by Dr. Soland and Chris Grant and others that spoke up on that. I think we have to be balanced. I think there are issues going both ways there. It's not one way or the other. There has to be a medium that is drawn, because I think there are issues on both sides of the table on that one. So it needs to be developed accordingly.

What I would suggest is that we provide careful review of this document over the period of the next month again and then return comments, and we invite everyone to do that.

DR. CHEN: Just to let you know, I've asked Gloria to pass out to you two additional documents that may be of help, that you may want to review before you provide your comments.

One is a WHO document in which they put their thoughts on combination vaccines to paper. Then the second piece is a report of a WHO steering committee on development of jet injectors, in which there is some possibilities in which perhaps a less painful modular approach to delivery of vaccines may be an alternative to combination vaccines, and get around some of the issues that we're running into that's introduced by these combinations, so just to let you know.

Thanks so much.

DR. DAVIS: Thank you very much, Bob, and thanks, everyone, for your input.

John Livengood.

DR. LIVENGOOD: I just wanted to come back to Bob's first sort of question here, and one was did we

capture your intent in the type of document? This is a complete redraft of sort of going back to general principles that you sort of enunciated at the last meeting, and does this sort of approach capture the type of document you wanted us to prepare?

And two, what do you want us to do with this document for the long term? Are we headed for an ACIP type of publication, or is this just a document we're preparing and could give out once it's finalized to other groups if asked, but would not necessarily be headed for *MMWR* publication?

DR. DAVIS: Right. Well, I think we should -- each of the Committee members and liaisons and others really should seriously think about this.

Is there any comment right now about what people would like?

Neal.

DR. HALSEY: I mentioned at the last meeting that the American Academy of Pediatrics Red Book Committee is developing a statement on combination products. This statement now is much improved from the last draft, and much more in line with what I think the Academy is trying to develop. We're in our second

draft of that.

Georges and I were just talking, and I think we would be potentially interested in trying to merge the two so we don't get into further confusion as to the Academy says this, the ACIP says that, and maybe the American Academy of Family Practice would want to join in; and we might be able to make a joint statement. That takes longer to get out, we all know, but in this case I think it might be worthwhile.

DR. DAVIS: I personally believe that users of vaccines are in need of direction and leadership and guidance. If we're using resources and carefully considering these issues, then it's prudent for us to provide a framework for others. And a document, I think, would be very helpful, whether it's called -- I don't know exactly what it would be called, obviously, but I do think we should commit ourselves to going on record on these issues.

I think Neal raises a very -- I think it's a useful suggestion for organizations that have important recommendations to make. If there's agreement, I think it's good to do it in a way that the policy statements are concordant, and if we can come out with one I think

that would be very valuable.

Are there other input or questions?

[No responses]

DR. DAVIS: Okay, it's -- actually we're a little early for lunch, but I think we can do that, and we'll return at 1:15.

[Whereupon, a lunch recess was taken from approximately 12:10 p.m. to 1:20 p.m.]

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DR. DAVIS: By my count we have seven voting members, so we can begin.

What I want to do is just briefly introduce this. You've all received a packet regarding a variety of VFC issues, and this will help resolve cohorts that are eligible to receive VFC vaccines, and this should allay a certain amount of confusion that's out there.

And we welcome back Steve Hadler to lead this discussion, as he has crafted these resolutions and has framed these for us. So Steve and John Livengood will be involved with this discussion. Everyone should have the resolutions.

DR. HADLER: I'm not sure where John is. He's actually going to lead the discussion once he gets

here. I can start introducing it, but he may or may not -- actually, he's walking in now.

DR. LIVENGOOD: We want to propose several what we're calling clarifying resolutions for Vaccines for Children to consider. And we really came to this because we had received some concerns, the first of which is summarized here, and it's that current VFC resolutions are a little unclear regarding which children are eligible to receive certain VFC vaccines, and there are several parts of this problem.

One, it applies to those vaccines for which VFC is recommended only for certain age groups, such as the vaccines for adolescents, varicella and hepatitis B, MMR second dose, and the recently licensed vaccines for infants, varicella and hepatitis B.

The reasons VFC was not approved for all age groups for these vaccines were the differing strength of the recommendations for different risk populations, and also programmatic and cost concerns. So we spent some time in past sessions debating exactly which were the specific windows and the priority recommendations, and the ACIP approved funding only for specific age groups.

Second, we've heard from some states that current resolutions are unclear regarding which children are eligible, and what would be an easy way for them to identify, and quickly identify, which children should receive or are eligible to receive the vaccine; one of which is we've identified a lack of clarity in some of the resolutions as to which date the resolution actually became effective.

And this came down to sort of three questions. Which date should be used -- the date the ACIP actually voted for VFC coverage; the publication of an ACIP recommendation in the *MMWR* (now this would really be applicable only for those resolutions that noted that they would become effective on the date in which it was published in the *MMWR*); or C, the completion or the signing of a Federal contract covering purchase of vaccine for VFC? And frequently it's item C that's the limiting factor that sets the actual date at which coverage becomes effective.

Second, we've received some questions as to what is the status of children who were initially age-eligible for VFC coverage, but who did not receive the vaccine at that recommended age. For example,

varicella coverage was voted for children 12 to 18 months of age, but is a child who is now 23 months of age one year after that went into effect eligible for VFC?

Our interpretation was that yes, it would be, and to clarify those issues we went through a process here at CDC to try to identify how best we could clarify this and make it easier for states to understand who was eligible, states and physicians.

What we did here is we met several times over the past couple of months. We had meetings to arrange a CDC staff here, with Dixie Snider and Kevin Malone representing the Office of the Director; Bill Nichols from our Office of the Director, who is the principal management official of the program; several folks from ESD, and also from ISD, which is our Program Management Division.

And we have a memorandum summarizing the conclusions of those meetings, which should have been mailed out to you in advance. I'm going to come through some of the conclusions again, and then we can go back; and if there are questions about some of the specific dates I have some supporting material that

covers how we got to those dates.

First of all, we came up with what we felt was a firm list of what vaccines and age groups needed to be addressed. We decided that we would present specific resolutions, and we have series of four of them, to clarify each of these issues at this ACIP meeting. Because I haven't mentioned the fourth one before, it dealt with tetanus-diphtheria booster at the adolescent visit rather than just the normal period, which would have been 15 years.

Second, we agreed that the last of the three proposed VFC dates -- which is usually, as I said, the contract date -- should generally be considered to be the effective date for the VFC resolution, unless noted differently in the resolution itself.

However, for the vaccines in question, specific dates needed to be agreed upon on a case-by-case basis. For example, for the MMR second dose, we already had a contract that was in effect at the time the resolution was passed, so we didn't have a time we had to set up a new contract date.

Clear instructions have also been given out to the states as to regard to when the infant universal

hepatitis-B recommendation was in effect, and so everyone born subsequent to that date would be covered.

Also, too, we decided that we would make an effort to have future VFC resolutions explicitly define the conditions and/or date the resolution becomes effective, as was done with the IPV-OPV and acellular pertussis vaccines, so that we don't face this problem in the future.

Third, we agreed that once a child became age-eligible for a vaccine under VFC, he or she should remain eligible until they were no longer eligible for VFC. So if you were in the target window at the time the resolution was passed, just because you have aged out of the target window you would remain eligible. So therefore the windows themselves expand over time.

For example, at the date that the varicella resolution went into effect if you were 12 to 18 months of age, those children would continue to remain eligible as they grew older if they remain susceptible and if they remained eligible for VFC.

We also agreed that the easiest approach to implement was to define specific age-eligible cohorts, and to try to do that in terms of birth date wherever

possible, thinking that for the nurse or the professional who was trying to assess whether somebody was or was not eligible for one of these vaccines, the easiest thing for them to determine would be when was the child born. So we defined our dates in terms of birth dates.

We also agreed that we would try to interpret the age intervals broadly, without leading to a major expansion of VFC. But, for example, we had said that you could do the adolescent visit at 11 or 12 years; therefore, we decided to define what that window was. It was from exactly 11 years through to 12 years 364 days.

So the group of kids who were technically eligible on that date were those children who were that age when we said 11 or 12 years; or 12 to 18 months, for example, became anyone who was 12 months to those who were 18 months 29 days at that time that resolution became effective.

For the three first issues, the first one being the varicella here, we thought -- and our consensus was that we ought to base any calculations on the date the VFC contract went into effect, which was May 10th,

1996. And I'll come back and explain some of these dates, and perhaps show you.

Therefore, the infants who were 12 to 18 months 29 days on May 10th, 1996, would have been those that were born after the 11th of October 1994, and were aged over 12 months, because you must be at least 12 months still to enter into the window.

So the window for varicella for infants would run from those kids who were just turning 12 months now to anyone who is approximately two and a half years old. Those are the children who were in the initial window and have progressed through the window over time to an age now just slightly over two and a half.

Maybe the best thing is to just come back to this in just a second, but to show you some of the background material here. And I'm talking mostly -- I'll walk through the varicella one, for the most part, first.

The age group that was eligible, again, were infants 12 to 18 months of age. We looked at what the dates it became effective were. The VFC resolution was passed on 6/28/95. The varicella contract was passed on 5/10/96, and the ACIP recs were published, as many

of you remember quite well, sometime later, the 12th of July 1996. Because the resolution itself did not directly require publication of the recommendation in the *MMWR*, the date we picked to be the active date was the establishment of the contract at 5/10/96.

The youngest any child could be to be eligible at this point would be 12 months of age, because you must be at least 12 months to be eligible for varicella vaccine. And the oldest you could be would be that if you were 18 months 29 days of age on the 10th of May in 1996, which we've calculated to be the 11th of October 1994. So that's how we get to that point in the main thing, in the initial summary here.

Again, just to show you background on this one particular point -- and we can go through them -- we considered a range of dates. If we took the consensus date of the date of the VFC contract and you were born at these different dates here, we tried to calculate what would be the best approximation of what the recommendation window was on that date that the contract went into effect.

And this is how we came up with this range of dates. And we decided that the date to go with was

those that were, again, 18 months 29 days of age on that. So item two was the final one that we thought best approximated what was the VFC resolution window during that date when it actually went into effect.

Adolescents, let's talk a little bit about adolescents. The adolescent recommendation said you could be 11 to 12 years of age, which again we interpreted from being exactly 11 through to 12 years 364 days of age. So that's now translated into what we believe, based on the date of the contract, the window to be anyone who was born after the 11th of May 1983, and is now currently 11 years of age.

For hepatitis B, we went with the date of publication of the ACIP recommendations for adolescents. And this had to do with, for some extent, because we had previously instructed the states to consider any child born after 11/22/91 as eligible for VFC for hepatitis B.

So for adolescents, we believe the current window of VFC coverage to be adolescents born after the 5th of August 1982 who are at least 11 years of age, through to the end of their eligibility of VFC. Right now that's just people through a little less than age 15.

MMR second dose, and this we did a little differently. As you recall, the states themselves were able to implement either the preschool booster or the middle school booster in the past. There's a real patchwork implementation as these cohorts have continued to age over time. In the majority of states, our estimates were at least 50 percent of all eligible children have received a second dose of MMR.

We are now proposing that it's best to consider a consolidating resolution for MMR second dose, and saying that the MMR second dose would expand to any child who would be eligible from school entry through age 18 years for the second dose of MMR vaccine.

We think that that would greatly simplify the recommendation, and also move states towards our goal of full implementation by the year 2001, if we went ahead and said that all children who were VFC eligible were eligible to receive a second dose of MMR vaccine. And eventually we would propose -- similar resolutions would be considered both for varicella and hepatitis B vaccine, where we have two windows already that are already beginning to stretch out.

Also, too, the next item on the agenda is a formal

consideration of whether or not the ACIP wants to expand the eligibility for varicella vaccine. The point of this session is simply to do clarifying resolutions of where we think those windows are in time right now, compared to when they opened on the date the contract was put in.

In addition, we have proposed a clarifying resolution to make clear that we are intending to cover tetanus-diphtheria booster if given at the adolescent visit rather than age 15 years, which would have been the normal time, 14 to 16, ten years after the preschool dose of DTP.

That is a lot of sort of technical stuff, trying to look at specific dates. I can give more background as to how we got to individual dates. We can talk about some of the other parts of this wonderful table that's provided in the material that we've prepared and sent out to the Committee in advance.

Varicella and hepatitis B are a little complicated in that they have two windows that have been identified for VFC coverage. MMR second dose, I really think the thing to do is to go with the consolidation.

DR. DAVIS: Let me have some discussion on this.

Dave Fleming and Steve Schoenbaum, then Jerry, and Rich Clover.

DR. FLEMING: Thanks, John. I really appreciate the effort that's you've gone to. This is a real important issue to clarify. It is something that is generating a lot of questions out in the field.

I have an alternate proposal to suggest for some of the timelines that you've created. Keying eligibility for VFC for different vaccines to a specific date that's a month, day, and year, that is not consistent to cross-vaccines and is not easy to remember. It's problematic at the best.

And both from just a practical standpoint of figuring out how to educate public sector providers to do this, and also thinking about our role as needing to market VFC to private providers, I don't think this meets the simplicity test.

And while I understand that it makes good logical sense to key eligibility to one of those three dates that's been proposed, I think as an alternate proposal I would suggest that we back up the date for all of these different vaccines to the first of the year of that year so you don't have to remember a specific

month and a specific day for a vaccine eligibility; but rather you just need to know that kids born after January 1st, 1994, or whatever the date happens to be, that that's all you need to remember.

I just can't imagine in a busy clinic practice people looking at these different dates and then trying to figure out whether the kid meets it or not. I do think that for these vaccines we do need to establish some of these date criteria; but again, I would strongly advocate for us just keeping to a calendar year date. People will be able to implement that much easier.

DR. DAVIS: I think that's a point well taken for our discussion.

Steve.

DR. SCHOENBAUM: I like Dave's suggestion.

It's not clear to me, though, why you chose to link the date to the date of contract rather than to the date of resolution. It seems to me that at the point where this group votes, its intent is fairly clear. And why should it be delayed for whatever period of time the contracting takes?

DR. LIVENGOOD: I think Kevin Malone, who

participated with us in these discussions, has an interpretation of the time.

MR. MALONE: There's basically three reasons to focus on the date. One is that the statute itself says that VFC providers are required to provide vaccines as of the availability under the contracts. It makes it a little bit more complicated to have to retroactively go back and figure out if some of your kids are now eligible who had been in there before the contract was in effect.

Two, another was the -- to put it quite bluntly -- the contracting power that it gives us with the manufacturers. If it does not go into effect until the contract goes into effect, that provides a strong incentive for the manufacturers to quickly resolve any kinds of negotiation issues when negotiating the contracts.

Do you want comment on that, Dean?

MR. MASON: Yeah. I think in our program operationally there's a very fundamental reason, and that is when the ACIP deliberates and makes a recommendation, to expect that that immediately translates into an operational provision of those

vaccines. It takes us a while to gear up.

And if the states are placed in the position of providers expecting the vaccine to be made available the day after an ACIP resolution, we haven't had time to negotiate the contract. So you have an expectation of supply that we can't meet until we have a contract in place.

It also affects state Medicaid programs, and that they are under obligations 90 days post-actions by HCFA to make available those vaccines in accordance with ACIP recommendations. And if we don't have the Federal contracts in place, the state health departments are unable to provide the vaccines to the Medicaid providers.

So the contract based upon the ACIP recommendation is what we believe is fundamental. We have to know what the recommendation is in order to gauge the size of our contracts. But likewise, we shouldn't be expected to provide vaccines, we can't provide vaccines, until those contracts are in place.

DR. DAVIS: There's a couple of people that want to kind of revisit this. I may want to have our HCFA representative make a statement right now.

MR. GRAYDON: Randy Graydon, Health Care and Financing Administration.

And Dean hits on the very issue that's the biggest concern that we have. Our time frame is tied to the ACIP resolution and not to the contract or anything else, so this puts states in the very difficult position of having to provide the vaccine whether that comes through the Vaccine for Children Program or not. Some states are beginning to even question the Committee's authority to make two separate decisions, one for VFC and one for your regular recommendations.

And going back to David's point, which is very well taken, this is in spades in Medicaid programs. Trying to do programs to audit claims to see who's eligible for free vaccine and when you should pay is virtually impossible with all these different dates. And I think you ought to be aware of the implications that the Medicaid program has above and beyond the VFC programs.

DR. DAVIS: Thank you for that.

Dave.

DR. FLEMING: I just wanted to make a comment, that I think it's important for us to distinguish

between when vaccine can begin to be provided -- and clearly that needs in the public sector to depend on when a Federal contract is available and when vaccine is available -- and a separate distinct issue, which is once the vaccine is available who is eligible for it.

And I would just argue for simplicity in deciding who is eligible by defining age criteria that are easy to remember, not that the vaccine should be made available to people in the public sector earlier than when the contract is in place. But those are two different issues. So one is when can you start giving the vaccine, and the separate issue is now that you can start giving it, who is eligible for it?

DR. DAVIS: I think that was done very lucidly.

Let's see. I know Rick Zimmerman had his hand up first, then Fernando Guerra, then Hal Margolis, and then Deb Wexler -- I'm sorry. Rich Clover, actually, I had called on you earlier. Rich Clover and then Rick Zimmerman.

DR. CLOVER: I want to take it a step further than David did in his comments.

We do need to decrease the confusion, but if I can focus our attention on the hepatitis B. If I am

observing your recommendation correctly, there's only three age cohorts on the adolescent side that would not be covered by the vaccine for children, and that is the 16-, 17-, and 18-year-olds.

Why not just make it simple? Any adolescent that walks in is eligible.

DR. LIVENGOOD: I actually sort of like that idea, because certainly it's a phone call I get -- why, unless my child says that they're using drugs or they're sexually active with multiple partners, why can't they get the vaccine, why do they have to come in and say those things?

But again, our intent in doing this was not to, from the program side, propose an expansion of VFC eligibility per se in the form of clarifying resolutions, although I'm certainly not opposed to the Committee doing it. I'm just not prepared to talk about what the differential cost implications are of implementing a rather simple approach like that.

And perhaps that could be something that could be proposed either at this meeting or at a subsequent meeting, for certainly consolidation into one simple "everybody's eligible," besides for the cost

implications, would be simpler at this point for programs to implement.

DR. DAVIS: Thank you.

Rick Zimmerman, then Fernando.

DR. ZIMMERMAN: There's data that my team has gathered that physicians who receive free vaccine are much less likely to out-refer to public health clinics. And I think I would propose to you that that is a good thing, to vaccinate when they are in their medical home.

It's also clear that the majority of physicians are satisfied with the VFC Program, those who are participating.

It's also clear that among their concerns, paperwork is number one. While we specifically didn't address this, it is issues like approximately 12 different dates of eligibility and different times and months and days of the year that is an example of the paperwork issues that drive private practitioners up a wall.

And so I would strongly back and encourage the Committee to vote to change all of these dates to January 1.

DR. DAVIS: Fernando Guerra.

DR. GUERRA: I would certainly echo the comments that have been made, and would add to it a couple other things.

Perhaps the cost savings by restricting the cohort within the more restrictive time frame would be exceeded by the cost incurred for staff time to try to readjust computerized registries and tracking systems, the excess time in figuring out whether or not somebody fits within the more restrictive time frame.

I think the other important consideration is that today so many of the individuals, the families, the children in particular that are being served are migrating across different systems both in the public and the private sector; and to add another layer of chaos to the state of confusion that already exists is probably going to set us back and perhaps cause some loss in terms of what we have been striving for, to really limit the missed opportunities.

DR. DAVIS: Thank you.

Hal Margolis, and then Deb Wexler.

DR. MARGOLIS: Just a technical point on the adolescent hepatitis B.

When the resolution was passed back in February of '95, one of the footnotes that was added to it was that the intent of the recommendation was to achieve vaccination of single-age cohorts, at least in certain programs. And thus we allowed for those states or those settings where they were doing it at an age younger than 11 years to do that.

This new recommendation would take that flexibility away, and I don't know how many states have now passed school entry laws that might suddenly put children outside of VFC. Just something to consider.

DR. DAVIS: An interesting wrinkle here.

Deb.

DR. WEXLER: My comment on this is that there is a big omission, and that's about the catch-up vaccination of high-risk kids, immigrant and refugee children. There are so many immigrant and refugee children who aren't getting vaccinated who are eligible for VFC, the kids between 3 and now it's 14. I think it's children born after October 1st, 1984, if we're going to put a date on it, or '83.

So I think we have to include a resolution -- something like all children, immigrant and refugee

children, or children of first generation immigrants born after October 4th, 1983, are eligible for hepatitis B vaccine -- to make it easier for providers to know who they should vaccinate with hepatitis B vaccine.

But going beyond that, I guess I'd like the Committee to consider opening up hepatitis B vaccine to all children between the ages of 0 and 18, because what's going on is that the Asian kids and the kids from endemic areas still aren't getting vaccinated because the providers really don't know the recommendations yet.

And if we put all children in the same boat -- vaccinate all these children 0 to 18 -- then we're not going to have questions anymore about who's eligible and who's not, and kids aren't going to have missed opportunities for not getting vaccinated when they should receive hepatitis B vaccine.

DR. LIVENGOOD: Just one point, that Asian/Pacific Islander children are covered under a previous resolution through age 11 years when they enter the adolescent cohort, so that's why they're not in here. They are technically all currently eligible.

DR. WEXLER: I know they're eligible, but when you're setting dates and putting it into a guideline that could be nationally distributed to physicians, it would be a reminder piece about the eligible age.

DR. LIVENGOOD: I think education on the fact that they are eligible for catch-up, and it's something that we're trying to work with states on to improve coverage in those populations. I agree with you.

DR. DAVIS: Thank you.

Walt Orenstein.

DR. ORENSTEIN: Yes. I wanted to make a couple of points. Part of the reason I think people have been restrictive, this program has been somewhat vulnerable to charges of runaway entitlement. And we need to be careful that this is still a concern, certainly within a number of people, in terms of just expanding to everyone. There may be groups that we want to expand to, but we don't want to throw the baby out with the bath water, so to speak.

The second issue deals with -- I think it's particular to the people who are in the public sector who are sitting on this Committee -- is as you consider these issues, many of you serve children who are not

eligible for VFC. And certainly any obligation that you put on with VFC, as I understand it, would either require a two-tier system or the need for, in a sense, matching resources for other children you would normally serve. It is something you need to consider as you consider these resolutions.

DR. DAVIS: Dave.

DR. FLEMING: Well, we've raised a couple of really good issues, and I think that in the absence of there being these economic concerns everybody is going to want to expand who we can give vaccines to.

One of the unknowns, at least from where I'm sitting, is what is the tolerance of VFC in particular to continue to exist if we get too expansive right now? Can you give us any words of wisdom on that?

DR. ORENSTEIN: Probably people in the room here who might be better able to comment than I.

I do not know. Certainly there is not anything recently that I'm aware of that has suggested increased vulnerability, but one never knows in terms of this as we increase the costs.

Clearly, I think the intention of VFC was to give the Committee the ability to make recommendations

without having to take into concern the pure funding issues, and to deal with what is best for public health. And I think for some of these recommendations, I think they are very well worth doing.

I think we just need to be cautious that there's always a potential, particularly with concerns of assuring VFC vaccines go to VFC-eligible children, and the whole variety of charges that have been leveled against the program.

DR. DAVIS: Steve Hadler.

DR. HADLER: I think it's unfortunate Barbara DeBuono isn't here because she did speak with the strong voice of the state that not only when a VFC resolution gets passed, the state she's in guarantees, I think, vaccine for any child who is partially insured out of state coffers, and so any resolution has implications for her state.

And I know from talking to my brother in Connecticut that often there are not state funds to expand things. It's not quite the same situation of who pays for what. And so while there is no question it would be desirable to simplify everything and say MMR-2, varicella and Hep B, everyone under age 18 ought

to be VFC eligible, it would put at least some states in an awkward position of having VFC vaccines available for some kids but not necessarily having funds for other kids that they normally provide vaccine for.

DR. DAVIS: Turning it back to Dave here.

DR. FLEMING: Just to follow up on that, I do think we may be in a situation, with expansion around the issues we're discussing today, of not having all the data that we need to make an intelligent decision.

We may never be able to get the data we need about vulnerability for VFC at the Federal level. Clearly, though, there are -- different states have developed different mechanisms for funding universal purchase, and in at least some of those states this degree of expansion of VFC would create a situation where the state could not follow suit in purchasing vaccines for kids who are not covered under VFC.

A third issue that we haven't discussed that I know is an issue for us in Oregon is in fact what private insurers in the state are covering. And in general, at least in Oregon, with these new vaccines private insurers have these same issues around start-up

costs and how much are they going to be willing to pay initially. And in one state, in Oregon, they have tended to follow VFC so that currently what a kid in the private sector can get, as far as eligibility, tends to match what VFC delivers.

I think we need to have a little bit of data on sort of what the general standards are around the country. I would hate to get us into a position of having VFC expand who vaccine is eligible for, and suddenly have a backlash from the private sector saying we can't afford that; where is all this government money coming from that enables you to do something that we cannot do? I hope that would not happen.

But I would like to have a little information on the extent to which private insurers are covering varicella or hepatitis B universally up to age 18 versus following VFC.

DR. DAVIS: We certainly don't have that at this point.

Mimi Glode, and then Rich Clover.

DR. GLODE: Well, then, I guess I would raise the issue of would it be helpful, or is it the responsibility of this Committee, to help to prioritize

that expansion, then, dependent on the financial situation at least.

DR. FLEMING: (Nods affirmatively)

DR. DAVIS: Rich Clover, and then Walt Orenstein, and then -- at the mike.

DR. NICHOLS: Bill Nichols.

DR. DAVIS: Rich.

DR. CLOVER: I understand the need for data, and especially as it relates to cost. And, David, I appreciate your concern in regard to that, although ideally I would like to see it open to all age groups.

If you take the statement I made previously and just look at the difference between opening it up to all adolescents for both these vaccines versus the current recommendation on, once again you're only talking about three age cohorts -- the 16-, 17-, 18-year-olds -- for varicella. Most of those children would have already had the vaccine. So you're really only talking about the cost implications of hepatitis B.

I think by making that recommendation, yes, you're increasing the cost by a little bit; but you're

definitely decreasing the confusion to providers and decreasing the cost of providers to be able to know when a kid's eligible or not.

DR. DAVIS: Thank you.

Walt, and then Bill.

DR. ORENSTEIN: I think it may be very good public health reasons for expanding a number of these, and I think we ought to look at them.

I think the first issue was not expansion basically, but to simply who is eligible. Because there's so much confusion out there that if you miss a child between 12 and 18 months of age for varicella and they come in at 19 months of age you no longer can vaccinate them, which is not at all what we intend because we intend at some point to have all children eligible for vaccination.

We'll hear data, I think, in the next presentation of real concerns with regard to varicella and deaths and a lot going on. There may be a real good public health reason to expand this. I think we just need to realize what the implications are as we think about it in a variety of fronts, including other public sector obligations.

DR. DAVIS: Thank you, Walt.

Yes.

DR. NICHOLS: Part of the problem that we would be confronted with in determining how vulnerable such expansions would make the VFC Program to claims of runaway entitlement is coming up with cost estimates of what these expansions mean.

I'm the one who comes up with these cost estimates, and I have no clue how to determine what proportion of an age cohort, if you expanded it to everybody 0 through 18 years of age, what proportion would be reached in each state. I'm sure it would be different in each state.

So the real problem would come in making those determinations, and when Congress sees that now it's a billion dollar program instead of a half a billion dollar program, based on estimates that I come up with based on the best information that I have, it's not going to be something that can be substantiated until the actual time comes to purchase the vaccine. And when we have data about how many children are actually being reached through this process of expansion, then we're not going to know how much it's going to cost.

So I just would like you to keep that in mind, that making cost estimates when you make decisions like this are difficult; and we're not going to know if there will be charges of runaway entitlement until the time comes when I have to go back to Congress or go back to HCFA and say we need more money for this program because my estimates were wrong, were low.

DR. DAVIS: Thank you.

Any other discussion?

[No responses]

DR. DAVIS: If not, I think we certainly touched on some sensitive issues, and there certainly seems to be three things that are potentially possible.

DR. LIVENGOOD: I would also just like to make the point that particularly in response to the varicella resolution, the next section will also have various proposals to expand varicella coverage including cost estimates. That just wasn't the purpose of what I was asked to do here.

DR. ORENSTEIN: This should be put off until the varicella presentation, because I think it seems silly to potentially go through this only to potentially change it.

DR. DAVIS: Right. To update something that we did moments earlier doesn't seem to be a good use of our time.

Basically, the way I view it listening to all of this, we could either change nothing; we can clarify current age cohorts, which would provide a service; and/or we could expand based on some of the discussion you heard. And I think there is certainly compelling arguments to do that, and compelling arguments not to do that. Given that, I think there is certainly a variety of opinions, and I think everyone certainly stated their positions very eloquently.

So at this point I think what we need to do is we do need to entertain these resolutions. Let's have some discussion in terms of process. It seems as though we would need to do these -- we will go through these in order, except that the varicella one was fairly prominent in the order. It was actually the first one that we would consider.

So we will wait on that, given our subsequent topic, and move onto resolution number 6/97-2. This one has to do with the vaccines to prevent hepatitis B virus infection, and as written this resolution would

clarify those who are eligible to receive these vaccines through the VFC.

DR. ORENSTEIN: Jeff, may I suggest that before voting we take David's original proposal that these be all January 1st of any given year as opposed to the dates here, as one generic thing, and that would simplify, I think, all of the others.

DR. DAVIS: I do hope that people understand that even though there was a list of 12 dates, that was just basically the dates that people had to choose from. But in actuality, the group that worked on this ultimately came up with a preferred date for each of the vaccines, so don't be confused by all of the dates that are there. It ultimately will not be all of the dates. But I just want to make sure that people understand that.

So right now what we have in front of us is a resolution, but we don't have any amendments to it. We certainly can entertain that.

Did you wish to amend?

DR. FLEMING: Sure. I'd like to propose that we amend this resolution 6/97-2 so that rather than using the date November 22nd, 1991 and August 5th, 1982, that

we make it January 1st, 1991 and January 1st, 1982.

UNIDENTIFIED: Second that.

DR. DAVIS: Okay. So we have a motion and a second.

All in favor of including the amended date as opposed to the date that was initially proffered in this thing can say so by doing -- all those in favor of that amendment -- and these are only the voting members of ACIP --

DR. GLODE: Jeff, there's a third date in there. Do you want to include that third date of August 4th, 1995, to be January 1st, 1995?

DR. LIVENGOOD: I think he's actually referring down in the "Therefore, all children born on or after" -- not changing the dates these things actually happen, but just given those findings, that those are the effective dates.

DR. GLODE: I see.

DR. DAVIS: Really, what this would do is for each of these groups, you're talking about a portion of an age cohort. It's not like it's a huge number. We're not talking about multiple age cohorts for each of these. You're talking about a portion of an age

cohort. It's anywhere from -- for one, of course, it's close to 11-12 age cohort.

So all in favor of --

UNIDENTIFIED: Actually, Jeff, you have to have people who have a conflict of interest with either Merck or SmithKline need to recuse themselves.

DR. DAVIS: That's right. Yeah, so even for the dates that would be true, wouldn't it?

UNIDENTIFIED: Well, actually no. I'd ask Kevin that.

DR. DAVIS: Kevin, what we're doing is voting on amending the dates in this resolution. Does that --

MR. MALONE: I think it would be best if [inaudible].

DR. DAVIS: Okay. So those who have any potential conflicts of interest with either Merck or with SmithKline Beecham would need to recuse themselves from voting, even to amend the dates in this resolution. Those without any potential conflicts of interest -- I can't remember exactly who or who wouldn't have, but you know who you are based on exactly what you said at the beginning of the meeting.

All in favor of changing the dates to the first of

the year for each of these groups signify by saying aye, or raise your hand.

[Show of hands]

DR. DAVIS: There's three of us that are voting. Davis, Fleming, and Glode are in favor.

Those opposed?

[No responses]

DR. DAVIS: There are none opposed.

Those abstained?

[Show of hands]

DR. DAVIS: Guerra, Modlin, Chinh Le, and Marie Griffin.

So we have currently seven voting members present. Three favored changing the date to the first of the calendar year. None were opposed to doing this, and four abstained.

The next issue now is to actually vote on this. That was just to decide what the dates would be. So now the issue would be to vote on who is actually eligible now that we've changed the dates. So we've broadened the age cohorts for each of these somewhat by going back to the first of the year. You'll notice that we didn't round off to the beginning of the next

year; it was back to the beginning of the year.

Now those of us that are eligible to vote can vote on the actual resolution. Is there any other change in the --

Yes.

DR. ORENSTEIN: One thing that Hal Margolis brought up to me is that the resolution that was in effect for hepatitis B allowed some flexibility on the adolescent to, let's say, ten-year-olds. This resolution would prevent that.

I don't know if you want to say it, and whether to say, perhaps, that in all states this is the groups that would be covered but allow the flexibility that was in before. We would have to think about how to word that, but --

DR. DAVIS: Well, it seems as though we had a problem in terms of clarifying age cohorts, so we're trying to simplify it to make it clear to people who is eligible. And I certainly wouldn't want our Committee to be doing something that is going to obscure the problem more than it was.

We certainly want to move in the direction of clarifying this, and we certainly don't want to do

anything that would interfere with states having some -- I don't know what the right word is, but some -- they could use some judgments to do this properly in their state. We don't want to get in their way.

DR. ORENSTEIN: What my comment was before and I honestly don't know, didn't realize this kind of until today -- some states may have now school entry laws for which -- and there are a number that have already started with adolescent school entry laws for which -- because of the absolute 11-year-old cutoff that's in the new clarification you may not be able to vaccinate children who are younger, and thus they don't become eligible for VFC.

DR. DAVIS: Well, if anything it would actually be -- I'm not so sure that that critical -- if people interpreted the VFC literally before they wouldn't have been eligible -- this won't diminish the number of kids that would be eligible. If anything it would expand it a little bit because we're going to the first of a calendar year.

DR. HADLER: Actually, a simple way to solve that is just add a phrase, all children required by state laws to have received hepatitis B vaccine prior to

school entry.

DR. DAVIS: Very good.

DR. MARGOLIS: That's already in the VFC, that anytime you're covered by --

DR. DAVIS: This will cover the prodigies, folks.

DR. HADLER: Do we need to add a phrase to this resolution, or is it in the hepatitis B resolution? Or, Kevin, do you want to clarify whether this is a principle that doesn't even need to be written?

MR. MALONE: That's a good way to put it. It really is a principle, that we've interpreted this law to have state school attendance laws set dates independently of the VFC-ACIP resolutions.

DR. DAVIS: Thank you.

MR. MALONE: You really don't need to have it in there. If you want to have it in there just in case someone reads that and it's unclear, it certainly never hurts.

DR. DAVIS: Deb, Deb Wexler.

DR. WEXLER: Just regarding the previous vote, I just wanted to make sure that those high-risk immigrant

children will be covered as of January of their designated year.

In that vote, will they be covered so that their date won't be October 3rd, 1983, children born after that date? Because then that will be the one oddity in this resolution, that except for the high-risk immigrant refugee children whose date is October 3rd, we have everyone else after January 1.

DR. DAVIS: Well, I guess we'll have to formally consider that. We would need some language to --

DR. LIVENGOOD: I can't recall off the top of my head exactly what the date is for the Asian/Pacific Islander children. I'm sorry. It is like an October 3rd or something like that.

DR. WEXLER: October 3rd or October 4th, 1980 -- do you have the date?

UNIDENTIFIED: [Inaudible]

DR. WEXLER: October 4th, 1983.

DR. HADLER: This says all susceptible persons born on or after January 1.

DR. LIVENGOOD: Who are at least 11. Asian/Pacific Islander children are the one group that we do allow catch-up for in that 6 to 11, or --

DR. HADLER: Like when it says other groups eligible for the vaccine are defined in previous resolutions, I'm not sure which one of these this is, but --

UNIDENTIFIED: If in fact the second portion about all susceptible persons would cover refugees, and I think it would, then it doesn't matter. Once you get back to 1984 all those people are going to be over 11 anyway who are potentially not covered. There is no window.

DR. WEXLER: No. But there are the children between the ages of five and ten years of age who are from endemic areas, or whose parents are -- who aren't covered in this language, that you recommended two years ago that --

UNIDENTIFIED: Maybe I don't understand --

DR. LIVENGOOD: His point is, I think, just that the children between that date in '83 and this January 1st, '82, it wouldn't be impacted. The only clarifying part, that this happened previously. Clearly anyone who is five now who's A/PI would still fit under the current Asian/Pacific Islander.

DR. ORENSTEIN: I think the issue here is whether

this is withdrawing previous resolutions, and my presumption is that it is not. I think the point that Deborah makes is an important one. When this is disseminated, we need to put all of it together, because I presume that those children are covered under the prior resolution, or no?

UNIDENTIFIED: Yes.

DR. ORENSTEIN: So they're covered under the prior resolution. If this was withdrawn, that's still in effect.

Am I correct on that, Kevin?

MR. MALONE: These other resolutions say that a kid is eligible based on their status, not their age. That's the reason why those resolutions were passed. This does not affect that at all. We'll review the previous resolution. If there's a problem --

DR. ORENSTEIN: I think the point, though, is an important one. When that's disseminated, if only people see this, then they would be excluded. And so I think what we need to do is put together that prior resolution so people will see those prior resolutions and that these are clarifying.

DR. LIVENGOOD: Right. They're only clarifying

certain pieces of it, and that when it goes out that we explain to people that this does not alter the eligibility of the Asian/Pacific Islander children.

DR. WEXLER: Right. Because that recommendation is not out there, and any opportunity that we have to get a message out to physicians and health departments about getting these kids caught up, and why not make it easier for those children, too, and move it back to January 1 of 1983.

DR. DAVIS: I believe our intent is to do that.

DR. SNIDER: What I have for resolution 6/94-1 -- I think this is what we're talking about -- children less than seven years of age born to first-generation immigrant women from countries where HBV infection is of high or intermediate endemicity, what we're talking about?

DR. HADLER: That was amended to actually extend up to 11 years.

DR. SNIDER: Yeah. But what I'm saying is the date there, people were talking about the date, it says all children less than seven years of age living in these families. For purposes of this resolution this is interpreted to mean children born after October 1,

1987.

DR. HADLER: That was amended about a year later back to October '83, I believe.

DR. SNIDER: Okay.

DR. DAVIS: Okay. Rick Zimmerman, and then -- oh, you're set on that? Okay.

DR. ZIMMERMAN: I think what maybe Deborah is pointing out is if you take a child who is of Asian/Islanders' descent who is born in 1990, they are now seven years old. They might be at risk for hepatitis B, but because they are not 11 they are not covered by the second part of it, and because they were born in '90 and not in '91 they're not covered. So it's the child who, for instance, was born in 1990 of those particular ethnic groups that is not covered.

DR. LIVENGOOD: But they are covered by the previous resolution. This isn't altering the fact that they are covered. Now we have a serious education problem, I believe, because I've seen -- clearly the majority of people in this room are not sure, exactly.

[Laughter]

DR. DAVIS: Let's focus on the resolution that's in front of us, and make sure that there is no true

inconsistency. If it turns out that after we complete our business on this resolution today, if there indeed is a problem, we will then attempt to rectify that at the next meeting.

DR. SNIDER: I think, though, one of the points that was made earlier is underscored by what I just read, because I do find now resolution 21/95, October 1, '83. So the point that was made earlier about when this is put out that the other elements be put in there is absolutely essential, it seems to me, that the other resolutions that are related to it. Otherwise it's still going to be extremely confusing.

DR. HADLER: Well, there is a chart that Dean Mason's group and the VFC Program have constructed which shows the eligible age groups. That's what needs probably to be disseminated. It needs to be updated following the resolutions on this, and then disseminated widely with an explanatory letter. Because to sort of reconstruct every resolution, especially for hepatitis B, we'll have about five pages of text which will be -- may or may not be confusing.

But I guess I'd propose that the chart that Dean Mason's group has done needs to be updated following

this meeting, and then disseminated widely both to state programs and to everyone else who we can think would possibly need it, need to see it.

DR. DAVIS: Yes, Georges?

DR. PETER: Isn't the issue that if you were to take any VFC resolution that had a specific date in it, that you would eliminate any month and any date and only leave the year in? Then you would solve the problem, correct?

UNIDENTIFIED: Exactly, yes.

DR. PETER: In other words, instead of saying October 1st, 1981, it would be 1981. If it was April 11th, 1991, it would be 1991. Doesn't that capture the principle?

UNIDENTIFIED: Yes.

DR. DAVIS: It seems like it does.

DR. PETER: Well, maybe the next step is to then take that proposal, to review all existing recommendations by Kevin and company to determine whether or not there are any inconsistencies or inadvertent problems that the ACIP has created.

DR. DAVIS: Well, I don't know about -- you may need a month/day/year, in which case it would just be

probably reverting back to the first of whatever that year is. I don't know about the -- legally, I don't know what exactly is needed, obviously. But Kevin is here for that purpose.

We seemed to have strayed a little bit from what we were -- we were confronted with a specific resolution, and now it appears as though we are dealing with globally amending all resolutions to go back to the first of the year, January 1st of each of the years. And that doesn't seem to be --

DR. HADLER: Again, this only applies to three vaccines with the windows. The other ones, it doesn't make any difference what age or when they were born.

DR. DAVIS: Right, only where there's windows.

DR. HADLER: And so that's what we're trying to resolve here. And these are worded in a way that they don't -- they were intended to be worded in a way where they don't -- where they supersede the previous resolutions where they can be superseded, and where a resolution needed to be rescinded it's rescinded.

DR. DAVIS: Right. And all we've done is amend the dates right now. But whenever a resolution needs to be rescinded, it's taken care of in this language.

Is that what you're saying?

DR. HADLER: Yes. And I would again propose that you act on these resolutions now.

I think Dave's suggestion is excellent, and that this is a step to clarifying it that can be -- the education part I would leave to Dean Mason's group and to reconstructing the chart, but urging them to get it out, and at least to do this much now. It may be for next meeting one wants to go back once again and look at and see whether there's anything else to clarify, but you can take a big step now to clarify parts of it.

DR. DAVIS: Okay. Certainly the dates are on the table, and the resolution is before us. So basically what we're voting on now is resolution number 6/97-2, with the amended dates.

All in favor of adopting this resolution with the amended dates?

[Show of hands]

DR. DAVIS: All in favor is Davis, and Fleming, and Schoenbaum, and Glode.

Those opposed?

[No response]

DR. DAVIS: Those abstained?

[Show of hands]

DR. DAVIS: Guerra, Modlin, Chinh Le, and Griffin.

So four in favor, none opposed, four abstained. That resolution carries.

Let's move on now to resolution number 6/97-3, which involves the vaccination with a second dose of MMR vaccine.

Do you have anything more, John, that you wanted to --

DR. LIVENGOOD: This doesn't represent an attempt to consolidate the various positions of the states that cohorts -- I forgot to pick up, but there is actually a chart that shows in some states, like Wisconsin, that everybody is already covered; and some states at which some ages are covered in primary school, and some other ages are in secondary school. And it's extremely difficult, and it's a very patchy approach.

And this is a slight expansion, that it would just make everybody school age and beyond eligible for a second dose -- I mean, everybody eligible for a second dose provided at least one month has elapsed since the previous dose of MMR.

DR. DAVIS: Walt Orenstein?

DR. ORENSTEIN: Clearly, this is an expansion. However, the ACIP has been expanding MMR to a point that it's gotten extremely confusing with two cohorts, three cohorts, or what have you. And there is a public health goal of 2001 with all kids K through 12 having a second dose, and this provides the financing for that, at least in part.

DR. DAVIS: Thank you.

We certainly haven't attempted to confuse people. We just attempted to move forward the frontiers of public health.

[Laughter]

DR. DAVIS: Dave.

DR. FLEMING: I support this resolution. I just have a picky question, and that is did we mean to say at any age from 15 months through 18 years, or should that read from 13 months through 18 years? Because two doses of measles --

DR. DAVIS: On or after the first birthday.

DR. FLEMING: Yes.

DR. DAVIS: Absolutely.

DR. LIVENGOOD: You would not believe the number of times we have read those. Thank you very much.

If you want to propose a change, I'm sure we would be --

DR. DAVIS: Well, I think we'd have to formally propose that, because even though it's just a simple error --

DR. FLEMING: I'd like to propose modifying this on the second line of the resolution, eligible children at any age from 13, instead of 15, months through 8 years, as an amendment.

DR. DAVIS: Thirteen means that it would be -- technically, it's 28 days after the first dose would be the earliest that you can give a second dose. But it's easy to say 13 months. Hopefully, those two days in there won't be problematic for anyone.

DR. PLOTKIN: Jeff, can I ask you a question?

DR. DAVIS: Yes, Stan.

DR. PLOTKIN: Just a point of information.

It says that the second dose can be given 28 days after the first dose. Do we have information on that point, regarding second doses of MMR? Is anybody giving them one month apart?

DR. DAVIS: Do I have information, or does anyone have information on that?

DR. PLOTKIN: I understand to some extent the thrust of that, but most second doses are given in the context of older individuals.

DR. DAVIS: Most second doses are given in the context of -- were given in context with school eligibility laws. It varies from state to state.

DR. PLOTKIN: Yeah. There was a suggestion from New York City, as I recall, giving a second dose three months after the first. I don't know whether that went anywhere. But I'm unaware of a body of data suggesting second doses at 28 days are useful, or safe for that matter.

DR. DAVIS: I have to defer to people with more information.

John.

DR. MODLIN: Yeah. Stan, I don't have any more information on who is actually giving a second dose at which age, but I know that we recently changed or amended the MMR recommendation for HIV-infected children to suggest that children who are HIV infected should get their second dose -- for those who have

received their measles vaccine to get their second dose as early as one month after the first dose.

And that's the only place where the Committee has actually specifically addressed the issue on the basis of a recommendation. I don't have any information on what's actually happening right now.

DR. HADLER: The other place the 28 days come is the minimum interval that has been listed in, I believe in past and present, is one month. Twenty-eight days is sort of making that more explicit. I'm not sure where the one month came from, but I think it was thinking that if a kid comes to school with no doses you give him one, and then you bring him back as soon as you can.

I don't know of data, but I think that's the chain of reasoning that made this acceptable, recognizing that the second dose is still recommended at school entry. But if someone has a reason to give it earlier, then it's okay.

DR. DAVIS: Sam Katz?

DR. KATZ: The one month comes not as you suggest, or not as you're questioning about, at one year of age. It just comes from the general principle from the

earlier studies that there's no interference with other live virus replication, that interferon elaboration has ceased, virus replication has ceased, and you have an antibody response.

So it was more a matter of interference among two live virus vaccines, not based on data as to the immunogenicity effects at one year of age versus 13 versus 14 months.

DR. DAVIS: Thank you for that.

Let's vote on the issue of changing the 15 months to 13 months. And I assume the same, anyone with a potential conflict with Merck would be recused, would need to recuse from this vote.

All in favor of changing the number in the second line from 15 to 13?

[Show of hands]

DR. DAVIS: Okay, there's four in favor, Davis, Fleming, Schoenbaum, Glode.

Those opposed?

[No responses]

DR. DAVIS: None.

Those abstained?

[Show of hands]

DR. DAVIS: Guerra, Modlin, Chinh Le, and Marie Griffin.

So four in favor, none opposed, and thirteen abstain. So we will change the months to 13 instead of 15, for that first number in line two.

If there's no further discussion on this resolution, we can actually go ahead and vote on the resolution itself. And the resolution we're voting on is that the ACIP recommends that the VFC Program should provide the second dose of MMR vaccine to eligible children at any age from 13 months through 18 years, provided at least one month, minimum 28 days, has elapsed following receipt of the first dose of MMR vaccine. The resolution becomes effective on the date it is adopted by the ACIP.

It says that the resolutions 6/94-2 and 2/95-4 are rescinded; the number of doses, schedules, and contraindications to MMR vaccine are those defined in previous VFC resolutions, which are resolutions 2/94-12, 2/94-13, and 6/94-7.

All in favor?

[Show of hands]

DR. DAVIS: In favor is Davis, Fleming,

Schoenbaum, and Glode.

Those opposed?

[Show of hands]

DR. DAVIS: None.

Those abstained?

[Show of hands]

DR. DAVIS: Guerra, Modlin, Chinh Le, and Griffin.

The resolution carries.

DR. LE: Jeff?

DR. DAVIS: Yes?

DR. LE: Can I backtrack a little bit for clarification for hepatitis B?

DR. DAVIS: Sure.

DR. LE: Does that resolution include the children whose states require hepatitis B vaccination for school entry?

DR. DAVIS: Yes. That has to do with a whole other resolution that involves coverage for those states that have those laws or regents' policies.

We'll now move to resolution number 6/97-4, which involves vaccines to prevent tetanus and diphtheria, and the clarification of timing of the routine booster dose of Td.

John, do you have anything to say there?

DR. LIVENGOOD: This is designed simply to clarify that there's VFC coverage for tetanus-diphtheria booster when given in conjunction with our recent recommendation that instituted an adolescent health visit at 11 to 12 years of age; whereas previously the resolution talked only about the booster given ten years after the previous booster, which would have been about 14 to 16 years of age. I don't think this will have any type of serious financial impact whatsoever.

DR. DAVIS: Okay, any discussion?

[No responses]

DR. DAVIS: Seeing none, I'll read the resolution. Actually, I don't see a written resolution here. Let me just see the previous language.

Well, the resolution really has to do with the last -- well, yeah, I think we can just do it -- it would be right after the word recommendation, so it really is those two indented parts. Well, actually, we would have to probably put the resolution before it to clarify.

It would say, resolution to clarify the schedule for providing the Td booster in the VFC Program: The

ACIP recommends the routine schedule for providing the Td booster dose in the Vaccines for Children's Program should be at 11 to 12 years, or 14 to 16 years of age. If no dose of Td vaccine has been received during the previous 5 years, the VFC booster dose of Td vaccines may be provided at any age from age 11 through 18 years if 5 years have elapsed since the previous booster dose. Then this resolution becomes effective on the date it is adopted by the ACIP.

Yes.

DR. LE: Is it kind of confusing that the routine schedule should be at 11 to 12 years or 14 and 16 years? Can we just make it 11 through 16? Why should there be a gap of 13 to 14 like that?

DR. LIVENGOOD: I believe that's consistent with the final wording of what cleared in the immunization of adolescents recommendation. It actually says that you could do it either time, but that we are actually on record at recommending that 11 to 12 years of age is part of it; but we also said that the old pattern was, I believe, still consistent.

DR. LE: It seems like we just can drop that whole sentence and just vote on the last sentence.

DR. ORENSTEIN: I like that, agree with Dr. Le. It doesn't make sense, if you've missed the child at 11 to 12, and the child is there at 13 years of age, that you're going to send the child home and tell that person to come back at age 14. It seems to me that adding that one more year in makes a lot of sense.

DR. DAVIS: Okay.

Neal.

DR. HALSEY: Walt is right, and Chinh Le is right. Also, in the harmonized schedule which is published every January, it's a bar that goes from 11 to 16. This would be inconsistent with one of the existing recommendations that calls for 11 to 16. So I would drop -- I would get rid of that break in the schedule.

DR. DAVIS: Chinh Le makes a good point. The issue of the VFC booster dose of Td vaccine may provided at any age from age 11 through 18 years, if five years have elapsed since the previous booster dose.

The one thing about that is that's broadening the interval. And if you are interested in attempting to provide Td vaccine, we really should be encouraging getting that booster dose in before age 18 or age 17.

And if all we said was that, then that sort of broadens it. I'd be concerned that we wouldn't be doing enough vaccinating with Td at an early enough age in terms of providing the booster. That's just my concern, even though this is simple.

DR. ORENSTEIN: I think this is a financing issue as opposed to the actual recommendation. What I read, this is permissive as opposed to waiting until age 18 to start giving Td boosters.

DR. DAVIS: Yeah, it's very permissive. Okay. Yeah, I realize it's a financing issue. I wouldn't want it to drive practice and cause it to delay. But clearly, the issue of 11 through 18 years in the second part of the resolution is very broad, and it would certainly -- there's not much point in saying in the first part if we have a second part.

So I will entertain any amendments to this.

DR. FLEMING: Well, just to get one on the table, I'll propose that we just delete that first section, the routine schedule for providing Td booster dose, those three lines. Because really what we're doing is changing VFC eligibility, and that's what this relates to. So I would just propose that the resolution should

be the VFC booster dose of Td vaccine may be provided at any age from age 11 through 18 years if five years has elapsed.

DR. DAVIS: Do I hear a second?

UNIDENTIFIED: Second.

DR. DAVIS: Okay.

Any further discussion?

[No responses]

DR. DAVIS: Hearing none, we will vote on the resolution --

DR. SNIDER: Just for clarification, I'm unclear on what the previous VFC resolution allowed.

Steve, can you tell me?

DR. HADLER: I don't have it in front of me. It basically said the routine -- that it's routinely recommended at 14 to 16 years. It probably didn't say anything more than that. That's why this was structured in a way --

DR. SNIDER: That's what I was thinking. That's why I wanted to clarify, because I think -- I'm not advocating one position or another. I'm just trying to get some clarification. I was looking at our recommendations for adolescents, and they are

essentially as stated in the first bullet or paragraph. They were issued in November of 1996, not too long ago.

So really what we're doing by either adding the second, or deleting the first and leaving the second alone, is expanding VFC beyond what it previously was and also changing this November 1996 document, and that's okay. It does raise the issue I raised earlier, how do you make minor changes in these recent documents without having to redo the whole thing?

DR. FLEMING: Just a clarifying point.

I didn't quite understand why we would be changing what's in there. We're not saying what the routine recommendation is here. We're just saying what VFC will pay for. We're not saying that those recommendations are invalid; in fact, those are still when it should be routinely given. We're just defining eligibility for VFC payment.

I don't think we would have to change the recommendations, but that's just my perspective.

DR. DAVIS: Do we need to make statement regarding the routine schedule on this?

MR. MALONE: Can I comment on that?

Actually the VFC resolutions do lay out the recommendations for VFC-eligible children. It's not just a payment thing, whereas the general ACIP recommendations are the advice to the medical community at large.

So I would argue that you are in fact laying out the routine schedule, and that was one of the reasons why we put two different sentences here, to note what you would expect the routine schedule to be but then also what you are willing to pay for beyond that.

DR. DAVIS: Okay. Well, as long as it's clear that we're willing to pay for this beyond the routine schedule, I would think that's fine.

Yes, Deb?

DR. WEXLER: I just wanted to say that I don't think it's clear as written. I thought these were two different resolutions that you were supposed to choose from. So I think the second one should be written in such a way that says if the tetanus-diphtheria vaccine is not given at these particular ages, then it will still be covered by VFC at ages 13, 17, and 18, just because it doesn't -- it wasn't clear to me when I read it.

DR. FLEMING: I think we may have gotten ourselves into a bind here a little bit, because going back and looking at the resolution we just adopted for MMR, we didn't lay out what the recommended is. We just said who we pay for it for. We don't say anything about recommended at school entry.

So we are being internally inconsistent already, if we think these resolutions say what is recommended for routine and what is being covered. We just didn't do that in the resolution previously.

DR. GUERRA: Jeff, the other concern relates to how the states implement some of these recommendations in the context of the periodic screening, diagnosis, and treatment programs that are covered by Medicaid in that if doses of vaccines are given to a child that presents for an examination as part of a periodic screening and they are required to be immunized, but that it is out of the chronological sequence that is then recommended by VFC, there are times when they will disallow that.

And so I think whatever changes we make we need to be very clear, and also to move quickly to certainly disseminate it to state Medicaid programs that

certainly try to keep kids current with their vaccination schedules in the context of EPSDT [phonetic] programs.

DR. DAVIS: Yes, Dean Mason.

MR. MASON: Jeff, I'd just offer my two cents on this.

I haven't heard anyone discuss Td as a funding budget issue for the VFC Program. I don't think anyone views it as a potential fund-buster of the VFC Program. And all I think you are trying to accomplish here is the VFC Program support of eligible children for a Td booster that is five years or greater, subsequent to their completion of the primary series.

And if that's all you want to say without getting into differentiating between 10- and 12-year-olds, or 14- to 16-year-olds, aren't you really saying that any child who has completed a primary series of DTP or Td or DT-Pediatric is eligible through the VFC Program for the Td booster dose if that series completion was five years or greater from their presentation today, with exceptions maybe being made for trauma, wound traumas and so forth.

DR. DAVIS: I buy that, too. My hang-up here is

do we need to -- are we creating a problem by having two parts, or not having two parts in this thing, that's all. And I'm fuzzy right now. The bottom line is that we want the VFC booster dose of Td vaccine to be able to be provided at any age from age 11 through age 18. That's the bottom line. That's all we want to do today. That's all we want to do.

DR. ORENSTEIN: It appears to me, is there anybody who is going to start doing it routinely at 18 months, reading this resolution? I don't think so. I think you've got your published ACIP recommendations, and I would agree with Dave that you can take out that paragraph on the schedule and just go to the financing part because I don't foresee anybody trying to change it and routinely giving it at 17 years of age.

DR. SNIDER: I hear that, and it seems to me that maybe one could say to clarify the schedule for providing the Td booster in the VFC Program and to optimize coverage and not miss opportunities to vaccinate, in the second bullet the VFC booster dose of Td can be provided any age 11 to 18.

That makes it clear why you're doing this. You don't want to miss opportunities. You want to optimize

coverage so you're not restricting it to the ages that are listed above. Maybe you don't need that, I don't know.

DR. DAVIS: I just want to resolve this in the next two minutes so we can move on to the next topic. I think we're belaboring this for an unbelievably long time.

DR. GLODE: I recommend we vote on the amendment to remove the first clause.

DR. DAVIS: Okay. So we have an amendment -- we already have that out there.

All in favor of removing the first clause?

[Show of hands]

DR. DAVIS: We have a unanimous eight people here, eight people voting in favor of doing that.

So now let's decide on the entire resolution.

DR. SNIDER: To explain a little further about why I made the comment I did, I think part of the problem is the introductory clause to say -- to clarify the schedule.

DR. DAVIS: Read exactly -- did anybody write down what Dixie said?

Yeah, Neal.

DR. HALSEY: Why do you need the introductory clause at all?

DR. SNIDER: You could, or you could say --

UNIDENTIFIED: Just say clarification of VFC coverage.

DR. SNIDER: Or you could say to not miss opportunities and optimize coverage.

DR. HALSEY: I'm not sure why we even need to put the rationale in there, because otherwise you have to ask for paragraphs.

DR. DAVIS: Why not just say for providing the Td booster in the VFC Program, the ACIP recommends the VFC booster dose of Td vaccine may be provided at any age from age 11 through 18 years if five years have elapsed since the previous booster dose.

DR. SNIDER: Take out "to clarify the schedule."

DR. DAVIS: Right. Just begin the whole thing with the word "For," take out the first four words, capitalize "For," and then take out "approves the following," change "recommendations" to "recommends," and then delete -- we're deleting those first three lines, and then the second, after the word "recommends" will be "the VFC booster dose," those two lines.

That's what we are voting on.

Are people comfortable with that?

UNIDENTIFIED: Yeah.

DR. MODLIN: Jeff, just a quick word of clarification. Do we need the word "recommendation" here? In other words, again we are voting on a finance issue and not a specific recommendation here, and I wonder about the possibility of that actually being confusing.

DR. DAVIS: Well, we have the word "recommendation" in there one way or the -- before we said we approve the following recommendation, which isn't the typical language. But this is a VFC recommendation as opposed to a statement.

DR. MODLIN: Okay.

UNIDENTIFIED: "Recommends" was in the MMR.

DR. DAVIS: Do I need to read it again, or are we clear?

DR. SNIDER: So providing that -- well, I'll read it so we have a double-check. I have "For providing the Td booster in the VFC Program, the ACIP recommends: The VFC booster dose of Td vaccine may be provided at any age from age 11 through 18 years if five years have

elapsed since the previous booster dose."

Is that correct?

DR. DAVIS: Yes.

All in favor?

[Show of hands]

DR. DAVIS: Davis, Fleming, Schoenbaum --

UNIDENTIFIED: Didn't you have an issue of conflict of interest?

DR. DAVIS: I don't know if we have conflicts of interest for Td.

UNIDENTIFIED: Who makes Td?

DR. DAVIS: Okay, hold on. We know Pasteur Méreiux Connaught does.

UNIDENTIFIED: Lederle and Connaught.

DR. DAVIS: Lederle does? Okay, so we have Lederle and PMC, Wyeth-Lederle and PMC.

UNIDENTIFIED: We're talking about Td. We're talking about Connaught, Lederle, Massachusetts, and Wyle [phonetic].

UNIDENTIFIED: Massachusetts and Michigan don't bid on contracts.

DR. DAVIS: Okay. Wyeth-Lederle and Pasteur

Méreiux Connaught.

All in favor?

[Show of hands]

DR. DAVIS: Davis, Fleming, Schoenbaum, Griffin, Guerra, Glode.

Opposed?

[No response]

DR. DAVIS: None.

Those abstained?

[Show of hands]

DR. DAVIS: Modlin and Chinh Le.

Motion carries six/four, none opposed, two abstained.

We'll now move on to the next topic. Thank you very much, John. Thank you very much, Steve. Thank you very much, everyone. It took us a little while, but it's important; and I think we have to be real clear on what we're voting on.

The next is varicella vaccine update, and Jane Seward will be providing us with information on this topic. This will also involve a VFC vote, and Fernando Guerra will also be providing some information in this overall discussion.

MS. SEWARD: Good afternoon. You survived one vote. Here comes another vote.

I think you are all receiving right now an updated handout, because I'm presenting some additional options from what was given to you all in the handout materials prior to the meeting.

Now you can note on here that I had 60 slides that I would have liked to be able to present today but time precluded that, so I'm going to first present some information on epidemiology of varicella in the 1990s. Then Dr. Guerra will present some local data from San Antonio Community Hospital, with local experience there with hospitalizations for varicella; and then I will come back and provide options for expansion of age eligibility for VFC vaccine.

I'd like to point out that the data I'm providing was very much a collaborative effort by a lot of people at NIP and outside of NIP. I'd like to thank personally some of the people who provided some data:

Jim Singleton in the adult branch; Barry Sirotkin, who did mortality analysis; Bob Snyder, who answers many, many questions for me on the VFC Program; and NCID people who may be here who participated in the

Boston outbreak, Stephanie Factor [phonetic] and Ben Schwartz; from CFCE, Pam Myer [phonetic], who has done a lot of analysis on mortality; from Minnesota, Barbara Yawn; from Medicaid, Joan Mahanies [phonetic]; and from Connecticut, Jim Hadler and Felix Ian [phonetic]; and people from the active surveillance sites. Lastly, thanks to Sonia Russell for helping me with the graphics, and many, many other people at NIP helped with this presentation.

Many of you are already aware of the burden of disease due to varicella. This is data available from in the prevaccine era, but we don't think that there's been very much change yet from these figures. Three to four million cases a year from varicella, 90 percent of them occur in children less than 15 years of age. There are an average of 4,000 to 9,000 hospitalizations a year.

Varicella is a much more severe disease. There's a high risk of complications in newborns and immunocompromised persons than in adults. And there have been in the last five years, on average, 104 deaths a year from this disease.

Again, just to remind you of complications that

occur from varicella in healthy children and adults, both Dr. Guerra and myself are going to talk a little on sepsis, which is -- and skin infections, common complication in children. We're both going to be discussing a little bit on Group A beta hemolytic streptococcus. Other complications in children: pneumonia, CNS, Reye's syndrome is now rare, although I had a case reported to me last month from New York City, so it's still occurring a little. In adults pneumonia is the most common complication, but other complications can also occur in adults.

The next overhead here shows age-specific incidents and death-to-case ratios for varicella in the United States from 1990 to 1994. The yellow bars is age-specific incidents, and the red bars are the death-to-case ratios. From this data we can see that -- well, you can't see, but I'll tell you that 45 percent of the deaths occurred in those less than 20 years of age; 55 percent of the deaths occurred in those over 20.

There's a much, much higher death-to-case ratio in adults, especially those 30 and over, and I would add that these ratio calculations excluded persons with

known high-risk conditions such as AIDS, immunocompromised states, et cetera, as best we could define that from death certificates. So this is low-risk individuals, as we can define them from death certificates. The death-to-case ratio in the 30- to 49-year-old age group is 60 times higher than children 5 to 9 years of age.

This shows that the majority of deaths, as I just stated, both in children and adults occur in individuals without an underlying condition that would put them at risk, again with a strong caveat, as best we can describe it, from death certificates.

So death certificates definitely have limitations as to what people state on them. They may not always state a condition, such as might have somebody on steroids, that would put them in a high-risk group. But as best we can define it by excluding malignancy, any immune deficiency, HIV, AIDS, the rest, the green bars are no risk. So a lot of deaths occur in people without increased risk for severe disease.

An *MMWR* article was published about a month ago which highlighted that deaths are still occurring in 1997 from varicella. These deaths were deaths in

adults that we chose to highlight in this article. But I would like to point out that transmission occurred in all three cases from unvaccinated preschool children, ages two to five. So expanding coverage to this age group could prevent morbidity and mortality in older persons as well.

The next two slides shows death, that varicella is the leading cause now, due to the decline in vaccine-preventable diseases, other vaccine-preventable diseases. Varicella is now the leading cause of death, vaccine-preventable deaths, in children and adolescents less than 20 years of age.

And this shows for each age group -- under 1's, 1 to 4's, 5 to 9's, 10 to 14's, and 15 to 19's. In every age group until 15 to 19 where hepatitis B causes the name number of deaths, in every other age group varicella is the leading cause. So pertussis is second in the under 1's, and measles is the other major cause in the under 10's, but varicella is number one now in each of those age groups.

The next overhead shows data on age-specific incidents from the National Health and Interview Survey from 1990 to 1994, and contrasts it with data from the

1980s. And for the first time in national data we've been able to demonstrate there's a shift in age-specific incidents to younger children on a national basis.

So younger children 1 to 4 are now the highest age-specific incidents, not children 5 to 9, as was the case in the '70s and '80s. If you go back even further, to 1920s, it was closer to 10. So it's been shifting down as children get into school, and now, I think, as more children are in preschool.

The next slide is data from Rochester, Minnesota, and I'd like to thank Barbara Yawn for allowing me to use this data for this presentation. In Rochester they did a telephone survey last year of about 4,000 households where there were 9,000 children less than 13 years of age.

In this community 80 percent of parents both work outside the home, so a high proportion, a very high proportion of children are in some kind of childcare arrangement. In this situation -- so this is very recent data using large samples -- the highest specific year was two. Again it shows shifts to younger children -- highest ages at 2, 3, then going down,

trailing off very dramatically after infants into elementary school and first grade.

The next couple of slides discuss an outbreak of varicella that occurred in Boston. Persons from NCID were asked to investigate the outbreak, because it was an outbreak of Group A beta hemolytic streptococcus disease among children who had had varicella, and I want to make several points from this slide.

Firstly, I'll talk about the Group A strep disease. This is a day care center, a small day care center with 39 children. There was one classroom of 14 children ages 3 to 4. Twelve of the children were susceptible. One had been vaccinated, one had had disease. The attack rate was 100 percent in the 12 susceptible children.

So in this classroom there were two invasive Group A strep complications. One of them was a necrotizing fasciitis. The child was admitted to a hospital for two weeks, had four surgical débridements, was extremely sick. The other case of invasive disease was a submental abscess. The child was in the hospital for a week and required drainage of the abscess.

The pink bars here show Group A strep disease.

These were culture-proven pharyngitis, children with fever, and were quite ill after varicella. And in addition, there were two children with cellulitis. They didn't get cultures of the cellulitis, but they suspect it may also have been Group A strep.

In the same classroom -- they cultured everybody in the classroom, in the day care center, all the families. They found two other children in this classroom who were carrying Group A strep, and it was an invasive M-1/T-1 strain.

There's evidence that there's been a change in epidemiology of Group A beta hemolytic streptococcus in the United States. Ben Schwartz from NCID has documented that in a publication showing that there's a marked change in isolation of invasive strains, the M type 1 strain that's most invasive, since the early 1980s in the CDC lab here.

That has been paralleled with an increase in severe disease caused by this organism. This may be a true increase in disease, or it may just be that people are more aware of it. But nevertheless, it's being reported more commonly now. We know that varicella is a risk factor for invasive Group A beta hemolytic strep

infections.

Getting back to the outbreak in Boston, at the National Immunization Program we collaborated with the people at NCID who went up there, and also were in close contact with the Massachusetts Health Department. And this outbreak highlighted the difficulties that they faced as a universal provider state in providing vaccine to other susceptible persons in this outbreak.

They've talked with us; they worked closely with us. And we advised that they vaccinate as a public health action, that they vaccinate other susceptibles, because this was a very severe outbreak. There was a lot of media attention surrounding this outbreak. Two hundred day care centers called and said, what do we do if we get an outbreak? And so the state was suddenly faced with a huge potential demand for vaccine to cover children of ages that VFC didn't cover. So it was quite difficult for them.

The next few slides show some data on hospitalizations. These are rates of hospitalizations per thousand cases. Two years ago when you had a long presentation on varicella, the new cost benefit study was the basis of passing, I think, or approving

recommendations for use of this vaccine.

The rate used in that study was 1.5 per 1,000 cases. I show here that some rates are much higher than that, reported since then, or especially data from the active surveillance sites. CDC collaborates with three sites in the United States for active surveillance of varicella.

And I want to highlight here the very high rate that's been reported from West Philadelphia, which is one of our sites. It's an inner-city population, poor, predominately black population, and they report a rate of 21 per 1,000. After adjusting for missing varicella cases they still have a rate of 8.8, which is very, very high. So there may be a higher burden of disease in inner-city populations.

Of the hospitalizations in West Philadelphia -- so this is data the last two years from this active surveillance -- 50 percent of the cases were among children in the 1 to 4 age group, and 75 percent of them were children under 10. And 83 percent of those children had no underlying risk conditions.

The next slide shows -- this is courtesy of Jim Hadler in Connecticut -- in Connecticut they did an

analysis of ten years of hospital discharge data. And one of the many things that they found there was a higher burden of disease among blacks and Hispanics. This is especially marked in children in the childhood ages. And these children may be groups that have benefited more by VFC vaccine.

Lastly, I have a summary slide to show you, by age, varicella incidents from National Health and Interview Survey data, hospitalizations from the Connecticut data, and deaths from the 1990 to '94 mortality file. A very high incidence, burden of disease, and deaths in children less than five and five to nine. Eight-five percent of the cases occur in that age group; 50 percent of the hospitalizations; 35 percent of the deaths. The vast majority of children in that age group are currently not covered by VFC vaccine.

I'd like to now hand over to Dr. Guerra, and then I will present options for expansion.

DR. GUERRA: Thanks, Jane, and thanks to all of you for your interest this afternoon.

I think what I would like to do is just very, very briefly reaffirm what Jane has had to say in terms of

some of our own observations in Community Children's Hospital in San Antonio.

And this really came about during the course of several conversations, primarily with some of the pediatric health officers who rotate through the Children's Hospital, in just learning from them that they were observing over the course of the last year or so a significant increase in the number of children that were either visiting the emergency room because of varicella and/or those that were hospitalized.

As you can see, this is a cumulative number of cases in one hospital in our community. Forty-three of the children that were hospitalized were previously healthy, and 17 of the children that ended up coming in with varicella or complications of varicella were described as being ill with a variety of conditions. So we had a total of 60 cases during this period of time.

In terms of length of stay, it is important to note that the ill children had an average length of stay of 4.9 days, which was a little bit less than those that were previously healthy, which was kind of interesting because the ones that were ill were

generally children that had the usual kind of underlying conditions that we often associate with complications from them. We anticipate that they're going to be in for longer periods of time.

The age distribution was 3.7 for the previously ill, and for the healthy children, and you can see it at the bottom there, it's 2.1 years of age, with a range from 1 to 7 years. And seven years in this particular group of patients, seven years was really the oldest child, and that really accounted for only two children in that age group.

In terms of cost -- this was an interesting observation -- I would say that over 80 percent of these children were covered by Medicaid, and about 85 percent of the children were Mexican-American in this particular group of patients. Our population demographics show a distribution of about 57 percent of the community is Mexican-American.

The average hospital cost is $7,500 for those that were previously ill. For the children that were described as being healthy at the time of admission, they had an average cost of $13,738, with a range being from $1,000 to about $260,000.

These are just some examples of the children that were described as being previously ill. As you can see, some of these had underlying conditions that one would perhaps associate with maybe having some complications. I would question the ones with bronchitis and asthma that I think we see on such a frequent basis these days, that I'm not sure that one could really put them into the category of previously ill cases as compared to those with leukemia or cancer or sickle cell disease.

These are the concurrent diagnoses that were noted at discharge, with cellulitis being certainly high on that list. And then there was one case of endocarditis, one case of hemolytic uremic syndrome, viral pneumonitis, encephalomyelitis, necrotizing fasciitis, and septicemia. By far, the overwhelming number of these children had either soft tissue infections or bloodstream infections due to Group A, invasive Group A strep or staph infections. The overall cost for this particular group of patients was $720,000 for that period of time and for the 60 patients.

Some important considerations for a local health

department obviously are the still ongoing myths and misperceptions about varicella in terms of many of the physicians that, even though having a vaccine available, will sometimes talk parents out of giving it to their children, or in some instances parents continue to think that -- and all of us -- that perhaps varicella is a relatively minor disease.

However, this is at a time when we've also been seeing a significant increase in the instance of invasive Group A Step infections and, of course, the other resistant strains of microbial organisms, especially methicillin- or bactomycin-resistant strains of staph, which we have certainly seen in increasing numbers in our community.

There's no question but that during this period of time there continues to be an increase in the number of children that are seen with a variety of chronic conditions, with asthma being very high on the list, accounting for many emergency room visits, clinic visits; and many children that are being maintained on a variety of follow-up and therapeutic regimens that perhaps affect their immune system, particularly the use of corticosteroids; and then also this is at a time

when we are seeing some children with immune deficiency states or HIV, and then of course leukemia, with many of them that are being followed and that are surviving for longer periods of time.

Very high economic costs; I've showed you the total figure for that. That doesn't account for the many, over 500 that visited the emergency room during that period of time. Obviously the loss of time from work for the parents, children from school or from day care centers, all of the additional costs that are incurred by families when children require hospitalization.

And then I think the changing health care system has certainly perhaps been another variable that we have not always clearly understood, but that seems to be contributing as children move from one system to another. And it's difficult to certainly know what diseases they have had in the past, what immunizations they have had, and those concerns about the populations that either are unimmunized or underimmunized; and whether or not we are able to track that information across the different systems has continued to make it somewhat difficult.

But essentially what I wanted to do was to just simply reaffirm what Jane Seward shared with us in terms of what is the observation of the local health department, and what continues to be over the last year and a half in our community a very significant public health concern.

Thank you very much.

MS. SEWARD: All these slides are in the handout, and more.

I'd just like to point out first some changes that have occurred since the earlier cost benefit study in 1993. That study was based on dollar cost in 1990. Actually, since then the cost of the vaccine -- the cost of $35 was used in that cost benefit study -- and this year's contract price for vaccine is $33.34 for orders of 500 or greater.

Other parts of the equation have only increased. Hospitalizations, the rate of hospitalizations has gone up, at least Connecticut, that we're aware of. Hospital costs have gone up substantially, 70 percent in Connecticut from 1990 to 1995. Mean income has increased, not very much though. So cost effectiveness is likely to be much greater in 1997 compared to 1990.

I'd like to show the current eligibility for VFC. So right now, of course, the age ranges I put in here, I was sort of calculating from the presentation before me, and that hasn't been resolved right now. But let's go ahead as though it's the date of the contract.

And so children 12 months through 2 years 8 months would be eligible in that window, and then there's another window at 11 to 12 years. And the interpretation of 11 to 12 is 11 years 1 day to 12 years 364 days. That makes that window children 11 to 14 years and 1 month now, if the resolution had passed on the date of the Federal contract.

And then the other VFC-eligible age group that was passed at the last vote was susceptible children, or any VFC-eligible children in close contact with persons at high risk for serious complications, immunocompromised persons. So those three groups are currently covered.

This shows the two windows relatively to the age-specific incidents that I just showed you from Minnesota in 1996. So as you can see, we're not covering a lot of the children with very high incidence of disease. The windows are pretty narrow, and the

high incidency is in the preschool and up to school entry especially, are not covered right now.

The next slide shows information on the first year of the Federal contract. There were essentially one and a half million doses ordered through the contract; 78 percent of those were VFC orders, 14 percent were 317, and 8 percent were optional use funds from states who chose to use other funding to purchase, for a total cost of $48 million dollars for the first year of the contract.

DR. LE: Excuse me. What is 317?

MS. SEWARD: 317?

DR. ORENSTEIN: I believe I can answer. That's the other grant program that's given to state health departments and helps to purchase vaccines served by those departments who are not eligible for VFC. An optional use is really state funds that are used.

DR. SNIDER: 317, it's called that because it's a section of the Public Health Service Act.

DR. LE: Thank you.

MS. SEWARD: I then took the doses of VFC vaccine that have been distributed or ordered, anyway, distributed, and tried to come up with some estimated

coverage rates for children one to two. In order to do this, I obviously had to make some assumptions.

Some of these, several of the important ones I made was that first, of the doses distributed, 1.1 million, that 75 percent of them had been administered. I just had to guess. I knew from talking with VFC people, I knew some states, it was all in their freezer still. Some states were giving it. I assumed that 100 percent of the doses distributed had not been given to children.

And then I applied two proportions of doses. Of all the doses, we know that some have gone to 11 and 12's, and some for catch-up probably, but we don't know for sure. And so I assumed 100 percent. If 100 percent of the doses had gone to 1 to 2's and 80 percent, we would come up with these coverage estimates. And I looked at the first and the second six months of the Federal contract.

Now these coverage estimates, in my own opinion, may be a little high because I'm sure there's been some catch-up as well in the 1 to 2's. Some states didn't get this vaccine until a few months ago, and so they are probably going out to kids 2 1/2, according to this

window. So these are likely to be on the high side, in my view, not on the low side.

Dr. Guerra has already pointed out some of the identified barriers to use of varicella vaccine. These have been documented in quite a few studies now in different states -- Connecticut, New Jersey, Maine -- and from focus group discussions that AAP has had, et cetera.

The concept that the disease is mild and that it doesn't have many complications and deaths; concern over waning immunity; the vaccine cost, which is substantial; and reimbursement issues, both in the private and the public sector; vaccine efficacy, being less than 90 percent for any disease, so you get some breakthrough cases; and safety of the vaccine.

Now with two years of use of this vaccine, in two years since licensure there have been six million doses distributed, there is evidence of long-lasting immunity from data from Japan and from the U.S.A. However, this is in the presence of circulating wild virus. Six million doses of vaccine has been considered very safe. There's a field efficacy estimate now since vaccine licensure which matches those from the clinical trials.

I'd like to thank Peter Strebel and Hector Izurieta for this data. It was on an outbreak in an Atlanta day care center. Again, I'd highlight the very high attack rate in unsusceptible children. In this day care almost half the children had been vaccinated, so we were able to get a field efficacy estimate. And the vaccine was effective 86 percent, and 100 percent effective against moderate and severe disease.

There have been some concerns prelicensure that the stringent storage and handling requirements may not be met in the field, so that is one piece of information that tells us that those requirements are being met, at least in that population.

I'll now go on and present options for expansion of VFC coverage. and these are not all of them; this is the first page. So I'll just read through them. You've got them all on your handout.

The first option is to expand to a one-year school entry cohort.

Second option is to expand to all preschool and school entry children from 2 years 8 months until just before the 7th birthday. So that would start at the end of the window that now exists, and so it would mean

continuous eligibility from 12 months to 7 years of age.

The third option would extend that up to 11, and that would result in all children under 13 being covered.

The fourth option is coverage for every VFC-eligible child.

The fifth option is covering children for vaccine required by state law, or state universities, or college regents' policies, for entry into day care, university, school, providing states have a law requiring this.

And the sixth option is to expand coverage to all the other high-risk groups who are not currently covered. Last time just the family contacts of immunocompromised persons was voted through. None of the other high-risk groups defined by ACIP are currently covered, and we get many questions about that through the program. I think the VFC people also are asked that question a lot. There are not many children under 19 in these groups except for this one, non-pregnant women of childbearing age. I've costed that all out separately so you can look at them one by

one.

I'll now go through some advantages and disadvantages of these various options.

For the school entry cohorts, obviously it covers children at high risk of disease at ages 5 or 6. It's only needed for three and a half years, approximately, until the currently window ages up to school entry. It's consistent with scheduled immunization visits prior to school entry at 4 to 6 years, and it would provide incentives for states to pass laws requiring vaccine for school entry, which we know is extremely effective in improving coverage for vaccine.

Disadvantages are that it doesn't include the preschool age group that I have shown you who have the highest incidence of disease. It also doesn't include children 6 to 9 that have a high incidence.

It's difficult to explain and implement. We wouldn't only have two windows, we'd have three windows, with ineligibility in between each window. I think it would be very hard for programs to implement and understand.

And many older susceptible siblings of children vaccinated at the routine age of 12 to 18 months would

not be eligible. Again, we get many, many questions about this, and difficulties that physicians and people, health care providers in the field, are faced with when vaccinating a 12-month-old and not being able to offer the vaccine to the 3-year-old susceptible older sibling.

Option two is preschool and school entry. Advantages are that it covers the majority of children at the highest risk of disease, so it would have a much greater impact. It would give us continuous coverage from 12 months up through 6 years, so no windows. There would be a window then until 11, but not three windows.

It would cover all eligible children for entry into day care and school; simple to explain and implement for programs; consistent with scheduled immunization visits. So some of the same advantages as the previous option.

Disadvantages, that it's more costly in the first year. I will be showing you costing estimates for all these options for one year and for four years. And I want to point out that there would be a lot more up front costs here in the first year, but over three or

four years it wouldn't make much difference because you're just putting it all in the first year. And it doesn't include children 7 to 10.

So going on to the next more expensive option covering children from 2 years 8 months to 11 years, this extends coverage to all children under 13, and obviously that's the age that one dose is recommended for all children under 13 by ACIP. It would cover all the high-incidence groups, so it would have a very large impact if coverage were high in decreasing disease and complications.

As I'll show you when you see the cost estimates, there is additional cost. It's relatively low for quite a high additional benefit. And then similarly to the other options, and obviously it's going to be more costly than option two.

And then being the most expensive that we possibly can, and covering every child under 19, the advantages are obvious. It would be everybody covered, it would cover all the high-risk groups, all the high-incidence groups. It would be extremely simple for programs to understand and implement.

Obviously it would be the most costly, by far, and

some of the age groups, especially adolescents, may be difficult to reach with immunizations.

Option five would provide incentives to states to pass laws. It's consistent with scheduled school entry visits, and as previously stated legislation is very effective in increasing vaccine coverage. However, I think many of the other earlier options, if vaccine were available, then states would also pass laws.

Disadvantages are that it takes a long time for states to pass laws even if they're motivated, so few children would benefit in early -- after passing this option, and that substantial additional resources may be required for vaccinating non-VFC-eligible children. And the third is that states may not act to pass laws, so then those children couldn't get the vaccine.

High-risk groups, the advantages are obvious. It just extends coverage to all groups defined by this Committee as being high risk for severe disease or high risk for exposure. The numbers are relatively small. We can see that better on the costing table.

In order to come up with cost estimates, I had to use a number of assumptions. They're all stated here. Susceptibility, I used from data we had from NHANES,

the National Health and Nutrition Examination Survey that Dr. Killgore here has been analyzing, 1988 to '94.

For children less than that I used the National Health Interview Survey data. I increased those rates by 10 percent to account for some underreporting, and then they matched exactly at age 6 years.

The others are self-explanatory. Vaccine cost is defined by the contract doses defined by ACIP. I used a yearly cohort of 3.5 million. I could have used one a little larger or a little smaller, but that seemed a reasonable middle-road figure to use.

Proportion of VFC eligible, I got from people in the VFC Program. And then vaccine coverage, I show coverage for year one in the table, and for catch-up years I used as stated here.

This shows what susceptibility was by age, from NHIS and from NHANES. So a marked decline in susceptibility after children get into first grade, and by adolescence it's only 5 to 10 percent of adolescents are susceptible.

So here are the costings. And I would heartily agree with Bill Nichols that it's extremely -- we do

the best we can with these cost estimates. By far the biggest determinate is this figure, is what you put into coverage.

I put coverage figures in here that I thought were realistic. If anything they are likely to be high, based on coverage data that we have for varicella right now. So if anything these costings are likely to be high, but we came up with something here for the coverage. But if you change it, if coverage is 80 percent, these are going to go up quite a lot. If it's 20 they're going to go down quite a lot. I think it's likely they're going to be lower than this.

So for each line I have a coverage for the first year, and then I had lower coverages for second, third, and fourth years when I calculated the four-year cost. Estimated million eligible, so that took children -- it took away children who were not susceptible, and then just those who are VFC eligible. So that's where that number comes from.

And then I have spreadsheets and spreadsheets and spreadsheets, but here's the summary of that data here: One year cost, so as you can see, obviously it's a lot more expensive in the first year to go with expanding

coverage to 2 years 8 months to 7. That's a 4.4 year cohort as opposed to a 1 year cohort. So in the first year it's a lot more expensive, but over four years it's actually not a lot different for a lot more benefit from now.

Interestingly, it does not cost a whole lot more to expand to children under 11, and the reason is that children from 6 on, the susceptibility drops so much that the eligibility only goes up from 3.9 million to 4.7, and the cost goes from $52- to $62 million for the first year. Again, I think the coverages here are likely to be lower than 40 percent.

And then if we look at covering everybody the cost jumps a little bit more, because you have to give two doses to all adolescents, so children 14 to 18 require two doses. And that's all on the handout.

We can go back and forth with these, too. I couldn't cost out option five, obviously, because we don't know how many states will pass laws.

Option six, the high-risk groups, I did my best, again with a lot of help from people, colleagues at NIP, with coming out with an estimate for the number of children and adolescents under 19 -- 16- to

19-year-olds, basically -- that would fit into these high-risk groups.

Health care workers: I looked at employment tables by age, and health care workers, teachers, children or staff in institutions; and the number is really small, 100,000 or something like that. And many of these are likely to also be included in the next group, childbearing-age females, but I couldn't -- I didn't know how to pull them out, so there may be some overlap here.

I did have different estimates, and I have an 80 percent coverage for those high-risk groups such as health care workers, teachers, people who work in day care centers, people in institutions, in colleges, et cetera.

And then for the non-pregnant women of childbearing age, I estimated a much lower coverage. I would actually think it's probably going to be a lot lower than that, at least in the first year. And there are 265,000 eligibles for the five-year cohort at a cost of $7 million because they require two doses.

So I now have the votes. Is it better to have a discussion at this point? I've got the votes, and then

I've got the resolution.

DR. DAVIS: Well, I think we need to discuss this. Mimi, and then Neal Halsey, then Steve Schoenbaum.

DR. GLODE: You've probably done this, but if you had a couple more columns with each option that said number of cases prevented per year, number of deaths prevented, number of dollars saved, then you could estimate what would be the most efficient use of those dollars. Do you have a sense of that already?

MS. SEWARD: Yeah. Well, as I did all these spreadsheets I thought I need to become a modeler. To go any further you need to be a mathematical modeler. It depends so much on the coverage and things like that, that I -- right now the coverage, we suspect, is about 20 percent. So the previous modeling studies have been done assuming a coverage of 90-plus.

So I think in the initial years it's hard to say. Obviously, as coverage goes up we would hope we would prevent the majority of deaths and complications. But I can't be any more specific than that. Sorry.

DR. HALSEY: I just would like to emphasize that the American Academy of Pediatrics' recommendation is that all children be immunized. There are no

limitations such as you have here because of VFC. And I think there is a credibility problem in the part of the public health as it's being delivered right now because of the inconsistency and the availability of the vaccine by different age groups.

And at a minimum I would like to strongly encourage that you vote for the -- at least through the 11 to 12 years right now in order to try to capture those children before they reach 13 years of age, and it will be the most -- that certainly is the most cost effective than going beyond.

I would be delighted if you also went through 14 to 18 years, because that would make it consistent with what the Academy has recommended. If you don't capture them, then they are either going to need two doses at a more expensive means to prevent it, or a higher risk of complications from the disease.

MS. SEWARD: Could I just make a comment? It's also ACIP recommendations that every child under 13 be vaccinated. So that also would be --

DR. DAVIS: Yeah, I think it's very important not to obscure -- this is a VFC issue that we're discussing here, but there are specific recommendations that the

ACIP has already made which are very consistent with the recommendations of the AAP.

Steve Schoenbaum and then Chinh Le, then Walt Orenstein and then Rick Zimmerman.

DR. SCHOENBAUM: I'm not going to get too many opportunities. There are more opportunities to raise in politics subject. But it seems to me that I'm having difficulty -- I am having difficulty framing this discussion or set of decisions, because it feels to me like underlying it is a negotiation.

All of your models, for example, assume the constant cost of the vaccine. And I think if I were the government and I were thinking about increasing the number of doses I was about to buy, I'd also wonder whether or not the price was negotiable and likely to come down.

Conversely, if I were the manufacturer and I was being approached about lowering my prices, I would want some commitment that in fact the amount would go up, some kind of volume guarantee, and some kind of assurance that your coverage estimates would be as high as possible.

So I'm not sure how one puts this. For me, I'm

having trouble putting this into the framework of a set of votes as opposed to the framework of a negotiation, the results of which come back to a group like this; whereupon I suppose it can choose which of a few options that came out of the negotiation it wants to choose.

DR. DAVIS: Thank you.

Chinh Le?

DR. LE: Steve, I'm going to have some questions later, but I guess just in reaction to your comment I would think that even if there is some changes in pricing and so on, it seems to me that the cost analysis for public health, as well as for the health of the children, the morbidity of disease is so overwhelming that whether you make a difference in two or three dollars here or there would make not much difference in cost estimate. I don't know.

DR. SCHOENBAUM: I recognize that. All of this was in the context of a positive benefit-to-cost ratio. The problem, though, is that one has limited dollars. So what one is really trading this off is against the next program that one could be spending those same dollars on, and therefore it becomes relevant again.

DR. LE: I have some question about the cost analysis a little bit. When you make the cost estimate for the older age group, do you assume that we are vaccinating on the basis of negative varicella history?

MS. SEWARD: (Nods affirmatively)

DR. LE: Or are you also taking in account that some providers will do sera testing of older children, and only vaccinate the seronegative?

MS. SEWARD: Well, I used susceptibility data from NHANES, and ACIP's recommendations state that history is highly -- very, very reliable with respect to serology.

DR. LE: But for the older age group it may be a little bit different, or --

MS. SEWARD: I assumed susceptibility according to the sera prevalence data from NHANES, so 7 percent of adolescents susceptible.

We're asked a lot in the program about sera testing prior to vaccination, and it is likely, as you know, to be cost effective in adolescents and adults if they have a negative or uncertain history. With a positive history it's probably not going to be cost effective to test.

DR. LE: And my comment in terms of the question of spending health care dollars and priorities and so on, you make a very strong case that the mortality of chicken pox now surpass measles and any other vaccine-preventable disease in the children's group, not influenza in adults, for example.

So I guess if one were to make a political statement now, now that many of the states are having surpluses because of the good economies, maybe this is a time to push this all the way to as much coverage as possible before the recession comes.

[Laughter]

DR. LE: Because otherwise we'll be playing catch-up five years later with a budget deficit in terms of health costs.

DR. DAVIS: Walt?

DR. ORENSTEIN: A couple comments.

One, on your VFC percentages, I'm not sure where you got them. They seem rather high in terms of what the actual experience has been. If I recall for 1995 -- and maybe Bob Snyder or Dean Mason --

MS. SEWARD: I got them from Bob.

DR. ORENSTEIN: What I've seen is that about 60

percent of the market share has been public sector purchase, and about 60 percent of that has been VFC. So roughly 36 percent as opposed to 54 percent, in terms of --

MS. SEWARD: So the cost estimates will be higher, then?

DR. ORENSTEIN: The estimates for VFC are likely to be substantially lower, based on that, than what you have here.

In terms of the negotiations, it's a chicken-and-egg kind of thing. It's a little bit difficult to begin that. I don't know if Merck wants to comment. I don't.

[Laughter]

DR. ORENSTEIN: But I think that, clearly, with resolutions it pushes us forward to do negotiations on different aspects of it.

DR. DAVIS: Okay, thank you, Walt.

I think Rick Zimmerman had his hand up next, and then Dave Fleming.

DR. ZIMMERMAN: My comments are very similar to Neal's in that our AAFP Commission would like to encourage the Committee to expand varicella coverage in

VFC, and I concur with him that at least through age 12 would be nice.

DR. DAVIS: Dave?

DR. FLEMING: A couple of comments.

First I'd like to speak in support of what Steve was saying about knowing the price. And maybe Walt can't ask Merck, but I'd like to ask if Merck would be able to comment on vaccine price if in fact VFC expanded coverage, because that is a critical issue for state health departments, particularly state health departments that are doing universal purchase and trying to figure out how much money is going to be saved or not.

In that context -- so I don't know if you all want to comment or not.

DR. PORGES: I wondered when we would get this opportunity.

[Laughter]

DR. PORGES: First of all, I'd like to congratulate Jane and the whole National Immunization Program for the work they have done on this. They have really clearly articulated the importance of widely using this vaccine, and it's a message that we have

been communicating for the past few years in the private sector with some success, but certainly not as coherently and cogently as she communicated today. So it was a really wonderful effort.

First of all, I'd like to respond to Dr. Schoenbaum. We have a contract with the VFC Program with the CDC now that has a maximum value that is in excess of the expansion that's being proposed. So the contract that we originally negotiated incorporated the potential for this expansion, is the first thing I want to say.

Nevertheless, we do believe that this is the right thing to do, and that the vaccine should be used according to the ACIP's original recommendations. And this expansion would be consistent with those original recommendations. And we also recognize that this will impose a significant incremental cost on the VFC Program and are sensitive to that.

So what we would propose would be a separate temporary contract with the CDC to cover these catch-up cohorts for the period of the catch-up cohort, and that would be at a price that would in some measure offset the incremental cost of the expanded coverage.

But I do want to go back to my original point, that we initially negotiated the contract in good faith with the assumption that the scope of the contract could incorporate such a recommendation. But, nevertheless, because we do want to be supportive of this initiative, we would be willing to enter into that negotiation.

DR. DAVIS: So that certainly sounds like a good faith effort here on everyone's part.

DR. LE: I have a question on that.

DR. DAVIS: Yeah, okay, that will be fine.

DR. LE: How much does the price for the private sector get tied to the public sector, meaning if Merck and the government negotiate a price, how much does that affect the private sector? Do you know?

MS. SEWARD: Well, now it's $39 a dose this year, and --

DR. PORGES: It's roughly $40 a dose, and we would not anticipate any change in the private sector price as a result of any change in the VFC contract.

DR. LE: Although you expect that the private sector would follow the expanded coverage. Once I think that the public sector expanded the private

coverage for varicella vaccine, I would think the private practitioner would be even more under pressure to really push and provide this vaccine -- talking about the insurance company, for example.

DR. PORGES: Do you want me to comment on the private sector a little bit?

DR. LE: I think it will help, because I think it's also for the AAP recommendation.

DR. PORGES: Let me comment just a little bit on what's going on in the private sector, because I think it is relevant to some of the discussions that you're having.

The AAP has recommended the vaccine for all susceptibles up to 18 years of age, and you're familiar with the ACIP recommendations. Consistent with that, most insurers and reimbursers, HMOs, et cetera, are providing reimbursement for the vaccine consistent with those recommendations, not consistent with the VFC eligibility. So in fact the private sector is already moving towards widespread utilization.

I can give you some percentages that we have from pretty expensive research sampling, interviews, et cetera, all the kind of things we do. The vaccine

utilization in the 12 to 24 month age cohort is between 60 and 70 percent of the susceptible population in the private sector being vaccinated.

It's significantly lower as you get older, but there's a big spike in the back-to-school group, 20 to 25 percent of susceptibles are now being vaccinated. And that's where we're hearing a lot of interest and requests for providing the vaccine, because kids are going to school, and that's where parents are sort of saying we want to get them vaccinated. Insurance policies are supporting that in the private sector.

DR. DAVIS: Thank you.

Dave Fleming?

DR. FLEMING: I just had some questions about whether you had had a chance to do any contacting of states that do universal purchase of vaccines.

And I guess the two issues that would help me in making this decision would be to know first what proportion of states that do universal purchase have been able to include varicella under the current VFC recommendations for folks that are not covered by VFC; and then second, what proportion of states that do universal purchase would be able to expand their

coverage according to what we've outlined here? Have you talked to any of these folks?

DR. DAVIS: Does anyone have any information on that, because that's certainly a very important issue?

MR. MASON: I believe we have currently 15 universal states, 14 or 15 universal states. And of those states, in terms of their supply of varicella vaccine to private providers and to their public clinics, they adhere with the coverage limitations of the VFC recommendations, so that this is not universal supply for all age groups but only as indicated by the ACIP for VFC coverage. I think that is almost true in all of those states.

DR. FLEMING: That wasn't quite my question, though.

Do you know whether those states that do universal purchase who are also getting VFC vaccine have been able to find state or other funding to buy varicella to match the VFC age cohorts, but for kids who are not VFC eligible?

MR. MASON: Yes. They try to -- they don't want to create a double standard or dual citizenship, so they try to apply the same policies for the

non-VFC-eligible children as they do for the VFC eligible. I'm not aware of any universal state, or for that matter non-universal, that has a more liberal policy for VFC children than they do non-VFC. They try to come up with 317 grant funds or state funds for the coverage at least equal to the coverage for VFC children.

DR. FLEMING: Have you had a chance to talk with any of them about potential expansion that's being discussed here to see whether they could find the money to go with that?

MR. MASON: Well, that's one of the major issues, is when you're talking about 317 grant monies or -- are quantified, and are already committed for the remainder of this calendar year.

And so in order for states to reach the children that are not VFC eligible -- and Walt's addressing that perhaps 40 percent or less of the state would be covered through the VFC program -- they would have to come up with state monies, because 317 grant monies, at least the remainder of this year, are simply not available in order to keep equal coverage of non-VFC-eligible children, which could very well

represent a majority of the children that they serve.

DR. NICHOLS: And it's not requested in '98 either, for more 317 funds. So it will be the same situation next year as this year for 317.

DR. DAVIS: Do you want to go ahead with your question?

DR. NICHOLS: Yeah. I just wanted to put in perspective what these different options would do to the entire cost of the VFC vaccine purchase.

We are estimating that in 1998 about 325 million will be needed for vaccine purchase. So if you look at some of these estimates we're looking at an increase of about 25 percent, if these are accurate. And I just want you all to be aware of that.

DR. DAVIS: That's pretty hefty.

John Modlin.

DR. MODLIN: I'm trying to put things in perspective for myself, and I did have, first of all, a comment; and then I think a question I was going to have here, which I think was just answered by that last comment.

But what we're really trying to do here with the vaccine program is prevent deaths and severe cases of

disease due to chicken pox as perhaps is measured by hospitalizations. And you've made a nice point that chicken pox now accounts for the largest number of deaths due to a vaccine-preventable disease.

But the number here that they showed on adolescents under 20 years of age over a five-year period was a total of 239 deaths, which is a large number; but it pales in comparison to the thousands of deaths that occurred with measles and the thousands of deaths that occurred with polio, both of which have been prevented with vaccines that are far less costly than chicken pox vaccine is.

And so in terms of the actual cost to prevent very severe disease, we're talking about much higher costs here. It may very well be because of that that targeting our vaccine policy, or at least the recommendations for the VFC Program, to trying to prevent deaths and hospitalizations in those that are amongst the highest, which are the youngest children in the preschool age group and adults, may make more sense.

Unlike the American Academy of Family Physicians and the AAP, this Committee is endowed with a fiduciary

responsibility. And I guess the question for Walt and for the others is does the incremental cost which we've just heard about of an extra 25 or 30 percent, what is this going to mean with respect to the way in which Congress and others views the responsibility of this Committee?

In other words, would we be jeopardizing the entire VFC Program by making such an incremental cost to prevent a relatively small number of deaths? And that's an answer to a question I just don't know. But I think it's very, very important to consider when we're considering it as a whole program.

DR. SNIDER: I think that's one of the reasons, though, John, going back to Mimi's suggestion, that although it's only one input, this problem, it seems to me, is one that's relatively ideal to do an incremental cost effectiveness analysis on with looking at the various options because it's not only a question of how much money you're spending, but how much benefits are you going to derive from that.

And it seems to me that making a major investment or in a relatively cost-effective intervention is a way of defending the additional expenditure of funds. And

so if we select options in which the cost effectiveness is in the same range as many other things we do in medicine, then I think it would be perfectly defensible to Congress, the public, the taxpayers, to do that.

And then there are these other policy issues. I agree with Steve that it's more complex than just doing a cost-effectiveness analysis. That's only one input. One has to figure what is the coverage, what is likely to happen to vaccine prices, could we get them to go down. So there are a lot of other things to put into the policy analysis, which I would also advocate that we do.

I think really what we have right now is kind of a mix between the two. What Jane has done has been very helpful, but it's kind of given us some information on the cost on the economic side, and some glimmer of what benefits we might derive. But we don't have that expressed to us quantitatively.

DR. DAVIS: I certainly concur with that. You have sort of articulated, or you have articulated, what I was feeling very uncomfortable with; and now I feel that we need that information. There was something about -- things seemed to be moving very fast, and we

were sort of hitting the wall on this thing suddenly, with all this information, without really critical stuff.

Presenting Tracy Lieu's information was fine, and saying the cost benefit is likely to be more but not actually following through and doing that analysis, is sort of -- it's tantalizing. But it's nice, it would be really good to have the follow-through. And I do think the incremental cost benefit is important, and for this type of a commitment to VFC I think it would be important to have that.

My personal feeling is that we need that information. It would be very difficult without additional information that probably could be generated without too much difficulty. It's going to take work; everything takes work. There are some realities here, I think, that we have to face, and all of us are interested in preventing and controlling disease and minimizing mortality, there's no question. But I think we have to be --

DR. SNIDER: But I think this is potentially the kind of issue, for example, that we would want to go to the epidemiology program office, the economists there,

and say that we have a major Agency issue, we really need some help on this; and get to work on it to provide that information for the ACIP, as well as do the policy analysis, which I think are pretty far along in terms of the pros and cons and so forth.

DR. DAVIS: And then just bring that back to the Committee for the next meeting. I hope that people aren't too frustrated in not taking a vote at this point, but we're still discussing this.

DR. SNIDER: Intuitively, some of the data -- and there's almost an intuitive thing about where you might want to draw the line. But given the investment we're talking about, it seems like you'd want to do -- have more quantitative information.

MS. SEWARD: Can I make a couple of comments?

Firstly, I think the cost estimates are high because we used a coverage rate of 40 percent, and we know from data from our active sites that right now in 2-year-olds the coverage is more like 20. So I think the first year of the program we're not going to see a 40 percent coverage rate. The VFC proportion I used had been given to me by the program, but Walt thinks it's lower. That also would lower the cost.

I'd just like to point out the conclusions from the Lieu study two years ago. I do have some data that I can show you that the mean charge per varicella hospitalization increased from 1990 dollar costs that were used in the Lieu paper. They increased 70 percent in just five years in Connecticut. This was Dr. Jim Hadler's paper, a study that he's done.

He also has information on increasing hospitalizations over that ten-year period. A number of hospitalizations, and that's paralleled by rate, so it hasn't been due to population changes. From 1990, again, the year the data from the Lieu paper was used, to '94 here, there was an increase in 26 percent of varicella hospitalizations. I don't know what's happened up through '97.

So it was on the basis of that, I assumed deaths would cost more now. Everything would cost more now.

DR. SNIDER: I really don't think it's an issue, though, of expansion. It's a question of how much to expand.

MS. SEWARD: Right.

DR. SNIDER: And that's where, I think -- that's the rub.

MS. SEWARD: Right.

DR. DAVIS: I think Pierce -- one minute, though.

It's getting late, and this is very important, there's no question. I think we as a Committee should try to probably decide which direction to go. My discussion was more just my point of view, not necessarily saying what the Committee should do. I just want to make sure that you understand that. But I want to bring this to some form of closure in the next three or four minutes.

Georges, and then Pierce; and make it quick, please.

DR. PETER: I don't disagree with any of the discussions about the importance of cost effectiveness, but I think in the early days of discussion of the VFC we were told that decisions were to be made based upon public health good; whereas this discussion is entirely centered upon cost effectiveness. And I don't disagree with the importance of it, because you cannot make these decisions in the absence of this data.

But I think one point that is lacking in these current discussions, is we have not developed public

health goals for varicella. We have no goal, as far as I know, for immunization rates against varicella at any given age, correct?

Secondly, is we've not targeted because the vaccine wasn't developed until after 1990, a goal for the year 2000 for reduction in varicella deaths. And I would think that would be an extraordinarily important step to take in developing these cost effective data, to prove that if indeed it is expensive, this is a commitment that we as a society has made.

DR. DAVIS: I think that's a point well taken.

Last comment right now, Pierce Gardner.

DR. GARDNER: Just a brief point, coming back to John Modlin's feeling.

Are we competing for various goals with our dollar? He summarized very nicely the 484 deaths that occurred over five years in vaccine. Just to point out, that's roughly 85 a year. The adult immunization diseases are in the 50- to 70,000 range. I would love to see your analysis of the cost per hospitalization, and the same sort of thing.

I worry that as we -- will the Congress pay attention to the adult immunization imperatives that

are, at least numerically, thousands of times numerically more? So I do worry about this competition. I hope these same kinds of analyses will be done for the other issues.

DR. DAVIS: Now at this point I just want to get a sense of the Committee. Do you wish to proceed with getting incremental cost benefit data and some of the additional supporting information that Dixie and others have asked for, or do you wish to proceed further on decision items here?

All in favor of getting the incremental cost benefit data and the other information that we need to further support our decisions, vote by saying aye.

[Ayes respond]

DR. DAVIS: And those opposed to that?

[Show of hands]

DR. DAVIS: We have one person in opposition.

I'm sorry to move it along, but we have to bring this to some closure.

We need more information. We're not done with this topic, in any stretch of the imagination. The question is, what are we going to do when we resume this?

Marie.

DR. GRIFFIN: I'm just wondering how -- is that information going to be available? How long with it take to get that, and are we -- how long a delay?

DR. DAVIS: I think you've raised an important point. We obviously don't want to put this on indefinite hold, because we do have -- we have important decisions to make.

DR. GRIFFIN: Is it possible to do it incrementally?

DR. DAVIS: I don't know. Somebody else will have to answer that question.

Steve, please explain your vote.

DR. SCHOENBAUM: I didn't cast a vote to be a contrarian, although sometimes I'm accused of that.

It seemed to me, or it seems to me as I've been thinking about this, in my mind I thought I hit the central point -- and I really appreciated the comment from the representative from Merck --in that assuming that in fact direct medical costs do exceed the cost of the vaccine, and assuming that most of those direct medical costs are also paid for out of the Medicaid program, I'm not sure that I have a problem with what

the total costs are once they're minimized.

So I'm still back to the fact that I think the central issue here is a business decision on just how one can minimize the total cost, but not necessarily am I impressed by what that total cost is because one way or another I suspect we're paying it.

DR. DAVIS: Well, I think the HCFA representative, instead of saying what the cost of the program is going to be proportionately, should balance that out. If indeed the Medicaid program -- if Medicaid and Medicare are basically paying for these costs and it's a trade-off between prevention and payment for disease, then I think we ought to know that rather than having those kinds of statements being made to us.

We get put in a box because on the one hand we're trying to make public health-related decisions; on the other hand we have to be shepherds of public resources. And there's mitigating arguments.

I think that you've stated it very well in the sense of there's a balancing issue here in terms of one payer funding it. It's the old oil filter thing -- you can pay me now, or you can pay me later. So that's certainly very important and very rational.

I do want to, for the sake of the other people that have presentations to make today, I want to bring this to closure. I can't emphasize that enough.

Neal?

DR. HALSEY: Just a brief comment.

There's an opportunity lost if you defer until October in terms of the preschool immunizations that will take place over this summer. And I wonder if you might consider just going with immunization, expanding it briefly now, not going the whole cohort, which I would really like to see you do; but go ahead and expand it to six years, to children who will be six years by whatever time, if you can figure out a way to word that. And then you could consider expanding beyond that in October.

DR. DAVIS: In terms of preventing morbidity and hospitalization, there certainly is a high impact in the first six years of life, as we've heard from the data today, and as has been presented. So that certainly is a thought.

Tom?

DR. VERNON: I'm Tom Vernon from the Merck Vaccine Division.

To the extent that this has become a cost discussion, there was a statement made by Bill Nichols, who has unfortunately gone --

DR. NICHOLS: I'm here.

DR. VERNON: Oh, good, Bill. Check me on this.

Next year's budget, now projected to $325 million, would be expanded by 25 percent with the adoption of the larger of these cohorts. I assume that that $325 million includes the existing contract for the vaccine.

DR. NICHOLS: Those estimates aren't based on contracts. They're based on actual purchases. And so what is available under the contract does not come into account in that estimate.

DR. VERNON: Your assumption, then, is that even though we calculate that all of the increases that have been projected could fall within the existing contract, as was stated by Dr. Porges, that that would still increase the budget for 1998?

DR. NICHOLS: Yes.

DR. VERNON: I just thought that needed clarification.

DR. NICHOLS: Yes.

DR. VERNON: Thank you very much.

MS. SEWARD: There are lots of options that aren't -- that are less expensive than the most expensive option. I'm wondering if there is room to consider --

DR. DAVIS: Well, I think we understand that there are a lot of options, and there's varying costs associated with each one. There's no question about that. But the question is what is a prudent course?

DR. FLEMING: A suggestion would be -- I think it would be reasonable to see the cost effectiveness stuff just as a process issue for justifying a major expansion.

But we could choose to follow what we did with the other vaccines, which is to clarify the eligibility dates to the first of the year, and for varicella that would result in the addition of almost an entire year's cohort, because currently it's children at least 12 months old who were born after November 11th, 1994. And if all we did was just to make that like the others and change it to January 1st, 1994, we would be getting a year's worth immediately. And then for adolescents, changing it from May 11th to January, we'd also be getting about six months.

So I think just by being consistent with what

we've already done, we could add one-and-a-half years of age cohort and then move in October to expand based on a cost-effectiveness analysis. That would be my proposal.

DR. DAVIS: Yes, Fernando?

DR. GUERRA: I think that's certainly an important consideration, especially if one could couple that with what the states are willing to do with the available 317 funds to maybe enhance that cohort of eligible children to try to get as many up to the preschool age group covered as we possibly can.

And at the same time I think it would be tremendously important to get a better understanding of what the different insurance plans and the managed care plans are currently doing for this population of children, because that has been very inconsistent across states.

DR. DAVIS: I think for an issue of this magnitude that we certainly would want as much information as we possibly can get. And with our initial VFC votes back in the early VFC days, the Committee really did have more information available to us to make those decisions.

Walt?

DR. ORENSTEIN: I think I'd like to agree a little with Steve.

It's going to get very, very complicated very quickly. The Tracy Lieu data did show that medical care costs were about a wash, about one-on-one with the dollars. Clearly the bigger expansion you do the more likely you are to get herd immunity and in fact get benefit for those that you are not vaccinating, whereas if you do it very incrementally it's much more difficult.

The other issue is an ethical one. This has put us in a quandary in the childhood arena. We have not had to deal with this before. Even when we went to the second dose for the measles/mumps/rubella vaccine and we implemented it gradually, we were in outbreak situations covering everybody. And there wasn't that much disease compared to what we're seeing now.

We're now putting physicians sometimes in very difficult positions. So there is the ethical issue of being able to prevent disease of patients who are normally treated in childhood immunization programs.

DR. SNIDER: I guess the problem I'm wondering

about, and maybe someone can help me, is basically how you decide between option four -- option three and option four, for example. What kind of inputs do we have that would allow the Committee to make that kind of a distinction?

It seems to me those are -- that's where it becomes difficult. It's not difficult to think about expansion. Where it's difficult is to know where to cut it. And I don't know what the voting rationale is to go with three or four, for example.

Since these things have to be justified to the directors of CDC and others, a well as to ourselves, to me that's where the difficulty lies. And if someone could help me through that particular part of it, maybe I'd feel more comfortable about it.

Because the expansion, to me, is a given. Expanding is a given. I think we've seen enough data about morbidity, mortality costs, and so forth, to tell us that we need to do more. The question is how much more, and that's what I'm personally trying to struggle with.

DR. SCHOENBAUM: I would agree that it's hard to decide between those. But I think that one could chose

to put one's foot in the ground, literally today, on either two, three, or four; and then assess the incremental cost effectiveness ratios for the other options because you know they're going to be incremental.

DR. GRIFFIN: I would agree with that. I think if you're really stuck between three and four, then we could at least vote on three and see what four looks like. But I think that's not a reason not to vote for number three.

DR. LE: Isn't the slide which shows that the incidence of hospitalization and death over 20 years old kind of like skyscrapers compared to the younger group and what percent of mortality? Meaning if we don't vaccinate the 14- and 18-year-olds now, we're pushing this disease into the adult age group that Pierce was worried about.

DR. SNIDER: Well, that's the kind of thing that intuitively you react to, and until you can get it to some kind of baseline in terms of quality or some kind of denominator that you can look at, it makes it very difficult to make those choices, is my point.

Although I do agree with Steve and Marie. I think

if the Committee is in some agreement that we ought to expand, we could do it in an incremental way -- take an intuitive approach to going a certain distance, either as far Dave is talking about, which is the minimal amount, or to a higher level that people are comfortable with, and then get additional data to see if one could go -- see if it makes sense from the economic standpoint and from the other policies' standpoints with regard to -- and Jane is raising those in terms of the issues of being able to reach certain populations and how much it would cost to try to reach those older populations, et cetera.

I think that's where it becomes much more difficult, and where you want to have more information before you jump into some of the more -- what might be some of the less cost effective approaches.

DR. DAVIS: Bill?

DR. NICHOLS: Just one minute. I didn't want to freak everybody out by saying it was a 25 percent increase.

DR. DAVIS: I can't hear you.

DR. NICHOLS: I didn't want to make everybody really scared about a 25 percent increase. The purpose

of my saying that was just to give you a knowledge of what the estimates are now.

This year we had appropriated $523 million dollars for this program, but we've adjusted our estimates based on actual usage down quite considerably to around $330 because the actual usage is not near what it had been projected to be by the states when this program first started.

I think the best thing to do -- and I know I don't have any say in this -- but I just wanted to say that the best public health thing to do would be, to me, option two, and I think that's -- the amounts that are talked about there definitely need some refinement. But I think that in my opinion those would be acceptable to Congress, and the charges of runaway entitlement probably would not exist so greatly there.

DR. DAVIS: Yes, Mimi?

DR. GLODE: I guess I can do the growth calculations myself. My problem is that I'm embarrassed to vote on option two, three, or four without having some basic information that would say number of cases prevented given these assumptions, number of deaths prevented, number of hospitalizations

prevented. Just the medical issues, let alone the economic issues. I'm going to have to go --

DR. DAVIS: I think you basically have a Committee that wants to move forward, and it's just asking for more data and is asking for some data to be developed over the next four months. It is four months, and in the next four months there will be kids that will be ill, and certainly there are opportunities to immunize during the summer before school begins and before there will be a lot of transmission.

There clearly are up sides and down sides to anything that we're requesting. We're certainly mindful of that.

John?

DR. MODLIN: I'd just point out that the incremental cost difference between option two and option three -- I'm sorry, between option three and -- right, option two and option three, is relatively low.

You're getting additional coverage of school-age children with option three. And since most of the disease, it looks like, that's occurring is occurring in both preschool and school-age children, you're

likely to get a much bigger bang with respect to reduction of disease as a result of increased herd immunity that may actually exceed the benefit --

MS. SEWARD: My other comment is, you can do those sort of cost benefit calculations, and it's all -- you're going to have to put in a coverage estimate. It's a guess. I'm guessing 40 percent. Actually it's probably going to be lower, so at 20 percent coverage you may not prevent many deaths.

So even with that additional data it may not help, because any cost benefit analyses I've seen had coverage rates of 90 percent plus. They assume full coverage. And we're proposing much more realistic coverage estimates.

DR. MODLIN: I think for the purposes of moving toward some closure here, Jeff, I don't have a vote, but I think I can make a motion.

I would move that the Committee move to adopt option three here, and perhaps we can bring this to a vote a little more quickly.

UNIDENTIFIED: Second.

DR. DAVIS: We have a second. We seem to have a rush to second this. We'll let Steve second it.

Okay, all in favor of -- just to put my two cents, too, with children under 11 years of age it's a simpler history. There's no need for an serologic testing; a single dose of vaccine.

DR. MODLIN: I agree. We still need to see the data that Mimi is asking for, and it's not to preclude any effort to garner that information. I think it's critical.

DR. DAVIS: Right.

DR. MODLIN: But I think we've seen enough and heard enough today that it would be reasonable to adopt option three.

DR. DAVIS: Paul Glezen.

DR. GLEZEN: What I'm hearing is the problem seems to be uptake of vaccine. I don't see how you can project any decreases in hospitalization and deaths unless there is considerable improvement in vaccine coverage. It doesn't look like the clinics have anywhere met their original projections for vaccine use, and how is that going to be improved? That's the question I have.

MS. SEWARD: I'll show you what's happened with hepatitis B, and I think we're right here with

varicella. Hepatitis B does have goals to reach, which is a little different from varicella. But five years after the ACIP recs the coverage was 20 percent, and it's increased now up to 80.

It may be easier with varicella because it's a much more visible disease. There's only one dose required. But we're right here, or maybe up to 50 percent in the private sector already, only a year after the ACIP recs. We don't know what will happen, but it may parallel our experience with hepatitis B.

DR. DAVIS: Alan Hinman.

DR. HINMAN: Alan Hinman, Task Force for Child Survival and Development.

Just to comment on the issue of goals, it's my recollection that there is a generic goal for attainment of 50 percent coverage within five year of licensure in recommended populations. That has been present since the 1990 targets, and is in the year 2000 targets, I believe. Is that not correct, Walt?

DR. ORENSTEIN: I remember it in 1990. I'd have to check, Alan.

DR. HINMAN: I'm almost positive it's still there. So that I believe there is a coverage target.

MS. SEWARD: Thank you.

DR. DAVIS: Yes, Fernando?

DR. GUERRA: I think there was some initial start-up problems just logistically in terms of getting the vaccine out to the providers and to the different programs. I think that there are several things that are in place now that are going to really enhance the coverage very quickly, at a rate much greater than the hepatitis B.

I think the WIC immunization collaborative has seen some very significant rates of increase and immunization coverage levels in populations that are quite vulnerable, as well as now the opportunity for using or accessing immunization registries and tracking systems that when we first started hepatitis B was not available. And I think those systems, together with I think more social marketing and greater awareness, et cetera, are going to take the increase, and we'll see that very quickly.

DR. DAVIS: Since we have a resolution on the floor, we should decide whether we will vote on coverage. This would be basically coverage as delineated in option three, which would be all

susceptible children from 2 years 8 months to less than 11 years. So that means through 10 years 364 days, just so everyone is clear about that.

All in favor of considering that option? Oh, we have to just vote on that option, I guess. Well, I'm trying to figure if we have to frame -- this is a VFC vote, so we have to -- I have to see the language here, the VFC language. I wanted to frame it as a VFC vote.

DR. ORENSTEIN: I thought the option is not the one up there, but the one -- at least that's what I heard John Modlin --

MS. SEWARD: I have votes overhead. I have a resolution overhead. Which one do I need?

DR. DAVIS: Plus we have the other issue from before that we didn't do, and that has to do with who is eligible.

DR. ORENSTEIN: If you vote for number three or any of the others, then that becomes moot, doesn't it?

DR. DAVIS: The following groups should be considered for inclusion in the VFC Program for receipt of varicella vaccine --

MS. SEWARD: That was preceded by proposals that

it be expanded following previous resolutions. Recommended dose is one for those less than 12. It can be given simultaneously with all vaccines recommended during childhood and adolescence. And then individual votes, and I have a resolution.

DR. DAVIS: Is that the only thing you have in writing, is just what you have up there?

MS. SEWARD: Yeah. No, it's there in your handouts, and it's here, number three. You're going to vote on three.

DR. DAVIS: I just want to make sure there's nothing conflicting in terms of the other stuff.

DR. HADLER: If you combine that with sort of the intent of the previous one, the dates intent of the previous one, it would basically be all children who were born since January 1, 1983. That would catch the adolescent window, expanding and clarifying that, and basically catch everyone younger than that. That's, I think, the intent of what was on it.

DR. DAVIS: That is precisely what I was mulling over.

MS. SEWARD: So this would change to --

DR. HADLER: You just say all susceptible children

who are at least 12 months old and who were born on or after January 1, 1983.

MS. SEWARD: Correct. The first of 1983, right. That would cover the existing 3 year, 11 to 14's, the 1 to 2 1/2's now, it'd just cover in the middle.

DR. GLODE: But doesn't it also cover now the 17-year-olds and 18-year-olds?

MS. SEWARD: No.

DR. GLODE: No?

MS. SEWARD: No. You'd have to go back to 1978 for that.

DR. GLODE: Okay. Great. Got it.

UNIDENTIFIED: John, do you accept that change in your motion?

DR. ORENSTEIN: I just have one question.

DR. DAVIS: Yes.

DR. ORENSTEIN: In terms of thinking about the Td issue, the way the ACIP recommendations are made it gives some flexibility about when one would want to do it. It says all children should be vaccinated; you may do this at different ages. Does this imply there ought to be a mass vaccination of everybody next year?

MS. SEWARD: Given at doses recommended -- given at --

DR. MODLIN: Walt, don't you think that's unlikely because of all the information received about the relatively slow uptake so far?

I don't have a problem with that. I think it's one of those things where it's a "build it and they will come," but it's going to take some time for them to come. And this has happened with hepatitis B, actually, so I'm not too concerned about it.

DR. SNIDER: I think there's another reason, Walt, why we put in the procedures and policies that the implementation issues really belong with the program, to try to figure out the ways to implement these things.

DR. HADLER: Actually, just one way to rephrase it would just be that varicella vaccine should be included in the Vaccines for Children Program for children in the following age groups. It doesn't say it should be provided or should be included in the program, so it's a little bit less inclined you run out and vaccinate everyone of those kids now. If someone wants to, they can.

UNIDENTIFIED: It's gotten pretty confusing now, because we have several different potential wordings of the motion.

DR. DAVIS: I'm very uncomfortable making a vote unless we're exactly clear on what it is. I think it needs to be written out.

UNIDENTIFIED: Right.

DR. DAVIS: And we need to take a break.

UNIDENTIFIED: We need to take a break, and need to have a motion written down.

DR. DAVIS: Yeah, I want a motion written down. We'll take a 15-minute break, and then we'll resume.

[Whereupon, a brief recess was taken from approximately 4:36 p.m. until 5:02 p.m.]

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DR. DAVIS: Everyone could please take their seats.

There clearly was an interesting discussion regarding varicella before all of this. And I think, speaking just for myself, I was increasingly uncomfortable with issues because I think we're all as a group committed toward rational expansion of varicella immunization in order to protect populations

that need it. There's no question that there's a large number of people that need it, and there's no question that there are morbidity issues and mortality issues that are very compelling.

I believe that in talking to our Committee members that we are all very interested in resolving these issues. There are a variety of other issues, however, that are overlaid here, that since this was the first opportunity that we've had to consider these and there were a couple of sort of 11th-hour things that were added on, I think it was a little bit too much for us to really come into full closure with.

We have options. We have a resolution on the floor, and we're going to have to resolve that since that's hanging right now. I certainly wouldn't want anyone to misconstrue our desire for more information as a desire to postpone an action, because we don't want to do that. But we want to make decisions that are appropriate, considering a variety of issues.

Historically, with VFC votes that have been very highly significant where we're really talking about initial outlays, we've had working groups that have worked together to make recommendations to the full

Committee. It seemed to have worked very well in the past.

And I know that if we were to do that, we would want to do it on a fast track so that information could be provided to the Committee in a timely way, and we wouldn't want to postpone this any more than one additional meeting, so that we would want to bring this to closure by the next meeting so we could have a vote. So that certainly would be one mechanism to deal with this.

However, we do have a resolution on the floor, and this involved taking a vote very specifically on one of the options, which was option three. So our options are to vote on it. If people felt very uncomfortable the resolution can be withdrawn.

MS. SEWARD: Resolution 6/97-1 that was not voted on in the previous presentation by John Livengood is the basis for this resolution, and you all have that in your handout.

ACIP has previously approved resolutions recommending varicella vaccine be included in Vaccines for Children Program for children ages 12 to 18 months and 11 to 12, and we would -- therefore ACIP would

recommend that varicella vaccine should be included in the Vaccines for Children Program for children in the following age groups. And option three would therefore read, all susceptible children who are at least 12 months old, born on or after January the 1st, 1983.

Currently, many of those children are -- the 11 to 14's are already covered. The 1 to 2 1/2's are already covered. We would be covering the middle group.

DR. DAVIS: So that would be the language based on the resolution that was proposed and seconded. We obviously haven't taken a vote. And that is basically the option three.

Any discussion?

DR. GLODE: Could somebody just speculate for me if this puts states in an untenable position in any way, or not? I don't understand exactly how people then respond to this.

DR. DAVIS: David.

DR. FLEMING: I could speak to that a little bit, and I'd appreciate any feedback that others might have.

I think that the difficulty with VFC expansion is that many states are, through other funds, providing money for vaccine for kids that are not covered by VFC;

and therefore anytime VFC expands, states are in the position of trying to see whether there is money available to match the VFC requirements, and if not to try to advocate for it.

As a consequence, there is a lot of angst at the state level every time VFC expands its criteria because of the concern about potentially creating a double standard of care within the public sector, which is that some kids coming in who are VFC eligible can get a vaccine that other kids coming in who are not VFC eligible cannot get because there is not state funding available.

In that context, this would be a fairly significant issue for many states because this would involve a fair amount of new money that would need to be identified. And I wish Dr. Le was a voter in my state, because despite the fact that there is an economic upturn in the country, in most states that has not translated to any increase in state funding.

So just to finish up, I think that it would be very useful before taking a vote on this if we could have data on cost savings that would accrue specifically to the Medicaid population, because I

think people could more easily at the state level live with this if we could say as a result of this, independent of whether you're going to need to establish a dual standard of care in the public sector, you are going to be saving taxpayer dollars because of Medicaid savings.

MS. SEWARD: This may answer your question to a little extent. This was the last year of the Federal contract, whatever states felt like they needed to provide to match within the existing VFC contract.

DR. DAVIS: Okay, Fernando Guerra, and then Georges Peter.

DR. GUERRA: San Antonio is not a state, but we have a direct grant for immunization program for the CDC, and we've had that for a long time.

We shared with you the cost data on a group of 60 children that accumulated costs of almost $800,000 in a 16-month period. Eighty percent of those were Medicaid patients. That's a tremendous cost. In addition to that, it is the burden of other diseases that this same population is very susceptible to, so that as they deal with varicella and the complications of varicella they also during that same time frame have recurrent bouts

of bronchiolitis or RSV infections, et cetera. I think the overall cost to that population, the savings, would be very significant.

I could see us covering the doses with what we presently have allocated from VFC if we could get some support from the state, from the 317, to cover that additional group of children, and have in place a system that we could very quickly demonstrate the cost benefit of this in that population because of the systems we have in place to track that group of children and the surveillance that we're doing with hospitals, et cetera.

DR. DAVIS: Thank you, Fernando.

DR. PETER: Well, I'm not in public health, but I am from a universal purchase state and a state that may be experiencing an economic upturn, but it certainly is not a wealthy state, and that is Rhode Island.

I would think that Rhode Island would have some concerns, at least initially, with a major expansion of VFC in terms of them finding the funds to provide the vaccine for the other children. But I'm still very much in favor of some expansion of the program as at least a beachhead in our commitment to reducing

varicella.

But you're absolutely right, Mimi, it does create problems for the states.

DR. DAVIS: Yes, Chinh Le.

DR. LE: I guess I need to say something, because I won't be able to vote on any of the options because of a conflict of interest with the Merck study we do at Kaiser.

But I guess it gets back to the charter of this ACIP group, which basically is evaluate the scientific data behind the merit of the option. the scientific data in terms of the morbidity of the disease, the burden of the disease, the costs of the disease in terms of if we don't do it now we're going to pay much more later.

All of this really makes a very strong case that we need to expand. We all agree on that. But we need to put our action where our words is, and it's all up to us. If we put our standard up high -- say, okay, we need to immunize the children up to whatever, 12 years or whatever it is now -- I need to go back to my own pediatrician and convince them about the efficacy of a vaccine, the safety of vaccine, and the duration of

immunity.

You need to convince your politician of this is a wise investment, that by not taking this window of opportunity now to act and immunize more children you're going to pay more health costs later. I think we all need to do our homework, and I don't think we should be shy because, well, the budget may not meet it, and so on. I think we need to put ourself up and fight the battle for the kids.

So even if you don't have option three, at least we should have option two. But I certainly would go for option three. And I don't think option four is not much more costly than option three, but --

DR. DAVIS: Can I ask Dave to speak here for a second?

DR. FLEMING: I very much agree with you, and I am in favor of expanding the varicella criteria.

I'm just concerned that we may not have done our homework yet as far as working with our constituent groups that need to be convinced, and a decision now could be perceived as precipitous. And by waiting a couple of months till at the October meeting, and having the hard numbers -- that is, the numbers that we

use to arrive at this decision as far as how much money would be saved -- would, I think, be advantageous.

It's always easier to convince people that you've taken the right course if you've alerted them that it's coming and that you've given them some data about it, as opposed to making a decision and then afterwards, in essence, sort of scrambling to find the exact numbers that you need to justify them. I'm not sure that we have those numbers right at our fingertips yet.

DR. DAVIS: And I would certainly concur.

Bill?

DR. NICHOLS: Yeah, just one quick point.

I think that states who would like to comply with VFC for children not eligible for VFC if we were to expand these varicella recommendations would turn a lot towards 317 funds to try to make up that gap, and there just aren't the 317 funds to do that. And I just want to make sure that people are aware of that.

DR. DAVIS: Alan Hinman, and then Rick Zimmerman.

DR. HINMAN: Alan Hinman, Task Force for Child Survival and Development.

Having faced the issue of introduction of new vaccines from both the state level and the national

level, I'd have to say that there's always a period of discomfort when recommendations are made for the use of vaccines and funds are not available at the state level to implement that immediately.

I'd also have to say that the funds do not become available at the state level until after the recommendations are made. That's the way the appropriation process works. And there has historically been this period of discomfort. Funds are not going to be available to vaccinate five- and six-year-old children who are not VFC eligible until a recommendation is made that VFC should fund it.

I would also concur that I think it would be important for the group at least to solidify its recommendations on children through school entry before going home. Thank you.

DR. DAVIS: Rick.

DR. ZIMMERMAN: I recognize that there are concerns that this will put some states in a difficult position, but it will also help a number of children in other states, and even in those states that are affected somewhat economically for the children that are VFC eligible and who, because of being economically

disadvantaged, may be at higher risk for complications because of problems with accessing medical care.

And so a delay can also have some costs, both in terms of dollars as well as patient morbidity.

DR. DAVIS: Okay. John.

DR. MODLIN: Well, if I heard Steve Schoenbaum correctly earlier, it's not an issue of whether or not we'll save money overall on this; it's an issue of how much. Is that correct, in terms of the overall cost to Medicaid programs and HCFA?

So that if that's the case, I don't see any reason why, just from a pure cost standpoint, why we don't go ahead and proceed today, recognizing it's still very, very important to see the ultimate cost benefit and outcome data with respect to disease and hospitalizations as well. But otherwise, it doesn't to me make any sense not to proceed.

DR. DAVIS: Okay. There's clearly arguments to proceed, and clearly there are arguments to not proceed. But not proceeding is not in any way, shape, or form a desire to be slow on this. It's just a desire for more information. I think all of us are committed to a -- I think probably everyone here wants

to expand this program.

We have an issue with regard to this resolution, and that is it's there, and we have to -- it either has to get withdrawn, or we have to vote on it. If it's not withdrawn, then we need to vote on it.

UNIDENTIFIED: Call the question.

DR. DAVIS: So the question is to vote, since it's not being withdrawn.

All in favor of the motion as -- do you want to read it one more time so we are all clear?

MS. SEWARD: ACIP recommends that varicella vaccine should be included in the Vaccines for Children Program for children in the following age groups: All susceptible children greater than or equal to 12 months of age, born on or after January the 1st, 1983.

DR. DAVIS: That covers option three.

Okay, all in favor?

[Show of hands]

DR. DAVIS: Those opposed?

[Show of hands]

DR. DAVIS: Those abstained?

[Show of hands]

DR. DAVIS: I'm abstaining, because I don't feel

as though I have enough information.

DR. SNIDER: Since this was a VFC vote, we really to call out the names, as you've done before.

DR. DAVIS: Okay. All in favor?

[Show of hands]

DR. DAVIS: Schoenbaum and Glode.

Those opposed?

[Show of hands]

DR. DAVIS: I'm going to -- I'm more opposed in the sense that I don't have --

[Laughter]

DR. DAVIS: No, no. I'm abstaining for the reasons I said. I'm abstaining, and I'm eligible to vote.

And there's four abstentions for potential conflict of interest.

So this is a very close vote.

DR. SNIDER: And that's Davis, Chinh Le, Griffith, and Modlin -- oh, Guerra.

UNIDENTIFIED: Two to one.

DR. DAVIS: As the chair, I want us to revisit this issue because I believe that we need more information that we didn't have. And I didn't feel

comfortable saying yes, and I didn't feel comfortable saying no. So I wanted everyone to understand why I voted the way I did.

I would like a full bit of information. I believe that vaccines are very important, that we should be preventing varicella, there's no question about that. But I do feel this is a very loaded issue.

DR. HALSEY: Jeff, as a point of information, your non-vote means it passes.

DR. DAVIS: Yes.

DR. HALSEY: You understand that?

DR. DAVIS: I understand that.

DR. HALSEY: In other words, if you're really uncomfortable with the proceeding, you should vote no. I personally would vote yes. But I'm just telling you --

[Laughter]

DR. DAVIS: I explained myself. I can't do any better than I did.

I feel uncomfortable with a lot of things -- the fact that there are people that clearly would have something to say about this that aren't here to vote; the fact that so many people can't vote. It's very

difficult. And the fact that this came about very suddenly, and we were given a variety of options and not enough information to deal with it.

I feel very uncomfortable voting under those conditions, and as a result I voted the way I did.

DR. SCHOENBAUM: You didn't vote the way you're speaking.

DR. DAVIS: Well, that's what I voted.

DR. LE: So I understand the vote passed, then, two to one, correct?

DR. SNIDER: Correct, it's two to one.

DR. DAVIS: It's two to one, with five abstentions.

I don't think I need to articulate that again. We've had other close votes in the past, and it's made people very uncomfortable. We've had one close vote in the past that's made people very uncomfortable in particular. Since this motion was not withdrawn, we needed to vote. And I feel uncomfortable in that sense, I'll be frank with you.

DR. SNIDER: Well, I can tell you from the Agency standpoint I feel very uncomfortable not because it passed, but because it passed two to one, and with one

person leaning in the minutes toward being against it but not voting that way.

So from the Agency's standpoint I would request that the Committee revisit this in October. I just don't feel comfortable from the standpoint of CDC of saying that we have done what we need to do to be responsive to the public. I don't know what else to say.

DR. LE: I think no matter how we're going to take the vote next time, there's still going to be four people, which is a significant number, four people who can't vote.

DR. SNIDER: There's going to be turnover in the Committee. There will be two more additional members of the Committee, and there are three people who are not here that hopefully will be at the meeting the next time. So there's the potential for a significantly different vote.

DR. FLEMING: Can I make a suggestion?

I obviously voted no, but I think it is a grey issue, and so it could go either way. And I think most people here could live with it going either way, recognizing that all we're talking about is maybe

asking for some more information.

But the suggestion would be, although there were four people here who could not vote because of the fact that they're excused, it might be helpful and might clarify, might make you all feel more comfortable, if you could take a straw vote for those people just to see which way they were going, and if in fact the results -- I guess the question I have is would you feel better if in fact you knew that the reason the vote appeared close was because we can't have enough people here to fully get a good quorum. Or is that irrelevant?

DR. SNIDER: I think it probably would be helpful. I still think that -- Georges, were you the one whispering in my ear something about $85 million dollars, a two to one vote? And the votes are --

DR. DAVIS: Well, I think this Committee has committed the resources, anyhow.

DR. SNIDER: The votes are the votes for VFC. The others are opinions, but they're not votes. So it is a difficult situation.

DR. HADLER: I have a couple thoughts.

One is it seems to me this kind of situation

happened in the polio, in some part of the polio negotiations, and we tabled it. It just -- there weren't enough people voting, and --

DR. DAVIS: I can tell you exactly what it was. It had to do with the first time the whole issue of the sequential schedule came up, and a motion was made to vote very specifically on the time that each of the doses would be administered -- literally, the formal schedule. It was basically with -- we voted to reverse it, basically. I can't remember exactly what happened. I probably should remember exactly.

DR. HADLER: At any rate, there's a precedent. I guess the two things I'm thinking of -- and I don't know whether they can be done this meeting -- is one, we haven't done the clarification resolution that, my guess is, is not controversial by itself, and as Dave said, would slightly expand the cohorts.

The other issue is would those people who were voting be more comfortable with a smaller increase, such as including up to elementary school, as Neal has suggested, and Alan Hinman?

DR. SNIDER: Alan suggested the one cohort.

DR. HADLER: Is it worth doing one step back to

see if there is more consensus there, because you are going to -- a four-month delay will basically miss this year's school cohort in terms of -- and you could do something with that.

But there is a need to take the clarification vote in any case. Is the Committee willing to consider a vote that would expand it up to school entry? If it has the same outcome, then I'd agree with Dixie's decision in terms of it's just not enough of a consensus to move forward.

DR. ORENSTEIN: I think the one thing about the two options is, as John Modlin said, there really isn't that much of a difference between options two or three, in terms of --

DR. DAVIS: Mimi.

DR. GLODE: A technical issue that apparently you've discussed in other arenas, but having been on a different committee that operates a slightly different way, having half the people not able to vote because of conflict of interest, when to a certain extent that is relative in that somebody should decide when and under what circumstances a waiver is granted.

Dr. Le, for example, I think is a perfect example.

If are not involved in any vaccine study but your organization, your giant organization, Kaiser Permanente is, my understanding was that you weren't an investigator or involved in any of that stuff, is that -- I just think there should be a mechanism that people -- that before the meeting you declare what your current conflicts are, and then someone decides whether those are substantial enough that you should not vote on various issues.

DR. SNIDER: Well, that's what I was getting at, Mimi, when I was making the quick presentation about the policies and procedures, because -- I don't know if Nancy Cherry is still here from FDA, but obviously people can look at CDC because we have contracts with all these different companies, and in fact we have a lot of CRADAs with companies with which I don't personally have any association.

You and I sit there, and you know that I vote on all of these issues because they've made the determination that I personally don't have a conflict. I think here, because of the political sensitivity of the VFC program, I have taken a very conservative approach based on advice of counsel. But at the same

time we've run up against the issue you raised with polio, and now we've come up with it again.

What I was proposing was that we use this opportunity and talk about policies and procedures to revisit this whole issue and see if we can't get out of this, dig out of this hole a little bit that we've gotten ourselves into, because I feel, as you know, very uncomfortable with this small number of people voting on major fiscal issues. And somehow we have to get around that.

One of it is to get all of our members here for the meetings. The other, of course, is to hopefully, by having the private practitioners here who may not have these conflicts, we'll have a larger pool of people who can vote that are less likely, perhaps, to have the conflicts that the academic folks will have.

But as of right now, the way things are interpreted, I don't know that we can make an ad hoc decision for this particular vote without coming up with some criteria, different criteria and guidelines.

I think Steve's -- we've got a real problem because we've got people who were supposed to present,

at 5:15 are supposed to leave -- I think Steve's point about we kind of jumped at one particular option, but there may be more consensus around option two. But still, I guess there are only four that can vote, is that correct?

DR. DAVIS: At this meeting.

DR. SNIDER: The way we currently interpret things?

DR. DAVIS: Today, there's four that can vote.

DR. SNIDER: I guess one way of getting at it is saying to Dave and to Jeff how much of an increment would you be willing to support, since you seem to be willing to support an increment, and then maybe the other people who voted for option three would at least be willing to vote for that increment.

DR. FLEMING: I will start off. I am, first off, in favor of expansion. My primary concern here is that we haven't laid the groundwork and that this will create some problems. I would be very prepared to support expanding the cohort to January 1st, as we described.

And I know we haven't talked a lot about it, but option five, which is the option that basically lets

VFC cover varicella if there are state rules or laws requiring varicella for entry into day care, school, or college, the reason I would do that is number one, it does permit, therefore, some state, local option here, that states can move to do that or not, so that states that have concerns can basically influence this to a certain degree.

The other instance is that I personally am troubled by the lack of uptake of varicella vaccine with an organ, for example, and think that expanding VFC is maybe one way to do that. But the better way to do it is to do what we've done with all our other vaccines, which is to get rules for day care and school on the books. And option five would provide an incentive for people to do that.

DR. SNIDER: Is the implication you would not support the school entry or through seven years of age?

DR. FLEMING: I would be unprepared to support option two at this meeting.

DR. SNIDER: Jeff.

DR. DAVIS: Well, I certainly concur with David on both of those issues, and I do feel it would be a while before any -- I don't know of any states with any laws

right now --

DR. FLEMING: Oregon has it.

DR. DAVIS: Oregon has it?

DR. FLEMING: It's on the books.

DR. DAVIS: It's on the books. Well, that's good.

UNIDENTIFIED: I think there's one other.

MS. SEWARD: Washington City has.

DR. FLEMING: But I need to be clear that I'm saying this not advocating for Oregon for VFC coverage, but rather that my sense is that we need to provide some local option here if we want to make a decision at this meeting, and also that we need to encourage folks to consider that as a way to go.

DR. SNIDER: Where I'm coming from is that technically we've made a decision.

DR. DAVIS: Right, we've technically made a decision.

DR. SNIDER: All I'm saying is I feel uncomfortable supporting that. Obviously, under the rules we've got to go with that.

DR. DAVIS: I was far more comfortable with everything through school entry, in that sense. But I

also feel as though, for the reasons I stated when I abstained, that there is a lot of information that we still need in order to be very conclusive about our decision.

I feel it was going to be four more months, and we would have substantially more information generated. We'd be more informed as a Committee, as we have been in the past, with regard to VFC issues that involved a substantial commitment of vaccine resources.

The mechanism for school entry is readily available. There are children that will be entering school that would be within that cohort that would be able to receive varicella vaccine this fall, or the summer before the coming school year.

Things are incremental, and it's not clear. I was hoping through a working group process that things could be made more clear.

I am a proponent of using varicella vaccine, and we have attempted to increase its use in our state. And it's just a question of sound policy. And since this is a policy issue, I wanted to make sure that we as a Committee had enough information, and so it was more of a technical abstention.

John, and then Walt.

DR. MODLIN: Just very briefly, let me just point out the problem with option two.

That is that your giving vaccine to the kids who probably need it the least with respect to their own personal protection, because that's the group in which you're going to have the least -- they're the lowest rate of severe outcomes in terms of hospitalizations and deaths.

If you want to prevent those, which I come back to what I said at the beginning -- which is I think this has got to be probably the primary objective of the entire program, is to prevent severe disease -- you're going to do that more economically by vaccinating preschool-age kids than you are school-age kids.

DR. ORENSTEIN: What I'm hearing is --

DR. DAVIS: That's what I mean, was everything up to school entry. I wasn't saying just five and six. I was saying everything up to that, and that would be 2 years 8 months, whatever it was, through -- that's what I was saying, not the five and six. I wouldn't do that.

DR. ORENSTEIN: What I'm hearing is a major

dichotomy between people in the public sector, at least who have been vocal at this meeting, who have to implement this and some of the people in private sector and academia who are recommending greater expansion.

One of the concerns is I wonder about whether some of the issues in the public sector are this is the first time you're getting to hear about this and think about it, and perhaps you've not talked with others in your states.

One of the advantages of a working group is to begin developing more of a consensus before the policy is made, and bringing in, for example, ASTHO as well as others into that working group situation.

The concern people have expressed is losing this school entry period in terms of waiting until the October meeting. And one potential compromise could be, even though these might not be the greatest at-risk children they may be the children most easily accessible, is the option one, which is the school entry cohort, which is an expansion in something that might have real impact between now and October; and in the meantime getting a working group to look at the other issues and try and build some greater consensus.

DR. DAVIS: It seems as though as a group we don't necessarily agree on the options. I think we agree on expansion, but we probably don't agree on the options.

DR. ORENSTEIN: What I'm saying is if you -- the real concern about speed, as I understand it, since we're ending varicella season right now, is the opportunity of one cohort entering school in October that might be impacted if VFC is covered right now in terms of health issues.

In the meantime, if we expand to that one cohort and in the meantime constitute a working group which will bring in more of the people to discuss it -- because I know if I've not thought about something I may want it, but I'm uptight to do it at that particular time and I may, a day or two later as I think more about it, do it. I think that may be one way of overcoming this impasse, and then bringing it up in October for the greater expansion.

DR. DAVIS: Okay, Alan?

DR. HINMAN: Alan Hinman, Task Force for Child Survival and Development.

I can understand Dr. Snider's concerns about having a vote on a sizeable issue in which only three

out of ten members of the Committee actually cast votes in one direction or another.

I wonder if there is any possibility of, for example, clarification on the issue of whether other members who are here in fact do have conditions or situations which would preclude their voting -- that is, by consultation, for example, with the Office of Counsel here at CDC to get some clarification on that item.

That could be accomplished presumably during the course of the next 12 to 15 hours, and you could revisit the issue in the morning. I would personally be very reluctant to make a recommendation to Dr. Satcher based on a vote of three members of a ten-member committee, basically.

UNIDENTIFIED: I think that's a reasonable suggestion.

DR. HINMAN: I also would, just in clarification, Dixie ascribed to me the view of only doing the school entrant people. My view is that you should incorporate, you should at a minimum adopt coverage through school entry -- that is, everyone up to the age of seven -- and that you'll miss an opportunity with

the children coming in for their preschool boosters for DPT and polio, which you will miss if you delay until October.

I'd also point out that the kids in between the age now covered and school entry are not going to be that numerous coming in for immunizations between now and October. They're not scheduled for any other visits for vaccination, and so that number is not going to be that large.

I guess my suggestion would be to try to clarify the appropriateness of voting on the part of the other members who are here, and revisiting the issue in the morning.

DR. SNIDER: Sounds like a good suggestion to me.

I think we had some people who may have already left but may still be here, I don't know, on the bone marrow.

DR. DAVIS: Okay.

Yes, Neal.

DR. HALSEY: I think Alan's suggestion is very consistent with what I probably would support.

DR. DAVIS: I can't hear you.

DR. HALSEY: If I were on the Committee I would

support what Alan is suggesting now, and we might just ask the two people who voted yes for this whether they would reconsider in an effort to try to get three votes against zero.

But I guess, David Fleming, you're not going to even vote yes for either of those two, or with -- you haven't declared yourself, whether you would vote in support of either option one or option two, as a way to come down and have a little bit stronger recommendation and be able to move off the dime right now.

So you should answer first, Jeff. Would you vote yes for option one or option two?

DR. DAVIS: You're asking me?

DR. HALSEY: Yes.

DR. SNIDER: Well, Neal, the problem is if we keep talking about this, we have some people who are going to leave, and we're not even going to have that topic.

DR. DAVIS: This whole thing is very discomforting. I do want to bring it to resolution, and I certainly concur with what Alan was suggesting.

As I said before, I was comfortable with provision of vaccine for children who would be through six years of age, basically, through school entry. That would be

everyone up to that age, up through that age.

UNIDENTIFIED: We can't hear.

DR. DAVIS: I said, as I said before, my comfort is initially with providing the vaccine for children which would expand -- it would be expanding it for the children from 2 years 7 months through 6 years 11 months, plus we would be going back to the first of the year in which the VFC vote was made or the contract was resolved.

So I said that before. That's where my comfort level was. But you have what I -- but I don't want to put members on the spot unnecessarily here. I want to resolve this issue. It's very easy to be a Monday morning quarterback, and I want to make sure that we do what is appropriate. But that is what I was -- where my comfort level was.

DR. PETER: Jeff, I know this topic has to conclude because of other people, but perhaps the best thing to do is to sleep on it and then to revisit it in the morning.

And I certainly would ask for at least you, who has the deciding vote in this case, to consider Walt Orenstein's suggestion very carefully. Because you're

not precluding any developments later providing more data, but I think to make a decision now, based upon this narrow vote at 5:30 in the afternoon with this amount of money, is premature, and at least delay until tomorrow the final decision.

DR. DAVIS: I think that's fair.

Let's move on to the next topic.

DR. LE: Chair? Excuse me.

DR. DAVIS: Yeah.

DR. LE: I think Dave bringing up option five is very, very good also, and maybe we should think about that as well.

DR. DAVIS: That would basically -- well, that's true, that certainly is important. I'm trying to think of the mechanism for that. If it went into a effect it would still have to be a vote that we would take in order to do that.

All right, I can't apologize for what happened. It happened, and that's basically the reality of it. I think it was a very good discussion, and I think the lack of clarity of this issue was reflected by what happened.

So for those of you who are interested, obviously

we're going to continue to get more information, and we will revisit this entire thing during the October meeting, and we're not going to let this rest. Our Committee wants more information in order to make an informed decision during its vote. We certainly are committed to expanding varicella vaccination in this country.

Who needs to take a plane among the people that are supposed to present between now and the end of the meeting today?

UNIDENTIFIED: The registry people have unbreakable commitments for tomorrow. We don't have a plane, but we --

DR. DAVIS: Okay. Is there anybody here that's going to -- I'm just thinking about the order.

DR. SNIDER: We were told that the last agenda, the people working with the last agenda item, had folks here who had to take a plane early this evening and would not be here. Is that incorrect?

UNIDENTIFIED: I was told that there were some representatives from some of the vaccine manufacturers who would have some knowledge about [inaudible] who would have to leave tonight. They would not be here

tomorrow.

DR. DAVIS: Well, we'll proceed with the current order here.

Dr. Kilbourne will discuss the issue of immunization registries and progress and development.

DR. KILBOURNE: Our one-hour time was over half an hour ago, so you'll get the very abbreviated version.

This is my last slide, or next to last slide. [Laughter; applause]

DR. KILBOURNE: How easy you are to please.

We would be very happy with your passing a resolution simply to create a working group on computerization of ACIP recommendations.

[Laughter]

DR. KILBOURNE: The reason for even considering it is increasing use of computers in making decisions and decision support for immunizations, particularly in the context of immunization registries.

We're going to get a little background now from Dr. Rob Linkins, hopefully a very little; some technical talk from Mr. Larry Blumen, and we'll end up putting the question to you.

DR. LINKINS: I can't do better than what Ed has just done, but I'll try to do my best.

DR. DAVIS: I want to apologize to you also for the delay. In no way does it de-emphasize the importance of what you're about to talk about, I just want you to know that.

DR. LINKINS: Thank you.

DR. DAVIS: In fact, those of in the state health departments are very interested.

DR. LINKINS: Great. I'm delighted to hear that.

We have immunization goals that we're trying to reach, and we, Ed and I, we consider one of our primary if not -- well, a very, very important strategy for reaching our goals is to develop and maintain what we are calling a nationwide mosaic of intercommunicating immunization registries.

We've tried the term "jigsaw puzzle," "stained glass window," you name it, but that's the vision we're talking about here -- local-level, community-based, computerized immunization registries that talk to each other and exchange data on patients.

We feel like these registries have four primary functions:

Ideally, they would maintain databases that enroll children at birth and store the information on all

immunization counters that those children have;

To consolidate the scattered records that are inevitable across providers and to enable accurate and complete immunization needs assessments -- when a child comes in and sees a provider, that provider would be assisted in making his decision as to whether the child needed a vaccine or not that day;

To promote automated and aggressive recall of underimmunized children -- and of course this also depends on an accurate and complete dataset which would be looked at by our immunization needs assessment;

And finally, to provide coverage assessments at both the provider level and in subgroups like geographic areas to promote immunization at every opportunity, and to target interventions in every pocket of need.

So that's where we're going with our strategy.

There are some other value-added functions of registries which could be easily included in this, or maybe not easily included, but certainly worth thinking about: Vaccine ordering, the VACMAN [phonetic] system, for instance; vaccine adverse events; adult tracking; disease and laboratory surveillance; and maybe

integration of other public health systems like LED [phonetic].

These data are probably what you're most interested in, which is the status of immunization registries in public health clinics. And ideally we'd want to be able to show you data in the entire birth cohort, because I think that's our target population. But this is really the best data that we currently have, and this came from the ASTHO survey that was conducted last year.

Basically, our best estimates of development of immunization registries in public sites is 13 states, in some sites 31, and then the remaining 8, which comes to 52 including D.C. and Puerto Rico. The remaining eight are developing immunization registries in some of their public sites.

It's not great data, and we're working very hard to improve the quality of our data. The third bullet up here, telephone survey, is just one of the methods we're currently and daily using to get better data. We're conducting a telephone survey which is targeted at all state health departments initially, and then we're going to go down to local-level registries and

try to get better information on registry development, legislation, that sort of thing, hardware/software uses.

We have a home page, that if you want really further information on what NIP is doing in this area, that's the place to look.

We're trying to write a plan of action, which might be one of the most exciting developments that I've been involved in. What we'd like to do, it was suggested that we might think about establishing a goal of our nationwide mosaic of immunization registries by a certain year, and what we would like to do is to propose a year and then try to develop interim objectives that would be met by the states every year in reaching that goal. So that would be our idea for a plan of action.

We also have some RFPs on the street, and you can find out more information about those on the home page.

Finally, going back to the functions of a registry, three important functions were a reminder recall, coverage assessments in providers' offices, and immunization needs assessments. And they all depend on an immunization algorithm, and this is one of the areas

which we're spending a lot of time thinking about now.

So that's the stage for Larry, who is going to talk to you about that process.

MR. BLUMEN: So Kilbourne told you he was giving you his last slide, but he didn't tell you he had two other guys coming up after him.

Here's the thing: There are a lot of immunization registries out there, increasingly. And you add to that a lot of pediatric practice management systems are coming into play. Every one of them has or needs to have a mechanism for evaluating immunization histories according to the ACIP recommendations. The problem with that is that there is no process in place to ensure that any of these algorithms is making the right recommendations right now.

The mechanisms, the development of them is being driven by programmers. I'm not trying to say that their work is not good. I'm just saying there's no way that anybody can validate or substantiate the claim that they all make that their algorithms are emulating, in effect, the recommendations of the ACIP.

So what we're proposing as a solution is that the ACIP itself should take the lead in providing guidance

in this area by forming a working group that we would see as an ongoing entity that would take up the issues that are raised by the development of these mechanisms which are increasingly making decisions about vaccinations, making decisions that are related to money as well, and the evaluation of managed care performance, and so forth.

A working group to make recommendations to this Committee about how these mechanisms can be brought under some kind of umbrella of guidance to determine whether or not they are doing what they claim to do would be something I think would be of great benefit. It's certainly something that the developers themselves of these systems and the users of the systems are asking us about.

It would seem, too, that the key element of this validation mechanism must be authoritative, and for that reason it was seem that the ACIP itself is really the only body that can provide that.

Such a group could also act as a forum to field questions coming from the developers of algorithms, and also their users, to deal with a number of questions. These are just a couple of samples of many questions

which arise about the ACIP recommendations in relation to these automated mechanisms.

For example, are the recommendations complete and consistent? Do they have an answer, a recommendation for every possible situation that might occur in a child's vaccination history? And then how should the old recommendations from one year be transitioned into the new ones?

Should everybody just start using the new recommendations, even for children who started out under the old ones? How would you handle that if the new recommendations tended to invalidate some shots that were acceptable under the old recommendations? These are examples of questions that could be considered by a committee of the type that we're proposing.

There are a number of other issues as well that would fall within the natural purview of such a working group. How much precision is really needed in the recommendations? Do these algorithms have to be accurate to the day, or is a week okay?

If you make a recommendation of a four-week interval in one case and a month interval in another,

is that really the way it needs to be in terms of the medical data to support the recommendation, or could consistency be obtained by standardizing in some way there?

What about vaccine types as opposed to brand names? The ACIP recommendations generally are stated in terms of general vaccine types. But in some cases the recommendations are different, depending on one manufacturer's product as opposed to another.

We also have the issue related to licensing in which certain vaccines initially are only licensed for certain doses of a vaccine series, and we wouldn't want an automated mechanism recommending a vaccine for a particular dose for which it was not licensed.

What is a minimum parameter set that would be required to specify the ACIP recommendations? Parameters such as age, minimum and maximum ages; minimum-maximum recommended intervals between doses? Is the age at which a series began important? Well, it is to determine whether an accelerated series should be used rather than the regular series, and so on.

If a group such as we're proposing could agree on a minimum set of recommendations, you could set up a

grid and then say, well, the recommendations are not complete until all the cells were filled in with recommendations.

What should be the balance between clinical judgment and the use of the automated mechanisms? The latest '97 recommendations do make some very interesting and useful delineations of areas within the recommendations that are available for customization by providers and even by parents. How could automated mechanisms leverage this aspect of the recommendations in order to assist clinicians in making these decisions?

And then, ultimately, how do we go about validating the operation of these mechanisms? A lot of people who have talked with us have said what they would really like to see are test cases, immunization histories with the appropriate recommendations attached, so that they could run them against their own algorithms to see if they got the right answers.

An algorithm can be configured to generate test cases of this sort. But in that sense, is the output of that algorithm just what it says? Is there any reason to believe that it would be any more

authoritative than the output of some other algorithm? Again, we come back to the need for an authoritative statement of what the correct operation would be.

So these are some of the issues that we feel would be meaningfully taken up by a working group of this sort, and we feel that this would fulfill a need that is arising in the country today with the operation of immunization registries, and is only going to become more urgent as these systems proliferate in the future.

Now Dr. Kilbourne is going to wrap up our discussion with a further elaboration of some of the policy issues that may be involved.

DR. KILBOURNE: Thanks, Larry.

Larry's told you about some of the technical issues. I think there are some policy issues that this group might consider. There is the issue of who should be developing immunization needs algorithms, INAs, and they are also called forecasting algorithms.

There had been a proposal at one point that one group in the country have a special link to ACIP and have their product basically approved by this Committee. There's also been the idea circulated it should be two or three groups.

It's also been widely circulated, and probably agreed to by everybody, that it is inefficient to have some 20 or 30 major medical software developers out doing this every time any small change occurs in the recommendations that you all develop.

What aspects should be tested? Say we have test cases. What are the important things that they should do? Should they straddle the boundary between a year when MMR is going to count? Have one child, a test case, 364 days old, another 365 days old? Is that who you're going to try to pick out? Or are there other issues that need to looked at before an algorithm is approved?

Basically we look at this as a question of whether we certify these things officially. We give a CDC stamp of approval, ACIP stamp of approval. If we do, when do we it? Do we do it on every version? Do we do it on minor version changes? Major version changes? When companies change? And on what basis do we do it?

So I've already mentioned the roles of ACIP and CDC, and the developers are also included and involved in this.

There are also areas that I think ACIP will be

drawn to, even though I think it's not gone to before. For instance, the concept of overdue, and whether that ought to be quantified in some kind of scientific way.

One of the major uses of registry and immunization needs algorithms is to decide whether recall has to occur. To my knowledge, you all have not opined on that in any comprehensive and authoritative way. You may not want to do that. You may consider that a programmatic issue that shouldn't be solved by you all. But to me that's an open question, especially when these algorithms are going to be so widespread.

But finally, I think you'll have to realize that -- I think that you write your recommendations in ways that recognize who it is that you're talking to and what they're likely to understand. You even put things grammatically in ways that are likely to be communicative.

I think you now have to realize that you have a whole new audience out there that now includes computer programmers who may not have a lot of background in health, and who occasionally, I find, come up with misunderstandings and don't necessarily do this well.

Partly it's a problem that the recommendations really aren't written for computer programmers. You really would like a parameter table of, give first at this month, next at such-and-such a month, and minimum interval is such-and-such. You have tables like that. I think those are things that the computer programmers go to occasionally.

Immunization recommendations are couched in more complex terms. You have to have to scan a variety of paragraphs to really get the whole sense of what it is a recommendation is trying to say. I think that's where this new audience may get lost.

So we would just propose that you consider our thought here. We think it is likely that you would like to have not just a subgroup of your own membership, but perhaps medical informaticians from outside participate in this; and we would be willing to supply some names that we think would be helpful and good additions to the group.

And that's basically it. We leave it for you to decide.

DR. DAVIS: Thank you, Ed, and others.

Discussion on this?

Yes, Rich Clover.

DR. CLOVER: I totally support establishing a working group. About a year or so ago in Kentucky we sent an RFP wanting to purchase such a system. Of the ones that responded, I developed some test cases and put them in their computers, and in literally less than two test cases none of the systems passed. And that became a concern to me that providers are using those to make appropriate recommendations.

There was nothing complex about the case scenarios I came up with. It wasn't a matter of a day or week of appropriateness. For instance, one of the cases was an eight-year-old coming in with an incomplete tetanus series, and how frequently the computers recommended DPT for that eight-year-old as opposed to DT in other scenarios up and down the line like that. So there's a real need for it.

Another thing which is maybe more on the technical side, not only do the algorithms need to be verified and some decision-making de-accept [sic] 360 days versus 365 days and those issues, it's also the logic that's built into those from the computer side. Simple logic cannot be used with the complexities of our

recommendations.

And that also has implications for the type of database that you're talking about, and that technical side, the software for databases are quite limited in how relational databases are built, and that has implications also in how to develop your systems.

DR. KILBOURNE: Those are all good points.

DR. DAVIS: Fernando Guerra, and then Chinh Le, and then Alan Hinman.

DR. GUERRA: I would suggest that we try to make available to the members of this Committee the information that has been accumulated over the last several years by the national All Kids Count project that has specifically looked at systems around the country and the projects that were funded, and that has some scenarios that relate directly to the lessons learned by any number of those projects in that one sees the array of systems that have been implemented in communities and within departments around the country from those that just have the basic elements of a system to those that are very sophisticated.

But something that was very clear is that, one, we have lacked standards that are consistent to cross

these kind of emerging systems that I think would be very helpful. And the other is that somehow we need to continue to be able to bring in the private sector into the systems as they are developed.

And if one can develop some consistent coding for the different vaccines that are given in a way that one can track that more efficiently through billing forms, or whatever can be accessed, it would be tremendously helpful. And I would certainly support the proposal for developing a working group to look at this.

DR. DAVIS: Thank you, Fernando.

Chinh Le, and then Alan Hinman.

DR. LE: My point is also this is very important and obviously very complex, and I really want to emphasize that you really need to bring in the private sector into making this thing, like either the Academy of Pediatrics, family medicine, internists, and so on, and also make it at the working level of a clinic assistant or an LVN can work this. It has to be so simple that the data can be entered by relatively non-sophisticated medical people, otherwise it's not going to be quite easily used.

DR. DAVIS: Thank you.

Alan?

DR. HINMAN: Alan Hinman, Task Force for Child Survival and Development.

We serve as the national program office for All Kids Count, which is 24 demonstration sites around the country on immunization registries. We'll be happy to make available to all the members of the Committee the recent issue of the *American Journal of Preventive Medicine,* which was a supplement on the subject of immunization registries.

I speak very much in favor of the need for the development of algorithms. One of the things that has become clear is that there is not going to be a single immunization registry set that is going to work for all locations.

One of the things in our meetings that has been brought up again and again is how to be able to deal with when a child really needs a dose, or when you count a dose, when you do not -- a big request that algorithms be developed.

And also some concern that with the vast number of information systems that are available in the private and public sectors, that not all of the ones that are

being developed currently are going to be correct. In fact, it has been proposed by a couple of people that CDC should see to the development of algorithms, which would then be made available in the public domain and then able to be incorporated into the whole series of proprietary packages. I would encourage that kind of action.

I would also say that I think it's very important for the ACIP to be involved in this, but I would hate to think of the ACIP getting involved to the extent of actually considering the development themselves. I think it's important for the ACIP to recognize what some of the issues are and the wordings.

I can recall when we shifted from 12 to 15 months, or even from 9 to 12 months for measles vaccine, that a very programmatic decision was taken both by the ACIP and by the Red Book Committee that that meant on or after the first birthday. If it was 364 days, it didn't count.

Things have gotten much more complex since then, and I think you could get very much tied up in trying to work out the exact wording of the algorithm. But to inform your recommendations by considerations of what

is translatable to an algorithm, I think, would be very important.

Thank you.

DR. DAVIS: I think there may be some NVAC issues, too. I know that Rob spoke to the issue of registries earlier, and certainly NVAC has a big interest in these issues.

I don't know to what extent you've been working with NVAC, Ed, but we'll certainly want to hear from Rob.

DR. BREIMAN: If I could just say that actually this probably would be one component of the many facets that the NVAC workshop would consider. I mentioned earlier today that you and Rob Linkins are going to be working on.

And we kind of share that perspective of what Alan just said, that there are details that are probably better taken care of outside of the realm of either NVAC or ACIP. But when considering sort of the larger issue of how to bring these registries closer to fruition, that the NVAC may be in a better position, really, to provide you with some advice.

DR. KILBOURNE: Yeah. I think a number of things

that I said sort of cut the boundary kind of close one way or another, particularly if you're talking about, as I said, the concept of overdue, which may be just a programmatic decision or may be a kind of scientific decision that this Committee wants to consider.

There are other things, there are plenty of things about registries that are -- particularly the implementation. And really, the realization of this strategy, if we really do get, as we intend to, promote a 100 percent registry coverage across the United States, I think that's the kind of activity that we have to devote a lot of energy to, and I think natural sort of advisor is NVAC, and I feel pretty strongly about that.

I think here we tread the line between the scientific and the programmatic, but I think there's something here on the science side that I think is where you cut the difference. I'm not sure.

DR. DAVIS: Walt and then Rick, and then I want to tie this up real soon because we have one more topic still.

DR. ORENSTEIN: I think the primary reason we came to the ACIP with this particular issue is the technical

side. When the ACIP formulates its recommendations, it may not consider certain issues that are important to computer programmers. Sometimes it will consider them and leave them purposely vague; other times they are by omission, and our desire is to not have or to reduce the numbers of omissions to the barest minimum.

I think the reason I think the ACIP is so important is to review those recommendations and see where issues are unclear, and see where they can be clarified. And the other issue is on a long-term basis whether there ought to be an informatics consultant that will work with us as we prepare drafts with the ACIP to see whether there are issues that come up that could be addressed more easily.

DR. DAVIS: Okay, thank you.

Rich, quick.

DR. ZIMMERMAN: Well, you were just actually moving in the direction I was.

I really think this is also an issue -- not only is it an important issue, it's also an issue to consider in the policies and procedures work group because it is an issue. If it cannot be put into an algorithm, if our recommendations can't be put into an

algorithm, then will they be implementable by managed care organizations, by delivery systems that are occurring now and will be occurring in the next five years?

And I would propose that if we can't put them in an algorithm, we're going to have trouble implementing them.

DR. DAVIS: There's certainly interesting, very compelling problems to solve. I think as a group we're very interested in participating in the process. I think exactly what our charge would be in terms of a working group would have to be defined.

You've provided a two-page document that we've had a chance to read, and I think that would certainly provide a framework for things to consider. I wouldn't want to do this in a vacuum. I think if we were to entertain that type of activity, we would need participation from other groups, as Dr. Le had mentioned, and Rob and others.

So I think as a group -- well, what's the consensus of the group? Do we feel committed to this issue? I think we all do, and so we just need to problem-solve now, but we'll be part of the process.

DR. KILBOURNE: So can we work together with you to determine who would be --

DR. DAVIS: Right. That would be very good. There may be among us ACIP voting members and liaisons who have a particular interest who could make a strong contribution, so let us know who you are.

Rich Clover already volunteered, so we'll get his name down. And Fernando Guerra will participate, Dave Fleming will participate, Rick Zimmerman will participate, and Chinh Le will participate. So you got five people there already.

DR. KILBOURNE: Okay.

DR. DAVIS: Okay.

DR. KILBOURNE: Good.

DR. DAVIS: Thanks, Ed. Thanks for being so patient and waiting.

We have one more topic which we'll get through, and that will be the issue of vaccination of bone marrow transplant recipients. And Clare Dykewicz and Chinh Le worked with this.

DR. DYKEWICZ: Good afternoon, and congratulations to those of you who are still here and awake.

The purpose of this presentation is to update ACIP

on our activities in the development of guidelines for the prevention of opportunistic infections in bone marrow transplant patients, and the development of an immunization schedule for these patients.

This first overhead shows the annual number of transplants worldwide, and in the past few years there has been a significant increase in the number of persons receiving bone marrow transplants, or BMT. The International Bone Marrow Transplant Registry estimates that in 1995 approximately 20,000 BMTs were performed worldwide.

The numbers of centers performing BMTs are increasing, as are the number of BMT recipients, and this is a rapidly changing field. Some centers are performing outpatient BMTs, and the current sources of hematopoietic stem cells now include not only bone marrow but peripheral blood, umbilical cord, and placental blood. Furthermore, BMTs are being used to treat an increasing number of disorders, not only cancers, but congenital immunodeficiencies and hemoglobinopathies such as sickle cell disease.

In general there are two types of BMT, autologous and allogeneic. An autologous BMT is the infusion of

bone marrow or hematologic stem cells from a patient back into himself or herself following high-dose chemotherapy. An allogeneic BMT is the transfer of bone marrow or hemopoietic stem cells from one person to another after the BMT recipient has received high-dose chemotherapy and radiation. About 70 percent of BMT recipients are adults, and 30 percent are children.

The development of the BMT guidelines is part of NCID's implementation of goal three of the emerging infections plan, which listed development and implementation of guidelines for the prevention of opportunistic infections in immunosuppressed persons as a high priority.

In 1995 the guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus, or HIV-OI guidelines was first published. A revised edition will be published this Friday.

Following the successful publication of these guidelines, NCID decided to develop BMT guidelines. On October 1st, 1996, I was detailed from NIP to NCID to work with Jon Kaplan to develop the guidelines for the

prevention of opportunistic infections in BMT patients, which is tentatively scheduled for publication in the *MMWR* in early 1998.

This is a list of the names of the members of the working group to develop the guidelines. We formed a BMT guidelines working group in the fall. We did find opportunistic infections as infections which occur with increased frequency or severity in BMT patients. The working group defined a BMT as any transplantation of hematopoietic stem cells, regardless of whether they were harvested from bone marrow, peripheral blood, or umbilical or placental blood.

This overhead consists of two tables, and we'll deal with each table one at a time. Like the HIV-OI guidelines, the BMT guidelines will be evidence-based, and they'll be an evidence-based statement of the recommended strategies for prevention of opportunistic infections, or OIs.

Each recommendation is followed by a rating of the strength of evidence supporting that recommendation. The rating system used follows the system developed by the Infectious Disease Society of America and the U.S. Public Health Service for the HIV-OI guidelines.

In table one, an "A" rating means that this recommendation is something you should always do. A "B" rating means it's something you should generally do. "C" is optional, and "D" and "E" ratings refer to things that you shouldn't do, with increasing degrees of contraindication. Table two lists the three categories used to rate the quality and the type of supporting evidence for a recommendation.

The BMT guidelines so far have eight chapters. There's an introduction and an overview of BMT, followed by chapters on dealing with prevention of infections from viruses, bacteria, fungi, protozoa; and then there's a chapter dealing with immunization in recipients and donors; an infection control chapter; and, last but not least, a blood and stem cell safety chapter.

We formed a BMT guidelines immunization working group to write the chapter on immunization in the BMT patients. The members of the working group are listed on this overhead:

The chair is Keith Sullivan, who is an oncologist from Fred Hutchinson. Other members of the working group are Donna Ambrosino; Deborah Molrine from

Dana-Farber; Bob Chen from NIP; Al Donnenberg [phonetic], who is from Pittsburgh; Beth Hibbs, John Livengood, also from NIP; and also Will Schleuter [phonetic] and Sherri Wainwright from NIP have provided assistance.

By the way, I wanted to historically to let you know that it was the NIP Vaccine Safety Group and Dr. Al Donnenberg who first proposed to ACIP in 1992 that recommendations for the immunization of BMT patients should be developed. So this issue has been around for a while.

On March 19th and 20th we held a meeting at CDC -- this was funded by NCID's Emerging Infections Program -- to review the draft BMT guidelines. We invited representatives from the infectious disease/bone marrow transplant communities, representatives from governmental agencies, university and community hospitals, the AAP, ACP, ACIP to attend the meeting. About 40 people from outside CDC came.

We asked the meeting participants to review the draft BMT guidelines and to make suggestions for revisions. Specific working groups were tasked with addressing areas of controversy for each chapter. To

our surprise, the immunization working group strongly recommended that the BMT guidelines include a specific immunization schedule for BMT patients.

We were reluctant to include any recommendations for an immunization schedule in the guidelines because of the limited safety and efficacy data available in this population. However, the clinicians who care for these BMT patients insisted quite strongly that we had to include a schedule, even one that was labeled as a preliminary or interim schedule, pending the publication of a more comprehensive statement by either the ACIP or another group.

The BMT providers argued that an increasing number of BMT patients are surviving longer and therefore are lived long enough to lose immunity to vaccine-preventable diseases after the bone marrow transplantation unless they get reimmunized. The BMT practitioners stated almost unanimously that they required specific guidance on how to manage this.

So let me briefly summarize what happens to the immune system after a bone marrow transplant and why immunizations may be beneficial to these patients. We know that all BMT patients become severely

immunocompromised post-BMT. Recipients who have successful engraftment will produce blood cells from their new bone marrow stem cells within about four to eight weeks after the BMT.

Total serum immunoglobulin levels will usually normalize within about three to six months post-BMT. However, we know that IgG-2 and IgG-4 subclass deficiencies may persist for greater than 18 months, and most BMT patients will have humoral and cellular immunodeficiencies for about one to two years post-BMT. Their immune system is pretty good by about one year post-BMT, but it takes a little bit longer functionally for it to be really recovered.

Patients who are immunized pre-BMT will usually lose antibodies to vaccine-preventable diseases within about one to four years post-BMT if they are not reimmunized. Data regarding immunization in BMT patients are limited, but suggest that at least several doses are necessary for diphtheria, tetanus and polio vaccines.

Despite, or rather even because of, the lack of published guidelines for reimmunization of BMT patients, BMT centers have developed a range of

immunization cocktails for BMT patients.

In April a paper by Henning, et al, was published in *JAMA,* which discussed the results of a survey of U.S. transplantation centers participating in the National Merit Donor Program, or NMDP, during 1994. Of 66 centers contacted, 45, or 68 percent, responded to a questionnaire which asked whether BMT patients were immunized post-BMT and which schedules were used.

This table reports the proportion of programs administering specific vaccines following allogeneic BMT by age of the transplant recipient. Programs with BMT patients less than seven years old were significantly more likely to immunize with IPV and MMR than programs with BMT recipients who were seven years of age or older.

At least half of the programs routinely immunized BMT patients of any age for diphtheria, tetanus, polio, HIV, MMR, Hep-B, pneumococcus, and influenza. In contrast, only 13 percent of BMT programs routinely immunized against meningococcal infection.

This is also a table from Henning's study. This table shows the number of programs using a vaccine, the percentage of programs giving at least two doses of the

vaccine, and the percent giving the first dose of the vaccine at less than 12 months post-BMT, when it probably is going to be less effective. The left column shows the number of different schedules reported overall for each vaccine by age group.

I'd like to start by having you focus on the second column. Of programs who had BMT patients less than seven years of age, only 26 percent and 34 percent routinely administered two or more doses of DTP and IPV, respectively, to their BMT recipients.

If you look at the same column in the bottom half of the table, you'll see that of the programs with BMT recipients greater than seven years of age or older, only 32 percent and 31 percent routinely administered two or more doses of Td and IPV, respectively, to their BMT recipients.

If you look at the last column in the top half of the table, you see that for the programs with BMT patients less than seven years of age the number immunization schedules ranged from three to ten schedules per vaccine. If you look at the same column in the bottom half, you see that for programs for BMT patients at least seven years of age, three to eleven

schedules were used per vaccine.

To help you understand the confusion that's caused by this, just imagine what would happen if schools used three to eleven different immunization schedules per vaccine for children at school entry.

Having concluded that vaccines are underutilized post-BMT despite convincing evidence of decline of titers post-BMT, should call for national guidelines for doses and timing of vaccines post-BMT. So let's recommend a schedule. The question is, which one should we recommend?

Several different immunization schedules have already been proposed for BMT patients. This table compares three proposed immunization schedules for DPT alone for BMT patients.

The first schedule is a naive patient schedule, the second is the BMT guidelines immunization working group schedule, and the third is the European schedule. Choosing which vaccine to use at which dose and with which schedule is difficult because data are limited and many controversies remain.

A few of the controversies are listed here. One deals with whether or not the goal of vaccination of

BMT patients should be to routinely vaccinate them against the usual vaccine-preventable diseases so that they can catch up to the level of VPD immunity in the non-BMT population. Or, alternatively, should we routinely vaccinate them against the usual VPDs plus additional pathogens, such as pneumococcus, HIV, and meningococcus?

The rationale for the second approach is that since they are immunocompromised and at increased risk of infections at least for a while, they should be given the benefit of vaccinations against all pathogens indigenous to the U.S.

Other controversies include whether a vaccination schedule for BMT patients should vary depending on the type of BMT, allogeneic versus autologous; the age of the recipient; the age of the donor; the previous immunization schedule; the previous immunization status of the donor and recipient; the presence of chronic graft-versus-host disease or immunosuppressive therapy in the recipient; and the source of donor stem cells, such as peripheral, blood, bone marrow, or umbilical cord or placental blood.

To help us sort out these controversies, the AAP

and ACP have already agreed to give us feedback and recommendations on the draft schedule prepared by the immunization working group for the BMT guidelines. It's clear that the train is already leaving the station. The question is, does ACIP want to be on it, and if so, does ACIP want to be a passenger or a conductor or an engineer?

I would like to ask Chinh Le, who is a new member of the ACIP, to respond to this question first, and to lead the discussion preceding the vote on this issue.

DR. LE: I'm a very newcomer to this. Within one week of my appointment I was thrown into this debate right away.

Let me just summarize very briefly what I came up with. But the sense I got from talking to the people in the group -- by the way, the working group, the bone marrow transplant group as well as the CDC, the AAP representatives and so on -- that list is very impressive of very highly respectable experts in the field.

The main problem is they don't seem to agree with some of the recommendations. And I don't certainly claim to be more knowledgeable, to be arbitrator for

that, but let me review with you the difficulty about the recommendations.

As Clare mentioned, I just want to just summarize. Basically, the difficulty of the recommendation has nothing to do with money or who can pay for it, obviously. It has to do with the paucity of the data. It is absolutely a very, very difficult group of patients to work with.

Number one, the immunologic issues with the host after the bone marrow transplant, not all the hosts are at the same level of immunologic recovery and competence; the type of transplant was mentioned; immunity of the donor, or retention of donor immune memory; presence of graft-versus-host disease; And not all components of immunity at the same level within the same host, meaning some have very good antibody production, some have very poor cell mediated immunity.

So even when we make a broad recommendation, there are so many type of patients, there are so many stages of the disease, that any recommendation probably will not give us the efficacy rate that we see in normal hosts, and so it's very complicated.

The second thing is the variability of the quality

of the immunogens in vaccine. Pneumococcal vaccine, for example, all the various serotypes even themselves have different strengths in terms of how good they are in terms of immunogen. And to try to make very broad recommendations on very limited studies, it's very difficult to say how those patients respond to this vaccine.

And then the risk of acquiring the disease. For example, we'll say, yeah, we should immunize against MMR, measles, mumps, rubella, polio, tetanus and diphtheria, although obviously the risk of the patients is very minimal for those diseases in this day and age.

On the other hand, the risk for pneumococcal disease is extremely high, yet we have extremely poor vaccine for this population. And then there is discussion about whether we should routinely immunize them against A or B meningococcus and so on. Again it varies.

The quality of life of bone marrow transplant patients now is such that about 80 percent of them who survive the first five years end up being very active students and working people; therefore, they will be at risk for disease that normal healthy people would be,

such as hepatitis B transmitted disease, for example; pertussis. There's a lot of unknown about epidemiology and what the degree of risk.

And the last thing which really makes the difficulty in the recommendation, obviously, is that the data is extremely poor, and this cartoon probably illustrates it best: "As you can see, my dear Dr. Watson, it does appear it makes some clinical difference."

When most of the papers may have a handful of five, ten patients, or maybe even with pneumococcal vaccine. one may consider -- some studies 40 patients, here 40 patients -- how do you make recommendations for such a complex issue, complex patient population, with such a limited amount of data?

So what are the present needs? Well, truly there's real chaos out there, as pointed out by the paper that Clare quoted, and there is a need to establish some kind of primary guideline. We don't even dare call them recommendations. I think they are probably guidelines, if anything.

I think there are issues, when I talk to Donna and other people in the group and their disagreement with

CDC staff, for example, there are areas that consensus can be reached, or an alternative schedule can be given within reason without creating too much chaos.

We need to work with bone marrow transplant providers to collect more data to validify or change the guideline in the future. We need to collect more data about vaccine-preventable disease, the incidence of that before/after immunization. The big debate is the incidence of hemophilus disease, for example, post-marrow transplant patients. Is it real? Is it not as high as we thought 20 years ago?

And then the outcome of intervention. Is the vaccine safe? Adverse side effects? We really need a lot more serological data to see how they will respond with those recommendations, and then hopefully, by having to be able collect more data, we would be able to revise those guidelines within two to four years, and so on.

So I guess the option for the ACIP is as summarized here. We could provide an advisory role, meaning provide input into the bone marrow guideline immunization working group, but let the provider, the bone marrow transplant provider group who have already

done the work, take the lead in developing guidelines.

The advantage for that is most of the work somewhat is done, at least on the graph. We may or may not agree on some of the specific recommendations, but the bulk of the graph is done. And then it is likely to be more acceptable to bone marrow transplant providers and their patients if the recommendation comes from their own experts.

The disadvantage for that is the bone marrow providers may have a narrower focus and may not necessarily be expert in immunization matters. Some others' academicians may be very knowledgeable about pneumococcal vaccine, but don't write anything about hepatitis B prevention, for example. So we need to fill in the gap there.

And the second approach is creation of an ACIP working group to develop guidelines with input from the bone marrow transplant group as well as the other expert group -- AAP Committee on Infectious Disease, American College of Physicians, Infectious Disease Society of America, et cetera -- with the goal of an ACIP document issued in the future.

The advantage of that is the CDC experience in making that kind of draft. The disadvantage is the process may take much longer. There is a tremendous amount of investment in CDC's staff and time and resources to be put into that.

And then if the bone marrow providers strongly disagree with some recommendations, the usefulness of the ACIP document may be undermined. Actually the American Academy of Pediatrics and the Red Book has already two pages on this issue, and so there are some guidelines, whether we could just join them in.

The last one, obviously, is to go for option one at this point in time, meaning let the bone marrow transplant people go ahead to develop a guideline, and then aim for an option two in the future would be a compromise. No matter what we do, I think the ACIP and the academicians out there should really try to get more data in, and I think this quotation probably says it the best.

My feeling is that we can make all kinds of statements, as we make, but if we don't study this population or if we don't study what the outcome of those guidelines are -- you say, okay, well, we go

ahead, immunize against pneumococcal diseases -- we don't connect data, we don't see how those patients respond, the outcome of disease, two or three years down the line we are not any better now than we are. So we really need to collect more data to be able to make better recommendations.

So I'll put the last transparency back in and see whether we are at any stage at all to make any kind of recommendation.

DR. DAVIS: Thank you very much. That was a very nice summary of the issues, Clare and Chinh Le. I think that was great, thank you.

I see Gina Rabinovich has her hand up, so why don't we start with you.

DR. RABINOVICH: I wondered if in your review of the data for bone marrow transplant patients the ACIP prospective may be that there would be similar issues with other transplant groups like renal transplant, et cetera, so that the ACIP issues related to immunization of transplant patients are broader than just bone marrow transplant?

DR. LE: Well, actually, there is an *MMWR* publication in 1993 which basically had that table.

But again, if you were to look at evidence-based recommendation, there is a lot of holes, a lot of fog and mist in all of those. And I think probably some of the recommendations are not written at all for bone marrow transplant. Plus, I think the degree of immunosuppression, the type of patient, the real diversity of that group really calls for more separate --

DR. RABINOVICH: For each of the transplant groups?

DR. LE: For the bone marrow transplant group compared to just the organ, a solid organ. Yeah, I think it's different. And even within the bone marrow transplant, as you know there are various different subgroups like the autologous group usually don't do as well -- I'm sorry -- do better than the allogeneic groups in terms of preserving immune function.

DR. DYKEWICZ: I just wanted to say that I think it's a little different, and I think it's a little like comparing apples and oranges.

I think that if you come up with a recommendation for immunization of BMT patients, it's not going to necessarily be something that is -- that you can

extrapolate to solid organ transplant patients. You're not totally ablating somebody's cellular and humoral immunity with an organ transplantation. What you're trying to do is keep rejection under control and minimize graft-versus-host disease.

It's different with a BMT patient because you are totally getting rid of their memory cells. And you have to start from ground zero, basically, and it's like dealing with an infant and a small child, that the immune system has to mature again.

DR. RABINOVICH: Okay, that's helpful. Thank you.

DR. DAVIS: Thank you.

John Modlin.

DR. MODLIN: Clare just made exactly the same point that I was going to make, that bone marrow transplants are different. She's obviously done her homework very nicely, and both she and Chinh Le have presented, I think, the relevant issues, that bone marrow transplant patients are different and they do require special attention.

However, it is important to point out that the ACIP has also, over many years, as well as the Red Book Committee, has generated recommendations for other

groups of immunocompromised individuals of all different types. I think it's critically important that the ACIP be actively involved in this issue because I think the perspective that members of this Committee have and liaisons have is as broad and as deep as any group.

If you know bone marrow transplanters as well as I do, you know that you're going to have a very difficult time achieving much consensus in that group, more so than you are with a group of immunization experts, perhaps. And I think they would readily acknowledge that their experience with vaccine issues is limited. I think it's very important that this group be involved to the degree that it possibly can.

DR. DAVIS: Thanks, John.

I think Dave had his hand up, and then Sam Katz, and I believe Paul did, and then Georges Peter. We'll let you all have a little input here, and then close up.

DR. FLEMING: I just had a question about the current process that's underway by the bone marrow transplant folks that developed this draft. Have we talked with them at all? Are they willing to not

abandon that effort, but stop that effort if ACIP will take this on? Or are they going to go ahead with guidelines independent of what we do?

DR. LE: I think Clare may answer that better than I can, because I'm late in it.

But basically the bone marrow transplant people have developed a preliminary guideline and table, and CDC people and others have looked at that and found that there's a lot of big issues that we disagree with. And I guess it came even to a point that it was a little bit difficult to work with between some of those experts.

And for some reason I was brought in because, well, maybe we need an ACIP arbitrator, which obviously I'm not because I'm bringing it to the whole Committee, obviously. But I think that's why I kind of very gently politically put those things up here.

The areas of conflict are very difficult to resolve, because the bone marrow transplant people say who are you to tell us how to immunize our own patients, because we did the study on those vaccines and we know exactly what those things are. Or if you read somebody else's paper a different method of assay

of antibody response may be entirely different. So the scientific data is the big source of conflict right to begin with.

And the second thing is there may -- I think the problem, if -- I do agree with you, John, that the ACIP probably needs to get very heavily involved -- but if we get involved to a point we make a recommendation or a table and the bone marrow transplant providers say, come on, I'm not going to follow this, who is going to suffer?

I think the patients and the private docs out there who look up to the bone marrow transplants docs as their expert, they're going to dump the ACIP document and they're going to follow their own expert. They're going to take the -- call up, get on the phone and say, look, I have a child, what should I do? They're not going to call you and me. They're going to call the bone marrow transplant center.

So I think it is very important that we work with them to get our difference clear, rather than trying to jab something down their throat.

DR. DAVIS: Thank you.

Sam was next. I wanted to recognize --

DR. CHEN: I wanted to just answer a question on that, if I can.

Since I was a part of the working group, I think there is a window of opportunity where they are -- I think they're in agreement that ideally there should be just one set of recommendations out there. I think they're willing to hear us out, though I think they feel there is a need to get this out in a timely manner.

DR. DAVIS: Thank you.

DR. KATZ: My name is Samuel Katz.

I was glad that Clare remembered Al Donnenberg. We had him here in 1992, and he was then at Hopkins before he moved to Pittsburgh.

And we suggested they do what they have never done -- and I think Chinh Le has pointed out the absolute absence of any data -- and we encouraged them at that time to do what they've done with protocols for treatment of cancer, for treatment of leukemia, for treatment of all the diseases for which they do bone marrow transplant, and that is no one center can acquire the data to provide what you need, which is how do you come up with recommendations.

And what they need is a collaborative group where they'll get together and they can have the numbers of patients and do the studies, but they've never done them. And I think the absence of data, as Chinh Le says, it's the patients who suffer, not the investigators. But the egos and the turf battles of the investigators have been such that I don't think they've ever gotten together and done a collaborative study. And that's the only way you're going to acquire the data on which to base reliable recommendations.

So I think you have to work with them, but I think you still have to try to push them to do some studies so that you can make recommendations that have some background.

DR. DAVIS: Thank you, Sam.

Paul Glezen.

DR. GLEZEN: Sam just said what I was thinking. We just argued for hours about lack of data on an issue that I thought we had a fair amount of data. But there is absolutely nothing here, so what are you going to base the recommendations on?

DR. DAVIS: A little poke in the side there.

[Laughter]

DR. PETER: Well, I would just mention the experience with a similar situation of the opportunistic infections in HIV-infected patients in which a schedule was developed for immunization of children, which had differences from the universal schedule that we now accept. And for their next edition, thanks to Neal's efforts, we've been able on behalf of the Academy to work very closely to develop a schedule on which both that group and we agree.

And I think the concern that Neal expressed so well was that with these different groups of patients you may end up with a different schedule for each particular group of patients, the HIV-infected patient, the bone marrow transplant; and I think we need to be the arbitrator and to work with these people.

Secondly is, I wouldn't put too much stock in the Red Book recommendations on the immunization of bone marrow transplants, because it was developed basically about five years ago when I sampled five different bone marrow transplant experts whose names were given to me -- they weren't selected necessarily as persons by consensus -- and came up with recommendations that aren't terribly different from some of the

recommendations that now exist.

And it's been clear to me ever since that this process that's now taking place has to take place. We need more data. I think we very much need to be involved.

DR. DAVIS: Thank you.

Neal, and then at the mike.

DR. HALSEY: I think I know some of these people who are involved, and the egos are very big and it's very difficult to get them to agree and collaborate. But there must be a couple of people who at least understand the principle that you've put forth, that you do need to have some consensus. And I would encourage you to work independently with them to try to get the foot in the door.

I do think they want an arbitrator. When you deal with people like them, and strong, independent units which are competing with each other, in a sense, in a number of ways, they would really welcome somebody who is not necessarily one of their group to take the lead and say we must have a consensus.

I think that you could find a couple of those people, and then just pick somebody who is outside

their group. And I think the AAP would be happy to provide a person to work with you, or somebody else from the ACIP, and go to them on an individual basis, one at a time.

But I think that's the role that ACIP can play as an arbitrator. And it's been done very effectively in other settings, with Group B strep, when were in major conflicts over the appropriate strategy. It'll take some political skills and tact, and you might talk to some of the others who have done it.

DR. DAVIS: Thank you, Neal.

DR. McHUGH: Yvonne McHugh, Chiron Vaccines.

This is with regard to your plans for recommendations for meningococcal vaccines. I think that meningococcal A polysaccharide would probably work in this population, but it might be critical for the men-C [phonetic] conjugate in this population, given their immune status. And I wonder if anybody's doing studies on that? That could be a very important part of your recommendation.

DR. DAVIS: Thank you.

Well, I think we've heard a variety of input. Clearly there is a need for a lot data to be collected,

a lot of sifting and winnowing in order to develop consensus among a fairly disparate group.

And I wanted to get a sense of the Committee. Do you want to vote on what our involvement should be, or should we just discuss it for --

Chinh Le, you've had the chance to work with them more directly. How are you leaning in terms of those three options?

DR. LE: Well, I think basically if we could agree on a very simple, basic guideline schedule, even with knowing there's not a lot of data there, but some general reasonable recommendation that's agreed with everybody; and then the following two years collect as much data as possible about -- let's say we give MMR, what is the seroconversion rate? What is the titer decay and so on? And then come back with a recommendation, I think that would be great.

And the main thing, if the ACIP wants to get involved, is how much staff commitment it is going to take to do that.

DR. DAVIS: Right. I'm not sure, because it ends up being support staff, and it ends up being program staff at CDC. And I'm not sure how much of those

resources we should commit. It certainly sounds like an important issue, and we need to have AAP involvement probably equally on that.

Clare?

DR. DYKEWICZ: Also, I was told by Pierce that ACP was interested in having us on this issue.

DR. DAVIS: Great. That'll be great.

DR. DYKEWICZ: I took your name in vain, Pierce. I'm sorry.

DR. DAVIS: Very good.

I think what we can do is probably develop an approach which would involve representatives from each of these organizations to try to --

Bill, let me have your input first. You were about to say something.

DR. SCHAFFNER: Bill Schaffner.

I think if we as a Committee, as an extended Committee, wished to be a player in adult immunizations, we're going to have to get used to the notion of working it specialty by specialty by specialty. And how the CDC organizes its support is the CDC's business, but it's clear that this Committee needs more support.

So I think in a sense the difficulties are clearly laid out, but I think this Committee needs to be a player here.

DR. DAVIS: Based on what I've heard from other Committee members, that seems to be the case. We just need to define our role. I don't know that at this hour we should be doing that any further than we already have.

I think the general feeling is that there should be a role which would involve some minimal efforts at first to develop some reasonable standards, and then clearly a multi-centered mechanism to collect information and analyze the data that's available to create useful information, and build on that. It just seems to be a step-wise process that needs to take place.

And the people involved with bone marrow don't have all the answers. Those of us involved more with immunization obviously don't have all the answers, and we all need to work together.

DR. LE: So you mean that basically the option two of creation of an ACIP working group is in order?

DR. DAVIS: I think it involves a group of people

with ACIP representation on it in order to gain consensus that people will agree on in order to build for the future. I don't know that ACIP should commandeer this. I don't know that that's the best approach. But I do feel as though, from what we've heard, that some ACIP involvement is important.

John.

DR. MODLIN: It sounds like time is of the essence with this issue, as it is with many.

But perhaps the thing to do is to just organize a small and efficient working group that is empowered to get together and to make some fairly quick and major decisions that are run by the chair and run by the program staff, and carry the ball in terms of getting fairly far along with this before our next meeting; and actually going ahead and organizing liaison people, put liaisons with the other groups.

Again, I sort of make that proposal in the spirit of trying to finish up things for the evening, but I think that would be the opportune way to go.

DR. DAVIS: Do we agree as a Committee?

Stan, did you have something you wanted to say?

DR. PLOTKIN: Well, yeah. I would say that sounds

to me like an inefficient way to do it, considering that a lot of the work apparently has already been done.

I would suggest co-oping the process. Why don't you add somebody, a representative of the ACIP, to the working groups that already exist, and tantalize them, if you will, with the prospect of participating in a major ACIP recommendation -- that is, have their work product be adopted by the ACIP through a liaison that is a member of the ACIP serving on those working groups? That way everybody gets something out of it.

If you try to take over the process by creating your own working group, as Chinh Le said, they're going to react negatively because they been doing the work.

DR. DAVIS: What I was saying was pretty much along those lines, that we shouldn't commandeer the process. But it seems as though we should be involved. And obviously an ACIP statement, or something to that effect, would be a valid product. So I think we have a motion.

John.

DR. MODLIN: Stan, that was exactly the intent, to try to get a small group of people here that can make

those contacts, those liaisons quickly, and establish those connections and do exactly that, and do it fairly quickly.

DR. DAVIS: That's a good plan. I'll take volunteers. You don't have to decide right now.

So it's late, and I appreciate those of you, your willingness to stay. And dinner was ten minutes ago. I'm sorry about that.

Thank you. We'll see you all tomorrow at 8:30.

[Whereupon, the meeting was adjourned at approximately 7:02 p.m.]

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C E R T I F I C A T E

G E O R G I A)

DEKALB COUNTY)

I, Kim S. Newsom, being a Certified Court Reporter in and for the State of Georgia, do hereby certify that the foregoing, consisting of pages 1 through 383, inclusive, was reduced to typewriting by me personally or under my supervision and is a true, complete, and correct transcript of the aforesaid proceedings reported by me.

WITNESS MY HAND AND OFFICIAL SEAL, this 20th day of July, 1997.

_____

Kim S. Newsom, CCR-CVR
CCR No. B-1642

[SEAL]

THE CENTERS FOR DISEASE CONTROL AND PREVENTION

convenes the

PUBLIC MEETING OF THE

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

VOLUME II

The verbatim transcript of the Public Meeting of the Advisory Committee on Immunization Practices (ACIP) convened at 8:30 a.m. on Thursday, June 26, 1997, at the Centers for Disease Control and Prevention, 1600 Clifton Road, N.E., Atlanta, Georgia.

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C O N T E N T S

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Legend of the transcript:

[sic]	Exactly as said
[phonetic]	Exact spelling unknown
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P R O C E E D I N G S

8:45 a.m.

DR. DAVIS: Sorry for the late start. I had a few things to talk about with folks.

I wanted to get things underway this morning, and we'll have a discussion of rabies postexposure prophylaxis and rabies immunoglobulin administration. And the issue that will be confronting us is should all RIG be infiltrated at the bite site, considering recent changes in the World Health Organization's recommendations, and Chuck Rupprecht is here to discuss this with us.

DR. SNIDER: Could I just for one quick moment -- Chuck, I apologize -- introduce Dr. Walter Faggett, who is here today as a liaison member from the National Medical Association. Welcome.

DR. DAVIS: Chuck.

DR. RUPPRECHT: Currently rabies postexposure prophylaxis in the United States consists of, besides local wound treatment, the prompt infiltration of rabies immunoglobulin into the bite site, and the first administration of five potent vaccine doses over the course of a month's time.

The current ACIP recommendations state that if anatomically feasible, up to one-half of the dose of rabies immunoglobulin should be thoroughly infiltrated into the area around the wound, and the rest should be administered intramuscularly, and preferably, it's stated, into the gluteal region.

Unfortunately, there was some very disturbing news reported in the *Clinical Infectious Disease Journal* last year by Dr. Wilde and his colleagues throughout Southeast Asia on the failure of postexposure prophylaxis using World Health Organization standards -- that is, of local wound treatment, passive infiltration of rabies immunoglobulin, and prompt administration of cell culture vaccines.

And it was because of a result of that particular paper and report, and disturbing news of other potential postexposure failures from throughout Asia, that led to a WHO Collaborating Centre meeting on new possibilities or reevaluation of rabies postexposure prophylaxis, particularly in regards to the infiltration issue for some of the more serious bites that could be involved in rabies in zootic countries.

Specifically, one of the changes that was proposed

on the use of rabies immune globulins differs somewhat from ACIP recommendations in that besides the infiltration issue of up to half of the dose and then the rest administered into the gluteals, rather the wording suggests that the RIG should be infiltrated into and around the wounds, and that any remaining RIG should be injected at a site distant from that of vaccine inoculation.

So in essence, it's tending to conform with some of the disturbing observations made by Wilde and his colleagues, that really the purpose of rabies immune globulin and passive immunization is to neutralize virus peripherally, preferably before it's entered peripheral nervous system, and hence infiltration and local wound treatment tends to be critical.

In essence what we're faced with, then, in terms of some of the parameters of rabies immune globulin usage in postexposure prophylaxis, is the issue of infiltration. Should it be kept at the same recommendation as present -- that is, half of the infiltration, half of the dose infiltrated around the wounds; or should all of the dose be infiltrated around the wounds; or rather something along the lines as much

as necessary, as much as possible, so that all the wounds will be infiltrated?

Beyond the issue of local infiltration of wounds, also the site of the remainder of the infiltration if in fact it's decided not to infiltrate all of the dose into the wound -- that is, should it be into the gluteals, considering the relative distribution of adipose tissue, particularly in rather obese patients that may require PEP?

And also the issue in cases of severe exposure and multiple lacerations, the dilution issue over rabies immune globulin -- one-fold, two-fold, et cetera -- to ensure that all wounds are being infiltrated necessarily.

Some of the advocate positions of just keeping the recommendations as they are now really have to do with the basic epizootiology of rabies. If one considers that dog rabies is the overriding cause of human mortality globally, versus in the United States and most developed countries dog rabies has been controlled, then obviously there are major differences in dog rabies in zootic countries from the United States.

Similarly, one has to take into consideration the differing epidemiology of postexposure prophylaxis in a developing country versus developed countries such as the United States, where not only is the number of patients that are seen on a daily basis fairly high versus the estimated 40,000 seen in the United States, but also there tend to be specialized treatment centers versus the United States. Oftentimes, most physicians will never be involved in human PEP investigations.

And lastly, the availability of biologics in the protocols used for WHO recommendations. For example, the use of intradermal postexposure prophylaxis, as recommended by WHO in developing countries versus the United States and many developed countries, only intramuscular vaccine is utilized. And similarly, the kinds of biologics that are licensed in this country versus heterologous biologics, equine anti-rabies serum, or other vaccines that are not licensed in the United States that also may be some confounding influences on some of the results reported by Wilde and their colleagues.

In essence, what we're faced with in trying to reevaluate, redefine, and update the ACIP for rabies

prevention in the United States to come out with a new draft next year, pending the licensure of some new biologics, has been the consideration of should we go ahead and keep current ACIP recommendations as they are regarding this local wound infiltration? Or rather should we go ahead and consider it to be more consistent with the WHO, at least to update with this new information to reinvigorate the idea of thorough infiltration of wounds with rabies immune globulin?

We're a little leery to start getting into too much the dilution issues, primarily because at least in our experience we've never even received a single call yet about multiple lacerations. Severe exposures due to dog rabies, or at least wildlife exposures in the U.S., are certainly nowhere near the incidence that they are in developing countries.

And hence, that may be one of the reasons the rarity of such exposures, as to why we've never received any queries from state health departments or physicians over this issue -- that is, having too many wounds and an inadequate volume of RIG based upon current dosage, 20 IU per kilo, to thoroughly infiltrate all wounds.

Because of all the variations in PEP that we see despite the relatively simplistic applications as they exist now, we're therefore a little bit cautious about changing too much to be in line with WHO because of the variations that might result thereof, and considering that since the current ACIP recommendations went into existence and were followed through the late 1970s, early 1980s with human rabies immune globulin and cell culture rabies vaccine, that with 40,000-plus a year we haven't seen a single postexposure failure in the United States.

So we think the there are some fairly strong grounds to suggest perhaps not changing, but at the same time implementing and emphasizing the need for thorough infiltration, particularly in severe bite cases involving rabies exposure, given some of the new observations that are coming out of developing countries such as Thailand.

Thank you.

DR. DAVIS: Thanks Chuck.

Questions? Stan Plotkin is back there. If you could just come to the mike, Stan, that would be great.

DR. PLOTKIN: May I show two transparencies?

DR. DAVIS: Of course. Yeah, it's up here.

One question I would also raise while Stan's walking up to the mike would be the issue of can more HRIG be used? In other words, when you have multiple severe wounds and you don't have enough to infiltrate all the wounds, is another option just to use more HRIG in those patients?

DR. RUPPRECHT: That generally has not been recommended because of the possibility of suppression of active immunization. Hence, Wilde and WHO's recommendation that when wounds need to be infiltrated, only the known suggested dose of RIG be used, but rather it be diluted so that the volume entailed can be used to thoroughly infiltrate all wounds, but the total dose not be increased.

DR. DAVIS: Okay. Thank you.

Stan.

DR. PLOTKIN: I just wanted to show two graphs from an unpublished paper on human rabies immune globulin. It happens to be a study comparing the current globulin with a heat-treated product, which gives added viral safety -- safety against viral contaminates, I should say.

But the importance of this in relation to the discussion is a new demonstration -- this was known before -- but a new demonstration that the actual serum levels of immune globulin after the injection of the usual dose are not very high, suggesting again that it's not the peripheral administration that's important.

The graph shows HRIG, or heat-treated globulin -- the upper line is the heat-treated material -- and the levels of rabies antibody. As you probably know, 0.5 units is considered to be presumptively protective. At no point were the geometric means in these patients anywhere near 0.5, and actually only one patient -- one volunteer at one time had such a level.

So that these levels during the period when vaccine is not yet producing an active response would not in themselves be high enough, theoretically at any rate, to prevent rabies. This is the graph of volunteers who received the vaccine. The point is still the same, the active response kicks in about seven days. But before that the levels are not very high.

Just to add that, in my own opinion, I agree with

Chuck that we should keep the recommendations as they are, but emphasize local infiltration. I also actually am fond of Wilde's idea to dilute if you don't have enough volume. But I would point out that in Wilde's paper I think in every case there was some failure in addition to the question of local infiltration, whether it was surgery or the timing, et cetera. So maybe we have explanations for his failures.

DR. DAVIS: Thanks, Stan.

Other questions?

Yes, Neal, Neal Halsey.

DR. HALSEY: Just a clarification on the volume issue.

It still makes sense to me to give larger volume of the passive antibody if that really is what's important to be protective. And based on the levels that Stan showed, I would doubt that a larger volume would seriously interfere with an active response to the vaccine. And I think that might be worth just some simple testing to determine if that's possible in some animals.

DR. RUPPRECHT: Yeah, the data Dr. Plotkin demonstrated, as he mentioned, had been known for a

while, especially in experimental animal models. And in essence, there are no protective titers in rabies, things that we discussed before. And that the total serum virus neutralizing antibody response that one measures in such studies is really irrelevant to what's going on locally.

It doesn't matter what your -- when you go ahead and take a mil serum sample over total body volume as versus what the active infiltration of antibody is at that particular site, it's totally irrelevant. Whether it's not 0.5 or less than that, we still can demonstrate passive protection even when antibody alone is used in animal models.

The issue that Wilde points out and you've discussed about having enough volume of product to thoroughly infiltrate all wounds is a sound one. Again I would just be cautious, given the kinds of information that we get from phone duty, of what some physicians are doing with RIG inappropriately now, as if they may start diluting it too much -- i.e., if they go beyond the calculations for known dose, and if they misinterpret what one means by dilution of the same known dose to have adequate volume for infiltration, I

start getting very nervous.

DR. DAVIS: Thanks.

Other questions?

[No responses]

DR. DAVIS: Well, we're at a point where we need to make a decision regarding what to do.

How comfortable is the Committee with the issue of, first of all, of recommending that more local infiltration occur -- in other words, to maximize the amount of HRIG that can be infiltrated locally, recognizing that in some situations there may not be sufficient to infiltrate multiple severe wounds, and also recognizing that even with small wounds that not all of the HRIG could be or may necessarily be administered in the wound, and some of it would also have to be administered at a distal site?

DR. RUPPRECHT: If I may make one mention, in that it is difficult, as Wilde points out, to find any scientific substantiation for the issue of why only up to half should be used to infiltrate and the remainder then be put in the gluteals. There actually isn't any scientific substantiation for the current recommendations.

DR. DAVIS: I certainly as an individual feel comfortable with attempting to maximize the amount of the antibody in the region of the bite. Certainly, empirically, that seems to be very sound, and I certainly would feel comfortable with that.

And it may very well be that a gluteal site may not be the best peripheral site for the remaining HRIG, that there's probably other muscle mass that probably would be a better site for administration of the remaining HRIG.

How do the rest of you all feel about that? Is there any discomfort in making that change from what we currently have, where we recommend half at the bite site or at the wound site, and the other half in the gluteal?

John.

DR. MODLIN: I certainly don't have any problem with what I think is a relatively minor change here.

However, I'd point out that the fact that we've not had any failures with 40,000 or more postexposure prophylaxes is exceedingly compelling data that whatever we're doing is close to right. I find that very surprising, because I doubt that there aren't a

high proportion of those instances in which it's not being given correctly, and which perhaps may be even very little HRIG is being infiltrated in many instances.

Chuck's shaking his head. I suspect that's the case.

On the other hand, this may actually be an opportunity to emphasize what probably is just as important, if not more so, and that's just a very thorough cleansing with regular wound care. That may very well be even more important in terms of local wound management; I don't know. But emphasizing local wound care, this may be an opportunity to reemphasize that. And so if that's the case, then I think we should go along with what I think is a relatively minor change.

DR. DAVIS: Yes, Chinh.

DR. LE: Are these five cases the only ones reported of failures? Because when you really look at those five cases, only two of them received the U.S. standard recommendations.

Case one and two, the first one was not infiltrated. The second one, the amount of volume was

inadequate, undiluted volume was inadequate. Cases three and four were the only ones which seemed to follow our recommendation. Case five, the vaccine was given intradermally, so probably not our standard.

So I would agree that despite those unfortunate two cases, the overwhelming data is we've been doing the right thing.

DR. DAVIS: Another option might be to say at least half should be infiltrated in the wound, and if a practitioner would choose to infiltrate more than half in the wound and the remainder at a distal site, that would also be a possibility.

DR. FLEMING: Or a priority should be given to ensuring adequate infiltration of the wound site, and to the extent that there's any left over after you've done that -- I'm just trying to figure out from a provider's standpoint -- I think we need to be clear what it is that we're trying to get them to accomplish, which is that if they feel comfortable that they've been able to adequately infiltrate all areas of the wound, then that probably needs to be the message here as opposed to an arbitrary amount, if you will.

DR. SNIDER: Chuck, do we have any data that show

us what the levels are in the blood if you do half and half versus 100 percent?

DR. RUPPRECHT: Yeah, that's the dilemma in that, as Dr. Plotkin demonstrated, regardless if you do it all or spread it around and then take your peripheral sample, the levels are the same in terms of systematic serum volume. And yet you can show very nicely in animal experiments that you will get differences in mortality, depending upon whether or not you infiltrate your product or deposit it at a peripheral site.

So your proportion of surviving animals will vary along the lines of what we see in the field with humans, but in terms of just measuring passively antibodies, there's no difference in systemic volume.

DR. SNIDER: I just wanted to make that point clear, because it seems to me that that's -- in terms of some science base for making the change, it appears you could make the argument that with what you're trying to give, and usually in the gluteal muscle you can do just as well with local infiltration. Plus, you're doing other things with local infiltration that biologically are plausible to have greater impact.

DR. RUPPRECHT: I think we would agree that we

don't really see anything wrong with if all of the RIG is given infiltrated in the wounds. Again, I find no scientific substantiation for why 50 percent is, and then the rest is given someplace else.

DR. DAVIS: Would there be a minimum amount that you would want to see, like at least 50 percent of the RIG?

DR. RUPPRECHT: I guess I'm more in favor of the "as much as necessary" so that we have thorough infiltration of all wounds.

DR. DAVIS: Okay. I get a sense from the Committee that that would be appropriate. We could take a vote.

All in favor of the language trying to infiltrate as much as possible in the wound?

[Show of hands]

DR. DAVIS: There are six of us here, and six of us in favor. So if you can just craft the words and just bring them back to us, I think that would be fine.

DR. RUPPRECHT: Do you also favor a change from the gluteal site as opposed to -- do you want to specify, or just -- because we're asked all the time about what about gluteals. Physicians read the

literature, they bring up the Wilde study, they say are the gluteals the best site for if there is any additional.

DR. DAVIS: How does the group feel? I would probably favor a site other than gluteal, based on what I've heard.

DR. MODLIN: I don't know that this is the case. Stan or others who know more about rabies immune prophylaxis than I do that might comment.

But I would suspect that the gluteal site may have come about by the fact that we typically give immune globulin preparations of all sorts into the gluteal site simply because volume has often been an issue in the past, whereas in this case here, it may not be. So there may not be any true clinical justification for favoring the gluteal site over any other site.

DR. DAVIS: Yes, Rick Zimmerman.

DR. ZIMMERMAN: I'm not speaking against any changes, but suggest that if there is going to then be a difference between the manufacturers' insert and ACIP recommendations, we'll need more than just a one-sentence change. We'll need to explain the rationale for having a potential discrepancy between

manufacturers' recommendations and ACIP recommendations.

DR. RUPPRECHT: Or in essence, wouldn't the manufacturers change their recommendations over time, unless they could substantiate why the half and half as exists now objectively?

DR. ZIMMERMAN: I can't answer that.

DR. DAVIS: Any problems with that, Carolyn?

DR. HARDEGREE: As always, any time a manufacturer brings us a proposed change we consider that.

DR. DAVIS: Okay, there you go.

Okay, so if you can craft the words and bring them back to the Committee, and then we can approve it. But that's the intent. Actually, we'd circulate it among the Committee. Just as soon as you've done it we'll have Gloria receive it, and then we'll get it out to the full Committee for their comments.

Thank you very much.

Next is the comparison of the safety of combined information: Adult preparation diphtheria and tetanus toxoids versus single antigen tetanus toxoid in adults. There is information and discussion, and there may be a decision as well.

Drs. Haber and Lloyd are here to discuss this. Thank you.

DR. LLOYD: Actually, the information I'm presenting this morning is only for information. There will be no vote taken today.

Today I will present a comparison of adverse event reporting after combined adult preparation tetanus and diphtheria toxoids, which I will call Td, versus single antigen tetanus toxoid, which I will call TT during the remainder of the presentation.

In the Vaccine Adverse Event Reporting System, or VAERS, between 1991 and 1995, the recent resurgence of diphtheria in the newly independent states plus the recent reports in the *MMWR* of the possible circulation of endemic toxigenic diphtheria in the U.S. highlight the need to maintain population immunity against diphtheria.

The ACIP has had a longstanding recommendation to administer Td instead of TT for primary vaccination of adults or as booster doses every ten years. Previous ACIP discussions have addressed the question of what, if anything, should be done to further discourage the use of TT.

Residual issues remain, including a relative lack of knowledge about the level of immunity to diphtheria in U.S. adults today, whether the recommendations for revaccination every ten years needs to be reconsidered, and the relative safety of Td versus TT. Today we will only be focusing on the last item.

Information from three clinical trials and from post-marketing surveillance will be presented today. Again, this is information only, and no vote will be taken.

Despite the longstanding recommendation of the ACIP to administer Td, some vaccine providers continue to use TT. Between 1991 and 1995, approximately 18 percent of all tetanus-containing vaccine indicated for use in adults was sold as TT. This is sold exclusively within the private sector. There appears to be a slight downward trend since 1991, where 24 percent of the tetanus-containing vaccine was sold as TT, until 1995, where 16 percent was.

The experiences of 1991 to 1995 represent a significant change since 1974, where Biologics Surveillance data showed that 69 percent of all tetanus-containing vaccine for adults was being sold as

TT.

We know that with excellent immunization coverage of children that most of our nation's children are protected against diphtheria. But what is the situation for U.S. adults? Studies that looked for diphtheria antitoxin levels in diverse adult populations found that anywhere from 23 percent to 98 percent of U.S. adults were protected.

It may be that the percent of the adult population protected against diphtheria has truly increased over time, from 1979 to 1996, although the populations studied are too diverse to be compared with one another. For a definitive answer to this question of U.S. adult susceptibility to diphtheria, NHANES III sera are currently being tested for diphtheria antitoxin levels, and results may be available by the end of this year.

We have a more definitive answer on tetanus protection based on the NHANES III serosurvey of tetanus antitoxin levels. Overall, 70 percent of people in the U.S. who are six years of age and older carry protective levels of tetanus antitoxin.

This varies by age, sex and race. While 88

percent of persons aged 6 to 11 years of age were protected, only 28 percent of persons over 70 years of age were. Men were more likely to be protected than women, 70 percent versus 62 percent. Finally, Mexican-Americans were less likely to be protected against tetanus than either non-Hispanic whites or non-Hispanic blacks, 58 percent versus 73 percent and 68 percent, respectively.

The diphtheria antitoxin levels are likely to be 5 to 20 percent lower than these rates, which can probably be attributed to use of TT instead of Td. It has been suggested that some vaccine providers continue to use TT because they believe that it is safer than Td to use.

What do we know about the comparative safety of these two vaccines? Three studies conducted in the 1980s compared the reactogenicity of Td versus TT. Participants in these studies were randomly selected to receive either vaccine.

Deacon's study in 1982 found no difference in the occurrence of local or systemic reactions after the two vaccines, although the study population was quite small.

Macko and Powell conducted a larger study in 1985 where 193 participants were enrolled. Local reactions were more commonly noted in Td recipients than in TT recipients, and there was no difference in the reporting of systemic symptoms.

The third and largest study was conducted by Zurrer and Steffen in 1986 where 1,426 participants were enrolled. There were significant differences in the occurrence of redness and swelling and in the occurrence of any reaction, with lower rates after TT versus Td.

The differences between Td and TT were not statistically significant for the other events. The findings from these trials suggest that local reactions are more common in Td recipients than in TT recipients. Systemic or serious events, however, could not be evaluated with these relatively small populations.

Each of the three studies concluded that even though there were more local adverse reactions after Td than after TT, the events themselves were self-limiting. Hence, the benefit of diphtheria protection would outweigh concerns about these local reactions.

To better assess the relative safety of Td and TT in a larger population, and to try to look at more serious events, we reviewed post-marketing surveillance data for both vaccines from VAERS.

We conducted a search of the VAERS database for all reports listing Td or TT as at least one of the vaccines administered. We included only reports that listed a date of vaccination between January 1st, 1991, and December 31st, 1995, and listed the vaccinee's age as seven years of age or older. Td is not indicated for use in children under seven, and TT is rarely used in this population.

Because public funds are not used to purchase TT, only reports from the private sector were evaluated. We first conducted a search for all reports, and then for only those reports meeting criteria as being serious. The patient died or experienced a life-threatening illness, the event resulted in the patient being hospitalized, or a preexisting hospital say was prolonged, or the event resulted in a permanent disability.

From 1991 to 1995, approximately 53 million net doses of Td and 15 million net doses of TT were

distributed to private vaccine purchasers. These figures are based on net doses of vaccine distributed from the CDC Biologics Surveillance System.

There were 1,924 VAERS reports that listed Td, or 36 reports per million net doses of vaccine distributed. There were 339 reports that listed TT, or 23 reports per million net doses. This translates to a relative risk for the reporting of any adverse event after Td when compared to TT of 1.6, with a 95 percent confidence interval of 1.4 to 1.8.

One hundred thirteen of the reports that listed Td described a serious event, which comes out to a reporting rate of 2.1 reports per million net doses. Twenty-three of the reports that listed TT described a serious event, which comes out to a reporting rate of 1.5 per million net doses. This translates to a relative risk for the reporting of any serious adverse event after Td when compared to TT of 1.4, with a 95 percent confidence interval that includes one, and ranges from 0.9 to 2.2.

This chart shows the reporting rates after Td and TT for the five events most commonly reported after these vaccines. There was a statistically significant

difference in the reporting rates for injection site reactions, redness, pain, and fever, with lower rates after TT, as shown in yellow. There was not a statistically significant difference in reporting rates for pruritus.

The five events most commonly described on serious reports were the same five events most commonly reported overall, although the rate for such events was less than two per million doses. Comparisons of serious reports found statistically significant differences for reporting rates of injection site reactions, redness and pain, but not for fever or pruritus.

On this chart we present the reporting rates for the next five most commonly reported events on serious reports. Based on the differences we found for reporting of injection site reactions and pain, it was not surprising to find statistically significant differences in the reporting rates for cellulitis and myalgia, with lower rates after TT, again shown in yellow. However, we also noted lower reporting rates after TT for syncope.

There was not a statistically significant

difference in reporting rates of rash or nausea. There were very few serious reports after either vaccine, with reporting rates for most individual events of fewer than two per million doses.

We do not have age-specific denominator data for how the vaccine doses are distributed, but we found a difference in the age distribution of patients reporting to VAERS. The distribution of Td reports by age group is skewed to the left, while there is a more normal distribution of TT reports by age group. This might suggest that the distribution of Td may also be skewed toward younger patients, but without age-specific denominator data we cannot be certain.

The distribution of serious reports by age group is similar to that for all reports, with the skewing towards the left for the Td, and the more normal distribution for TT. We found that 9 of the 14 serious reports of syncope were from persons between 7 and 29 years of age. When all reports of syncope in VAERS were examined by Dr. Braun and others at the FDA, they found that 77 percent of these reports described patients younger than 20 years of age.

So if younger people are both more likely to

receive Td, which may be the case based on the reporting, and to experience syncope regardless of which vaccine they receive, which appears to be the case based on the study from the FDA, this may explain some of the difference in the reporting rates for syncope. Without age-specific denominator data, again we cannot confirm these suspicions.

The Vaccine Safety Datalink could not be used to make this particular comparison because, much to their credit, the Vaccine Safety Datalink study sites follow the ACIP recommendations and only use Td.

Our conclusions are:

One, adverse event reporting rates, particularly for serious events, are low after Td and TT, suggesting that both are safe and well tolerated.

Two, for local reactions, recording rates were higher after Td than after TT, which concurs with the results of the clinical trials. Based on the rates from the clinical trials, the reporting efficiency of local reactions to VAERS for TD and TT is well below one percent.

Earlier evaluations of VAERS found that reporting efficiency to VAERS was high for serious events, such

as vaccine-associated paralytic poliomyelitis, where the reporting efficiency was calculated to be near 70 percent, and much lower for less serious events such as rash after MMR, where the reporting efficiency was less than one percent. The low reporting efficiency for local reactions after Td and TT may suggest that such reactions do not trouble the vaccinee enough to persuade them to report to VAERS.

Three, while there was a higher rate of reporting serious adverse events after Td than after TT, this difference was not statistically significant overall. We were especially concerned, though, about the significant difference in the reporting of syncope, and based on our review suspect that confounding may explain at least part of the difference that we discovered.

In summary, Td appears to be slightly more reactogenic than TT. This is not surprising as two versus one antigens are being administered. We hope that these safety data should assist the ACIP in weighing the risks and benefits of recommending the use of Td versus TT.

And I'll answer any questions.

DR. DAVIS: Thank you very much.

Are there questions?

Bill Schaffner.

DR. SCHAFFNER: Jenifer, this is just a lovely study. Thank you very much.

And I guess my -- I have a series of little things here, but the first might be a request. I'd love perhaps for the Committee to have your text and the figures as a handout sometime, so we could put it our files.

DR. LLOYD: We'll get those.

DR. SCHAFFNER: Do you have any idea about whether the administration of either of these antigens is confounded a whole lot by the indications for the use of the antigen? You can't sort out whether the antigen was given as a consequence of a traumatic exposure versus routine immunization.

DR. LLOYD: No. No, we can't do that.

Based on the younger distribution of patients, I would guess that some of the Td is being used for more routine use versus the TT. And we have some indication, based on the requests from emergency room physicians to be able to access single antigen tetanus

toxoid, that it might be used in emergency rooms more than Td. I really don't know.

DR. SCHAFFNER: Yeah, that's our guess, too. We were just wondering whether you had data.

A couple of other things very quickly. I was curious, and I'd love for you to comment, your serious reactions that led to hospitalizations or were designated as serious, when you put the actual reactions up on the figure, don't look all that serious. Perhaps syncope, but even that usually doesn't get you into the hospital in this day and age. Can you comment on that?

And that's one of the reasons I was wondering about the use of one antigen versus another in the setting of trauma. Perhaps it's really the trauma that gets you admitted.

DR. LLOYD: Some of the reports when we looked at them, even the cellulitis reports, these people, the arms swelled up and they maybe stayed in the hospital overnight for observation, someone was concerned about an infection.

The really serious reports tended to be events that were not listed on those. There were some just

you-name-it type, a couple of folks with nephrotic syndrome, that sort of thing, which I -- those were very rare.

DR. SCHAFFNER: Thank you.

DR. DAVIS: Thank you.

Pierce Gardner.

DR. GARDNER: One of the newer adverse reactions that is now being compensated by the National Vaccine Injury Program and has been recognized by the Institute of Medicine is the issue of brachial neuritis. And I wondered whether that showed up in your study at all, and the incidence of that is an issue. Do you have any comment?

DR. LLOYD: The way that VAERS is coded, to pick out brachial neuritis reports you actually have to review the reports by hand. We looked at reports of brachial neuritis. Most of them, the people aren't hospitalized or sent to an emergency room, and there are far fewer of those reports than there are for those first five events. That's why they didn't really come out on either report.

We have some information on brachial neuritis. I can get that information to you, but I don't have it

with me.

DR. DAVIS: Geoff, did you have something you wanted to say about that?

DR. EVANS: A couple of things.

One percent of our claims are TT or Td, and off the top of my head I know that we haven't received any, quote/unquote, fresh brachial neuritis cases. But we certainly have mononeuropathy and non-GBS, as well as GBS kinds of conditions that have been filed with the program.

And I believe we also a case of syncope that was actually post-tetanus-containing vaccine, where an adolescent got into a car and drove afterwards and got into an accident from a syncopal event. So those kinds of things are making their way into the program.

DR. DAVIS: Thank you.

Steve Schoenbaum.

DR. DAVIS: It sounds like a voice from the sky here.

[Laughter]

UNIDENTIFIED: Just about brachial neuritis -- this is Miles [inaudible] from FDA -- we've done a review of the cases of brachial neuritis that were

reported to VAERS after tetanus-toxoid-containing vaccines, and we're in the process of preparing that for publication. We have reviewed those cases in VAERS.

DR. DAVIS: Thank you, Miles.

Steve Schoenbaum.

DR. SCHOENBAUM: I thought Pierce was going to raise a different question, so since he hasn't I will.

DR. DAVIS: Yeah, he thought you were going to raise it.

DR. SCHOENBAUM: He has often asked this group in one form or another how often these vaccines ought to be given, which really relates to the total burden of adverse effects. And I don't know where we are in the schedule for reviewing. This looks like a perfect set up for a policy analysis, trying to figure out how often one would give it, and all of the various benefits and risks.

DR. GRIFFIN: I would second that.

I think we need a review, given that there are -- how many cases have reported? Even though we're saying that these serious events are rare, tetanus is very rare as well, and I think we have to worry about

whether we're over-immunizing our population.

The ACIP reviewed this several years ago, and I think their recommendation is that we don't necessarily have to give decennial boosters, and that every ten years is probably too much for the adult population who have been adequately immunized.

DR. DAVIS: Any thoughts on that?

Yeah, Bill and Pierce, in that order -- I'm sorry, Bill's pointing to someone there. Oh, Neal, I'm sorry. Neal.

DR. HALSEY: I don't know that we're over-immunizing against diphtheria, based upon the studies that have been done so far, and we'll wait for the NHANES survey. But about five years ago there were a couple of manufacturers that were interested in developing improved tetanus and diphtheria toxoids using new technology.

The current tetanus and diphtheria toxoids are relatively impure preparations. I don't want to quote a percentage of the protein antigen that's in them, but it's nowhere near as high as I would have anticipated. It's less than -- well, it's less than 90 percent, I'm certain of that. And so there are a number of other

things that we don't know what causes some of these significant local reactions, especially.

But I think what you have presented is a good argument to go to the manufacturers to say, look, we know you have the technology to produce improved vaccines, more purified vaccines; and I think we should give them that charge to do so.

DR. DAVIS: Pierce Gardner.

DR. GARDNER: I thank Steve and agree. Let me just make the point in a slightly different way.

Serologies are used, serologic antibody levels or antitoxin levels are used as predictors of who might be susceptible to disease. And these studies are somewhat helpful, but we have something that's far better.

We have 50 years of epidemiology that shows us that the far more powerful predictor of who gets disease and who doesn't get disease is who has received a full primary series. Once you've done that, no matter what your antibody levels seem to show, the correlation of who gets disease and who doesn't get disease is who has completed a primary series.

The NHANES blood studies are, I guess, helpful, but the fact that they show half of the adults being

susceptible doesn't really correlate nearly as well as who gets ill as compared to the much more precise predictor of the history of who has received a primary series. I'm eager to move epidemiology ahead of serology as the consideration here.

DR. DAVIS: Rick Zimmerman.

DR. ZIMMERMAN: I would agree with Pierce's comments, and I would also note that the U.S. Preventive Services Task Force has a different recommendation than ACIP, and that AAFP has chosen to follow ACP. It would be nice to see, instead of what currently are three different national recommendations, it would be nice to see a little more uniformity. And so I would encourage the community to readdress this issue.

DR. DAVIS: I think we can come to bring this discussion to a close at this point.

Based on the existing information and the fact that it would be timely at this point to review the recommendation with regard to what is the appropriate interval, or what is the appropriate issue in terms of what we should be encouraging, and certainly primary series administration is what is critical, that we

reconsider the language in our current statement for that purpose.

DR. SNIDER: There's also the diphtheria piece of this. And you alluded to that, you said probably very diplomatically, toward the end of the year. I wonder if toward the end of the year means in time for the October meeting or the February meeting?

DR. LLOYD: I don't know. Is there anyone in the audience that might have an idea?

UNIDENTIFIED: What was the question?

DR. LLOYD: When the diphtheria antitoxin levels might be ready?

DR. WHARTON: Melinda Wharton, National Immunization Program.

The NHANES III testing will be complete, I believe, sometime in the spring of '98, and it'll take a while to get the dataset cleaned up and analyses done. So in terms of having those results available, it'll probably be a year.

DR. DAVIS: Well, certainly that's an important element in all of this in terms of decision-making, so those data should be available before any decision is made. Otherwise it would be a two-step process, and I

think it would be a little bit more seamless if it could be done as a one-step process. But it should be done.

So if the program can begin working on this, and then when all of the data from the diphtheria testing of NHANES sera is available and the Committee has all the information it needs to adjust the statement, that would be the appropriate time, I think, to move with it.

DR. SNIDER: I think we also could look at if there is any other information we have that bears on the topic, and also re-look at the timetable that NCHS has proposed for this and see if there's any possibility --

DR. DAVIS: Okay. So it should be done as soon as possible, given the availability of information. We recognize that that won't be for -- certainly it won't be before the next meeting, and it probably won't be before the October meeting.

DR. GARDNER: We could start doing the cost benefit analyses and some of the other things that are part of the process now, that certainly don't need to wait for the serological --

DR. SNIDER: And I think Steve's suggestion about a policy analysis, at least laying out what the questions are that we think are terribly important, no reason we can't start doing that either.

DR. DAVIS: Right. Okay.

With that, thank you very much.

Next is the discussion of the recommendations on the use of RotaShield, which is rotavirus vaccine, as part of the routine childhood immunization schedule. And you have received a draft of a statement that has been in process. Roger Glass has taken a lead in this and has shepherded this through to this point, and he'll lead the discussion.

Roger.

DR. GLASS: Thank you, Jeff. Delighted to be here again to speak with you.

We have rotavirus working group now for ACIP, chaired by John Modlin, and we've decided at this presentation to review the data upon which -- and really the disease burden and cost effectiveness data -- upon which the last recommendations were based; as well as at the end, the last 15 minutes will be Peggy Rennels discussing a rare adverse reaction that's been

identified and its significance; and then in November to concentrate on the recommendations and the nitty gritty and all the specifics.

The issue before us is to consider today the data upon which the recommendations will be based. The cartoon, the gentleman on the right standing over the dead body says, Okay, stranger, what's the circumference of the earth, who wrote the Iliad and the Odyssey, what's the average rainfall? And the other guy is saying, Bart, you fool, you can't shoot first and ask questions later. And so I want to ask the questions now before we shoot, and try to give you a little more solid basis.

The first recommendation that you have in your handout is for a universal immunization. This recommendation is based upon previous estimates that I presented last time, that every child is infected with rotavirus in their first few years of life; and based on previous estimates we would estimate almost every child is infected, 3.9 million birth cohorts, and this is 75 or 80 percent of the total children.

About 1 in 70 had an outpatient visit; 1 in 72 -- and I want you to remember that number -- seek

hospitalizations, and the cost of medical cost about $400 million; indirect and direct over a billion, with about 20 deaths per year. And that's our starting point.

I have the same anxiety about these numbers as many others have, because we've used a single method to develop these. And I wanted to review the methods and then present to you some new data that's been developed since January by medical officers and collaborators to try to expand and provide a broader base of these estimates.

These estimates have been based primarily on hospital discharge surveys. We've done at CDC three distinct surveys -- two are published, one is not -- using NCHS data. This is about a half of one percent representative sample. It's about 1,000 discharges a year that we're looking at to estimate the total for the nation, and it excludes Federal hospitals and Indian Health Service hospitals, so it's an underestimate of a small fraction of those hospitalizations.

We've used ICD codes for diarrhea of any sort. And remember that until 1993 there was no specific code

for rotavirus. We've used a code priority that rotavirus or diarrhea could be in the top three positions, and we've found in previous studies that about 70 percent of the diarrhea codes are in the first position, and by the third position we have about 90 percent coverage.

Now you can choose your poison. If you think that diarrhea is only important in the first position as the cause of discharge, our estimates are overestimating by about 20 percent. If you feel that rotavirus could be a cause of nosocomial diarrhea, that any position would prolong disease, then we're underestimating by about 10 percent. So I would say the top three positions are something to consider.

And finally, the estimates of rotavirus have been made by two different methods. One is a direct standardization where we've taken the total number of hospitalizations in the country for childhood diarrhea and multiplied those on a monthly basis by the rates of detection at D.C. Children's Hospital, the study by Carl Brandt, which is the largest in this country. That data is about 15 years old, but it's a very sizeable sample.

Our other method was a purely epidemiologic method of using a residual -- that is, to say the excess winter hospitalizations for diarrhea over summer hospitalizations, and I'll show you what I mean.

Of course, you recognize this curve which I presented last time, and I want to just point out two features of this curve that are interesting. One is that we demonstrated that there's been about a 13 percent decline in diarrhea hospitalizations over this period, and when we continue this now to '95 it's about an 18 percent decline over about a 15-year period.

Second, while we have nice peaks of hospitalization in children from six months to two years of age, we have poor definition of peaks in the older children and the younger children, something which may well be due to small sample size, because our total sample is about 1,000 events a year. So when we cut it this many ways, we have poor definition.

Well, the residual method that we've used is to take -- this is the monthly hospitalizations for diarrhea by the age of the child, and then we've done attack rates by month. The dark blue curve on the bottom are hospitalizations in the summer, about

10,000, 11,000 per month here. The green curve up at the top are hospitalizations in January and February.

And what we're saying is that the difference between -- the area between the top curve and the bottom curve is our proxy of rotavirus. So it's a very nonspecific, indefinite event. But because of the seasonality and the age distribution, we worked with this quite a bit and we think that this is a reasonable estimate.

The other estimate is using the Brandt data, in which about 33 percent of children hospitalized in Washington had rotavirus as their cause of diarrhea. When you look at those rates compared to other rates in developed countries -- Japan, the U.K., Sweden -- the rates that we're using are lower, and in fact as we get rid of other causes of diarrhea in this country over time, it may well be that the fraction which are attributable to rotavirus will go up. So we have, if anything, a low estimate on that side.

When we compare these two estimates, if you take the black curve as total hospitalizations each year for diarrhea, the first estimate by Brandt, in red -- you can see the red curve underneath -- estimates about

55,000 hospitalizations a year, with a synchrony which is right on mark with total hospitalizations.

Our residual estimate here, in blue, and the color is almost superimposed on that. The correlation coefficient is about 95 percent, so that we have a correlation both in time and in numbers between our two estimates which gives us some confidence that it's reasonable, although we still don't have definitive rotavirus confirmed cases. So those are the bases of the estimates that were in Jin's paper.

Well, when we look at our three estimates, the first was by Ho, with hospital discharge data to 1984, a famous date. The second was a study by Jin which was published last year, and the third is one that Umish Parashar, who should be up here today speaking, has just developed to bring the data up to 1995.

In the middle we have Jean Smith's cost effectiveness paper, which is an extrapolation, and I want to explain what Jean did so it doesn't seem so bizarre.

The first estimate we had for hospitalizations for diarrhea, about 210,000, of which about a third, 67,000, were for rotavirus. This equates -- and we use

a figure of accumulative incidence, what's a child's risk of getting rotavirus by the age of five -- for diarrhea, about 7 1/2 percent of children will get hospitalized for diarrhea by the age of five, of which about one third of those, 2 1/2 percent, 1 in 40 children would be hospitalized for rotavirus. The birth cohort in 1980 was 2.7 million.

When Jean tried to do her cost effectiveness in 1991, she updated the population to 1991 when the birth cohort had raised by 53 percent. She used the same incidence figures, and that led to an increase in the number of hospitalizations, which was published in the cost effectiveness.

When Jin repeated the National Hospital Discharge Survey, his data was 55,000. At the same time, the birth cohort had risen from 2.7 to 4.1 million, so the actual incidence of diarrhea hospitalizations had been cut by nearly half, and rotavirus hospitalizations by nearly half. So that's the reason for this high number in the middle of the others.

Umish has just completed another analysis since 1993. Here again diarrhea hospitalizations have come down slightly. Our estimate of rotavirus has come down

slightly again, and the estimate of incidence is about 1.2. This comes out to be about 1 in 72 children are hospitalized for rotavirus in their first five years of life, and this is about 1 in 80, to give you an idea. So our estimates are coming down slowly.

Well, for outpatient visits we have much less robust data to deal with. For outpatient visits we've used the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey. This gives outpatient visits to hospitals, whereas this gives outpatient visits to doctors' offices.

So this rate right here, 53 percent of children by the age of five, will visit a doctor's office for diarrhea, of which about 10 percent of those would be for rotavirus. For ER visits we have similar data. About 1 in 5 children will visit an ER for diarrhea, of which about 1 in 25 will visit for rotavirus.

In terms of looking for comparisons, we've taken the two vaccine trial placebo groups, which have all their inherent problems. But what's interesting is that in both the two multicenter trials in this country looking at doctor visits, for two years in the Bernstein trial or one year in the Rennels trial, the

rates of visits to doctors for rotavirus in the first five years of life -- and this is really only two years or one year -- are on the order of 10 percent; 1 in 10 children seek medical care. So are estimates are somewhere in the right ballpark, and this is one of the lesser important features in the cost effectiveness, as you'll see.

Well, where do we go from here? Is the sampling that we have from hospital discharge representative? There are no codes for rotavirus. Are the codes too nonspecific? Does the priority position -- where does diarrhea fit on a discharge summary -- important, or should we change it, and which way? How could our estimation methods be refined? What other agents might be influencing winter diarrhea? Have you heard any good anecdotal evidence lately?

We wanted to go on and expand our database, and I'm going to present this morning the first three of these new surveys, and Joe Bresee will present the new cost effectiveness survey.

The three surveys, first by Umish, is National Hospital Discharge data. But since 1993 there's been a specific code for rotavirus, the first time we've had a

specific code, and it allows us to compare our estimates from the past.

The second, we've gone to two states, Connecticut and New York, where they have a 100 percent sample of all hospital discharges. The database for New York, for instance, in one year is ten times the database for the nation, and it gives us much more robust estimates, particularly of the older age groups.

And finally, we've gone to the HMO, the Vaccine Safety Datalink project of Bob Chen and his consortium of four HMOs on the West Coast, Kaiser Permanente, analyzed by Umish Parashar in our group. This is data from a 2 percent birth cohort in an HMO which has the lowest hospitalization rates nationally.

And finally cost effectiveness in the study done by Joe Bresee, Bob Holman, Matt Clarke, and myself.

Well, in the first study of hospital discharge surveys, since 1993 rotavirus, which you can't see at all here, has just begun to be coded since 1993. And to our surprise, in 1993 13 percent of the discharges for diarrhea were for rotavirus, overall at 17 percent. Trust me, it's here.

And the impact is that when we look at hospital

discharges, which have gone 163- to 160,000 over the past three years, there have been changes in diagnostic codes. Viral, which before was about a quarter, has gone up to 32 or 33 percent, an increase of 7 percent, at the expense of the etiology unspecified and the bacterial etiology. So we now have about 32 percent of these diarrheal diagnoses that are viral, of which half of them, 16 1/2 percent in the average, are for rotavirus.

This is very important. When you introduce a new code and the first year you have 13 percent of the diagnosis properly coded, and by the third year 20 percent of diarrheal discharges are coded, it's very interesting. It means that if we're going to monitor the impact of an intervention program, a vaccine program, we have a potentially specific diagnosis upon which to base those analyses.

Now, I don't want to say this blasély, because we have to go back and see which of these are actually confirmed by antigen detection, which would be the senaequinone [phonetic]. But at least we have people looking at that code, and now we're in a position to introduce diagnostics or encourage diagnostics in a way

that they haven't been encouraged before.

Well, from this data and analysis of the rotavirus-specific codes, we see something interesting. Before, and last year, I would have told you that 90 percent of the disease occurs in the first two years of life. Now that we have a specific curve, two things are evident.

One is that less than 40 percent of the coded diarrhea, rotavirus diarrhea, occurs in the first year of life. By the second year we're up to about 75 percent. So there's significant disease occurring after the second year of life.

Also, we have a small fraction here that occurs before three months of age, a time when we don't expect rotavirus because of whatever reasons, perhaps a maternal antibody, and it gives us a target for future investigations for issues such as prematurity, rotavirus in premature children.

Well, from that national study we went to Connecticut and New York. Here's the data from Connecticut, done by Mark Chung at Yale and Robin Ryder [phonetic] and Dr. Hadler, the state epidemiologist. What you see in the hospitalizations looks just like

the nation. They've used quarters instead of months because that's the way they gave us the data for a ten-year period. Same peaks, slow downward trend over time.

You can see again that the older-aged children -- and this is diarrhea of all causes, the older-aged children are more highly represented than children under one, another feature which we saw with the rotavirus-specific codes.

So rotavirus is not only a disease of the first year, but probably the second and third as well. And if we don't get the children completely vaccinated by one year of age, we still have a window of 60 percent of these diseases which we can prevent.

If you're finicky about the position and the priority of diagnosis, this study shows us what that means. The bottom curve is rotavirus as the first diagnosis, or diarrhea as the first diagnosis. The second curve is diarrhea as the second diagnosis, and the top curve is diarrhea as any diagnosis. So that once you get to the second diagnosis, you're almost mimicking the total picture. And we don't know how to distinguish or what might be the second diagnosis of

this individual, but these may be interchangeable.

Well, when we look at the data from Connecticut, there's some other things that are interesting. First we get a cumulative incidence of diarrhea, about 1 in 40 children, 1 in 111 would have rotavirus. Our national figure is 1 in 72 or 1 in 80, so we're in the same ballpark, a little bit less.

We have a duration of hospitalization of about 3.1 days, and we have a cost per case of rotavirus here from the rotavirus-specific code of about $3,500, which will figure in the next presentation by Joe Bresee in the cost effectiveness.

We've gone to New York, which is a megastate, 8 percent of the total deliveries, births in the country or so. And this is in collaboration with Helen Cicirello, Perry Smith, and Wa Dun Chung [phonetic]. What you can see again is the same peaks. The rates, the numbers of hospitalizations, has not gone down in New York State as it did in Connecticut. We see here rotavirus diagnosis introduced in 1993 in a small number that we can work with and analyze.

What do we see? Again we see that that winter peak of diarrhea in New York State, which occurs here

in March, February/March, later than the rest of the nation, occurs in all age groups. So with a more robust dataset we can actually see rotavirus occurring in an older age group of children.

So that's what we get from New York, we have a lot more robust calculations estimates. And from New York the hospitalization rates from diarrhea are about 1 in 25, and for rotavirus about 1 in 75, so that's comparable to our national data.

I want to move on, then, to the Vaccine Safety Datalink project that's been handled and organized by Bob Chen, and this analysis by Umish Parashar, and the collaborators are Kaiser Permanente in Northern California, Southern California, the Northwest, and Group Health.

This is a group that examines the total number of complications in a 2 percent birth cohort of children who come to the hospital for any cause. Diarrhea is the most common cause of coming to a physician or being hospitalized in that group.

And you can see that in the first -- in two years of data about 2,500 hospitalizations have occurred in this group of children. This is a rate of about 1 in

60 children being hospitalized for diarrhea, so it's about half of the national data. Of these, 29 percent are coming in for viral causes, or what's coded as viral causes.

Also from this dataset, this cohort population, we have new data on emergency room visits, and in some centers clinic visits for the entire population, so we can begin to make better estimates for a cohort.

And this data as displayed here, as we've done elsewhere, was very interesting to us and to the people at Kaiser, because what it showed was -- and I'll take a look at the Kaiser Southern California, since I think it's probably most visible from the back of the room -- these are just hospitalizations in the Kaiser system, about 600 a year in Southern California.

And you can see when those hospitalizations occur. They occur in December, and there's a big peak, and about 80 percent of the hospitalizations for diarrhea in the whole year are occurring in that peak. So we have no diagnostics, and Kaiser specifically discourages physicians from making a diagnosis of rotavirus because it doesn't change treatment.

But I would expect that greater than 50 percent of

that peak, or 80 percent of that peak could be rotavirus, which means that for the year in this study in this center about 60 percent of those hospitalizations will be rotavirus, twice the national average from the old data. You can see that that peak is mimicked in the data from emergency room visits, for which we have no good national data. And again, that peak is very significant.

Is this rotavirus? Can we tell that this is rotavirus from this curve? Well, one way we have a clue that it is, is to look at the seasonality. If you'll remember that the seasonality in California occurs in November/December, right around here; in the Northwest it occurs a couple months later. You can see that this peak right here is offset to the right, to February and March in the Northwest Territories. That peak is also mimicked in the emergency room visits in all centers.

Well, how can we confirm that this is really rotavirus? The only way we can confirm this is to introduce a diagnostic test, and one of the proposals we've had from two of these centers is to introduce rotavirus testing into those 1,200 kids a year

hospitalized for diarrhea to try to find the fraction which is really rotavirus.

Using that same data with confirmed cases we could also get good cost estimates for this, which would be the most severe test of the cost effectiveness of a vaccine in a center which hospitalizes less than the nation.

Well, this is a summary, then, to draw things together, a summary of the estimates we have to date. The first summary's estimates were done by the Institute of Medicine, about 23 hospitalizations a year, and by David Matson about 110,000, for rates which range from 0.6, 1 in 166 children, to one hospitalization for rotavirus in 36 children, a big range.

When we started our studies with Ho, we had a rate of about 1 in 67,000, about 1 in 59 kids hospitalized for rotavirus. When we've updated this with Jin's study, we have a rate of about 55,000 hospitalizations, 1 in 71 children, and with the latest data from 1995 about 1 in 77 children, about 48,000 hospitalizations. So this shows there is a slow and steady decline in hospitalizations, and a much larger decline in rates as

the population of children has increased.

From our state studies, in New York this rate is about 1 in 77, just like the nation, for one of the largest states in the country. For Connecticut about 1 in 111 children, and for the HMO data, the VSD, about 1 in 142.

Well, are these rates high or are they low? I have three international comparisons: One by Mike Ryan in the U.K. of 1 in 42; he looks just like the United States 10 years ago or 15 years ago. From Tema [phonetic] Vesikari's study, the vaccine trials in Finland, about 1 in 50 children are hospitalized for rotavirus. And from the recently completed study of Irene Perez-Schael in 1996, about 1 in 33 children in Venezuela are hospitalized for rotavirus.

So the rates are going to be somewhere between -- in the U.S. now -- are going to be somewhere in the rage of one percent, greater if we include all hospitals, probably less if we concentrate on HMOs.

Well, what we don't have -- this is not quite the stool sample we had in mind -- what we don't have are rotavirus confirmed cases. All of this is based on conjectures, past studies.

There have only been two real sentinel hospital studies in the country, and our hope is to try to get sentinel hospital studies going in groups like the Kaiser group on the West Coast where we have a full catchment of children, and we can get both hospitalization rates as well as rates for the entire cohort for the variety of illnesses, hospitalizations, ER visits, and outpatient visits.

Well, that's the end of my presentation. I want to turn it over to Joe Bresee -- this says level with us, doctor; can I afford what I got? -- and Joe's going to talk about whether we can afford what we have based on new data from Andy Tucker, who is not here today, and Anne Haddix, who I think is in the back of the audience and who is our economist, and who can answer all the sophisticated economic questions.

Joe.

DR. BRESEE: I won't have nearly as sexy slides as Roger does. All mine are black and white, and they're overheads.

Well, a couple of years ago, I think Jean Smith, Roger's EIS officer at the time -- actually four years ago now -- Roger and Anne Haddix in EPO realized that

the projected cost effectiveness of new vaccines would be really important to ACIP recommendations. And so at the time, in 1993, they performed a cost effectiveness of the rotavirus vaccine program in the U.S.

What they found was that using a $20 base vaccine dose cost and a 50 percent vaccine efficacy against all disease, and a 75 percent against severe disease, that a rotavirus vaccine program in the United States would prevent about a million cases of rotavirus diarrhea, about 58,000 hospitalizations, and 82 deaths each year in the United States, using the data that Roger just talked about. And this would save the country about $79 million dollars in direct medical costs, and about half a billion dollars in indirect costs.

The problem is, since these estimates about -- all the estimates used in these analyses have changed. Not only the burden of disease estimates that Roger just talked about, but vaccine coverage has increased, two new vaccine trials have been completed, and all the costs have changed. And so in light of all the changes we repeated the study using Jean's model with some updated estimates, and I'll present some of that data here today, some of the preliminary data.

The objective of the study was to estimate the projected total cost savings and cost effectiveness of a program for universal rotavirus vaccination for U.S. children, compared to no vaccine program. And what we did, the way we did it was we assumed the children would receive three doses of RotaShield, the Wyeth product submitted for licensure, it would be given to all U.S. children at two, four, and six months along with routine childhood immunizations.

We looked at it from two perspectives, the health care system, using only direct medical costs, and the perspective of society using, in addition, indirect costs and non-medical costs.

We assumed that one complete U.S. birth cohort, annual birth cohort would be vaccinated. In this case, the projected 1997 birth cohort is 3.9 million kids. And they would be followed up for health events and costs in their first five years of life when they would incur all the rotavirus costs, and for indirect costs for a lifetime.

And so the next four slides, I'll run through the base estimates we used, some of which Roger has already presented, but we'll be brief. You don't have to

memorize it. We can supply you with this.

Basically, Roger reviewed the estimates of burden of disease already. We assumed that about 75 percent of U.S. kids would get a case of rotavirus diarrhea in their first five years of life, based on prospective studies in the U.S. and Canada.

We split up the more severe outcomes into four levels: Clinic visits, ER visits, hospitalizations, and deaths. And estimated all these from national databases -- the MD visits and ER visits from the National Ambulatory Hospital Surveys; hospitalizations from the National Hospital Discharge Surveys; and deaths from a published study looking at national death certificate data.

For vaccine coverage we used unpublished NIP data. The current data for vaccine coverage is six months of age, which show that about 90 percent of kids have received at least one of their first three vaccines by six months of age, and about 61 percent of kids had received all three vaccines.

There have been four large vaccine trials in developed countries that we used for vaccine efficacy estimates. Bernstein, Rennels, and the Santosham study

were all performed in the U.S., and Vesikari in Finland. And basically all the studies reported vaccine efficacy against all rotavirus diarrhea that ranged between about 48 percent and 68 percent.

Two of the studies presented data on vaccine efficacy against clinic visits and two against hospitalizations, with relatively few hospitalizations. But all reported vaccine efficacy for a range of severity of disease based on the clinical scoring systems in one of the couple of clinical scoring systems used.

So what we did, using these numbers our base estimates generally reflect our intention to include the estimates that reflect the data but use a low-end estimate, assuming the vaccine effectiveness would be lower than the vaccine efficacy in phase three trials; but also to use a range of estimates -- higher estimates for more severe disease, hospitalizations and deaths; and lower estimates for mild disease; with intermediate ranges for the outpatient visits.

Efficacy among children that received less than three doses was assumed to be 50 percent of the efficacy for children who received all three doses.

The final set-up slide represents all the costs. And I don't want you to memorize all the costs, just to know that we split cost into two categories -- direct medical costs, which were used in the cost effectiveness model from the health perspective, health system perspective; and non-medical cost, which was using the societal perspective.

The direct medical cost include all the costs for treatment of a child with rotavirus diarrhea in any setting. And again, as Roger said, our estimates for the cost of hospitalization for a child for rotavirus agrees with an independent source, the Connecticut hospital data.

We also included in the direct medical cost the cost of the vaccine program, which we estimated to include a $10 charge for vaccine administration for each dose based on OPV use; and two estimates actually, one for a vaccine cost of $10 a dose and another one, which I'll show later, for a vaccine cost of $20 a dose.

The indirect costs include both non-medical cost, like taking a child to the doctor, for transportation and child care, as well as indirect costs like lifetime

productivity loss to a child who has died of rotavirus disease.

And so to wrap this first part up, comparing to Jean's study, this is a summary of our estimates. As Roger said, the birth cohort is slightly smaller than what Jean estimates, from 4.1 to 3.9 million.

But the biggest change has been in hospitalizations. Jean estimated the 140,000 hospitalizations; we estimate 50,000. So it's cut in half, and that's reflected in the medical costs associated with rotavirus diarrhea, which is also cut in half, from $564 to $274 million dollars a year.

The vaccine efficacy that Jean used, she used two levels of vaccine efficacy. We used four levels, and including a broader range that I think better reflect the current vaccine trials.

UNIDENTIFIED: Why did the non-medical go up?

DR. BRESEE: The non-medical went up because of inflation mostly. They've just been inflated from 1991 dollars to 1996 dollars, actually.

The vaccine coverage estimates have increased since Jean's estimate, and besides Jean's estimate of $20 per dose of vaccine we also included a model with

$10 per dose. Those are the main differences.

And these are the results, the first part of the results. And as you would expect, if you give a lot of rotavirus vaccine out the disease will go down. And what we found is that we prevent about a million cases of diarrhea, just like Jean did, about a 40 percent reduction. Outpatient visits would be reduced by a little over half. And hospitalizations, we would prevent about 32,000 hospitalizations, or 64 percent, consistent with increasing vaccine efficacy against the more severe outcomes.

This is a more complicated slide, and we'll take a little more time with it. This is structured the same way the cost table was two slides ago, and that is the direct medical costs on top, the indirect medical costs on the bottom, and the subtotals here in the brackets.

Now what I want you to see is that these are the costs for each of these categories, with no vaccine program, with the addition of a vaccine program, and the difference. And what you see is that without a vaccine program currently we spend about $270 million dollars on rotavirus disease each year, mostly accounted for by hospital costs, which account for

about 66 percent of the cost.

With a vaccine program you would reduce these medical costs by about $166 million dollars, but you would add about $180 million in vaccine program costs using a $10 vaccine, for a net difference, net cost, of 8 million dollars to the health care system, which is about a 3 percent increase. If we decrease the vaccine cost, a per dose cost of $9, we would break even. So the vaccine break-even cost is $9 from the health system perspective.

But if you look down here at the indirect cost, you'll see this huge cost savings, mostly from loss of caregiver earnings, which go from $772 million to $373 million dollars per year, so a 50 percent reduction in that.

And the indirect costs, the non-medical and indirect costs, drive the cost effectiveness model. So from the societal point of view, a $10 vaccine would save society about $440 million dollars, or about 30 percent of our total cost. And the break even point for a vaccine from a societal standpoint is about $56. So any vaccine that costs less than $56 a dose would save money.

We did some sensitivity analyses on the model using the health system perspective just to see what we found, and the model was sensitive to hospitalization costs, the vaccine efficacy rates, and the vaccine cost; and was relatively insensitive to our poorest estimates, which are the outpatient visits, luckily.

And what you see here is a graph where on the X axis represents the vaccine twice, the Y axis represents the cost effectiveness ratio, which is the number of dollars saved per case prevented. And this line here, zero, is the break-even point, where a health system incurs no cost but saves no dollars with a program.

And the middle line here, the dashed line, represents our estimate of hospitalizations of $50,000. And you see that if we estimate $50,000, the break-even point of the vaccine is about $9 per dose. But if we underestimated the rate of hospitalization, it's actually $70,000, the curve shifted this way; and the break even-point goes up to $14. But in an HMO setting where we may have overestimated the rates of hospitalizations it would be shifted to the left, and again dramatically changing the break-even point of the

vaccine.

The same is true for vaccine efficacy. The middle line again represents our vaccine efficacy estimates, where the break-even point for the vaccine is $9. But again, if we increase our vaccine efficacy slightly we'll shift the curve to the right, and the break-even point may be about $12; and to the left, a lower vaccine efficacy.

So these two variables really do affect the cost effectiveness of the model for direct medical costs at least, not so much for indirect costs.

So to wrap it up -- and Roger may have a couple of statements, too, I don't know -- to wrap it up, what we found is that compared to Jean Smith's data again, just to give you a reference point, we found that a rotavirus vaccine program would reduce the hospitalizations by about 64 percent or 32,000 hospitalizations each year, MD visits by about 300,000, deaths by about 13, or 65 percent.

But whereas Jean Smith estimated that whether from the medical perspective or the societal perspective a huge savings for a vaccine program was either $79 or $466 million dollars, we found that using a $10 dose

rotavirus vaccine program would actually cost the medical system about $8 million dollars, almost break even, but would provide a huge savings given societal costs of about $440 million dollars.

If we use Jean's estimate of vaccine cost of $20 a dose, we would still lose money from the medical system perspective, but still make it back from the societal perspective big time. The break-even point of the vaccine again in our model is $9, with a range from our worst-case estimate of negative $4 to our best-case estimate of $30. But again, for the break even point from the societal perspective, including indirect costs and non-medical costs as well, is about $56 per dose.

And I'll leave it there. And I don't know if Dr. Rennels is going to talk now.

DR. GLASS: Thanks very much.

I want to save about 15 minutes at the end for Peggy Rennels to talk about complications, but open this part, the disease burden of cost effectiveness, up to discussion. And Jeff, you'd better warn me 15 minutes before we're scheduled to be rooted.

DR. DAVIS: Well, we have a half an hour until a scheduled break, and we're going to stay on schedule

today.

So Walt Orenstein first, and then Paul Glezen.

DR. ORENSTEIN: If I understand the model you used, the 61 percent coverage at six months of age and then no more vaccination, what would happen in reality, in my presumption, would be is it would be very similar to DPT, such that by a median age of 27 months there would be about a 95 percent coverage.

Now the fact the later it is and the less likely its impact, that's going to increase the cost; on the other hand, there will be more diarrhea that could be prevented. Can you incorporate what would actually happen into your model, and have you done that?

DR. GLASS: Well, we would love to have that data, because what we really need is coverage data at six months and one year to put this into greater perspective, and we haven't been able to get that yet refined.

The other issue with coverage is that coverage is probably much, much greater and less important for two reasons. One is that this is a disease where I just showed you 65 percent of the disease occurs after the first year of life. So if you stagger your

immunizations and a child isn't immunized till nine or ten months, it may not be so bad.

The second feature is that it's a very seasonal disease, so a child has to be immunized by December 1st, say, in your neighborhood, or January 1st. And if a child is born in January and finally gets immunized by December, he'll be completely covered so there will be no loss in coverage. Whereas, the child born in July or August who is not fully immunized on January 1st is a child at risk.

That reduces the size of the children who can be missed greatly, and so we're actively trying to get a model of what happens with a seasonal disease for immunization coverage, for seasonal disease where much of the disease is not in the first year of life but continues in second and third.

But for this model we would love to have better coverage rates at one year, or even 18 months, and any help that you could give us would be great.

DR. BRESEE: We decided that for the base model we'd use the six month estimates, figuring we'd underestimate the proportion --

DR. ORENSTEIN: That probably didn't get recorded.

UNIDENTIFIED: Can't hear, Joe.

DR. BRESEE: Oh, sorry. I was just going to add that for the first run of the base case model we decided to use the six month date, and knowing that we'd probably underestimated the proportion of kids that were protected and so bias our case against the cost effectiveness so we'd get a low end.

DR. FAGGETT: I have a question. Walt Faggett, National Medical Association.

I called Jessie Sherrod out in California -- somebody might have asked this question already; I really enjoyed your slides, too, by the way -- but the question is in terms of a representative sampling; you raised it yourself. You mentioned the fact that Kaiser discourages physicians from making a diagnosis of rotavirus. As a past HMO medical director, I'm sure they also discourage hospitalization and ER visits.

So I was asking Jessie if she had any direct involvement in the study through her school. She did not know of any. So I guess the question is what steps were taken to make sure that disadvantaged populations were adequately included in this study? And I think that's the basic question.

And I know in Washington, I would like to know if Howard University was a participant in the study with D.C. Children's Hospital.

DR. GLASS: This is from the National Center for Health Statistics and the National Hospital Discharge Survey, and it's a representative sample of hospitals around the country. And I can't give you the specifics of the survey; I'd have to get someone to address that. But it's the one that's been used for all estimations of hospital discharges by CDC. I believe it's representative, but I'd have to have someone from NCHS explain it to me because it's a very complicated sampling frame.

If anything I was heartened -- one of my concerns was then to go to Connecticut, where I was heartened to find that the estimates for diarrhea hospitalization in Connecticut, in the state of Connecticut with 8 percent of the population of births, was exactly the same as what we get from the national sample.

So I can't answer your question about representativeness or not. I know that we do have gender and race on the National Hospital Discharge Survey, and there hasn't --

DR. FAGGETT: I think it would be interesting. I know Dr. Schaffner and I, in Tennessee, have some real experiences with this in terms of a lot of kids being excluded for a lot of reasons. So I don't know if maybe we need to get some of that data if we don't have it already.

DR. DAVIS: Thank you.

Paul Glezen, and then after that Marie Griffin.

DR. GLEZEN: Roger, I have a simple question related to the hospital discharge diagnosis records. When diarrhea is the second diagnosis, how often is the first diagnosis dehydration, which would be related, and how often is it some completely -- a diagnosis related to some other organ system?

DR. GLASS: We haven't looked at this, Paul, recently. But we -- with our first review of priorities, and when we chose the third priority, we tried -- we had very few that were just diarrhea. We couldn't figure out why. Then we included this code, diarrhea presumed noninfectious, and that was a huge winner -- 70 percent or 60 percent are diarrhea, noninfectious, etiology unknown.

Joe, who has worked at a pediatric clinic, shows

us their coding form, which has -- 568 is the big check, and then all the other little boxes are small checks, so it's easy to make that diagnosis. We found 558, this unusual code, because we searched for dehydration. And dehydration was the first code in about 40 percent of those where 558 was the second code.

So we haven't looked at this extensively for other codes, but we could. We've done it for diarrheal deaths in the past, and the associated codes were dehydration, electrolyte abnormality, and cardiac arrest for the deaths. So I think it would be actually interesting to go back and look.

Also, for the rotavirus code, the diagnosis that are coded today is rotavirus. I would love to have some confirmatory study to know what percentage of those really have a swab taken or a stool sent for confirmatory diagnosis. And that's one of things we would like to do with more aggressive surveillance, or surveillance at a few sentinel sites.

DR. DAVIS: Thank you, Roger.

Marie.

DR. GRIFFIN: Roger, you showed data where the

incidence of hospitalizations in the U.S. are decreasing for diarrhea. Do you have -- can you speculate, is that for all types of diarrhea? Or is rotavirus decreasing, and why is that happening, and is it likely to continue?

DR. GLASS: It's decreasing for all causes. But if you look at the subdivisions within the causes, the viral causes are going up. So total causes are coming down. I think there's just less hospitalization for diarrhea now than there was in the past. But within the group -- and most of those are non-specific, no etiology -- of those poorly defined diarrheas, the viral diarrheas are growing. And that's been continuous over the last ten years.

DR. DAVIS: Thank you.

Rich Clover had his hand up first, and then Rob Breiman.

DR. CLOVER: I was impressed in the cost effectiveness analysis that the indirect or non-medical costs seemed to really drive the equation, yet minimal assumptions or definitions of how those costs were determined were made. Can further clarification of what assumptions were made to come up with the

non-medical costs that were used in your analysis?

DR. GLASS: Actually, I'll refer that one to Anne Haddix, who is sitting right behind you, and is our economist on this.

Anne? She's in the prevention effectiveness unit at CDC.

DR. HADDIX: Well, I think that Joe didn't go into the assumptions.

The two costs that drove the indirect costs are the cost of caregiver time to take care of a child with rotavirus, and the productivity, lifetime productivity losses due to premature death in the children who died as a result of rotavirus. We used the productivity loss as estimated by Dorothy Rice, which are published in the *Guide to Prevention Effectiveness* that's published by Oxford, that is a CDC recommendation for doing cost effectiveness analysis.

And I think what really drives this is just the sheer number of days in all children with rotavirus, including children who neither sought physician care or were hospitalized, that a huge percentage of the children with rotavirus are just home for a few days and require parental care during that time.

So the way that we calculated this was to try to estimate the number of days of parental care required to tend to a child with rotavirus, to all children with rotavirus, and then multiply it times weighted average income that we estimated for parents.

DR. DAVIS: Thank you, Ann.

Rob Breiman.

DR. BREIMAN: Roger, I was interested in your efforts to validate your estimates using the placebo, the control subjects from the vaccine efficacy studies. And it was encouraging to see that the medical visits were validated very nicely, but I wondered about the hospitalization data.

Joe went through it fairly quickly, but except for the Finnish study where hospitalization rates might be very different, indications might be different, it looked like there really weren't any hospitalizations to speak of with the other studies. What's your thinking about that in terms of being able to validate?

Given what you said, that 75 percent or so of the hospitalizations should be in the first two years, you might have expected a rate of 1 in 100, if I'm guessing

right, based on your estimates, and perhaps should have seen that.

DR. GLASS: There were very few hospitalizations in the two multicenter trials in this country, lower than the national average. Some of that -- and there's a lot of literature in the epidemiological literature saying that you shouldn't make estimates from placebo groups. So I'm very well aware that that's fraught with difficulty.

I think some of that is that these children were called by a nurse weekly during the rotavirus season, and if something happened they could either be advised, referred, or handled by phone, so that may have discouraged hospitalizations. In fact, we probably won't know about hospitalizations in this country until we do a number of studies the size of the Finnish study or the Venezuelan study, large catchment trials where hospitalization is an outcome.

If we go to the Kaiser of Southern California where we have estimates, there's a birth cohort of 40,000 children. We expect about 600 hospitalizations for diarrhea a year, so that would allow us adequate numbers. If 40 percent of those are rotavirus --

that's 250 hospitalizations for rotavirus -- we could easily see an impact on hospitalizations if that's that cause.

So one of the ideas is to introduce rotavirus testing in those 600 children hospitalized, get a good fix on how many of those are really rotavirus, and then figure out what the costing is in the most conservative setting where hospitalizations are actively discouraged.

DR. DAVIS: That certainly seems like a reasonable plan.

John Livengood had his hand up first, and then Chinh Le. And I want to cut this part of it off, because we still have another presentation, and I want to finish at a quarter of two.

DR. LIVENGOOD: A quick question.

When I looked at the list of costs, I didn't see any costs for adverse events of vaccine, which is something that I'm normally used to seeing.

Are you really sort of postulating that there will be nothing of any consequence after this? Because my understanding is that there was some mild diarrhea and fever frequently in the week after immunizations, which

might conceivably then result in medical costs or at least parents being home from work during that time.

DR. GLASS: We haven't factored that in to date, but I'm going to let Peggy address that when she speaks.

DR. DAVIS: Thank you.

Quick, Chinh Le.

DR. LE: I guess much of the emphasis has been discussing the hospitalization cost, but I can tell you in private practice in a managed care setting, the burden of disease is very much in an outpatient.

And just before left I looked at our cohort at Northern California Kaiser, and I asked the computer people to look at the data between 1995 and '96, which basically -- now I only looked at 0 to 2 years of age, because I thought the incidence of disease is mostly in that age group -- we had a cohort of over 100,000 kids. And the brief data is that 33 percent of those kids are seen at least once for diarrhea, and the incidence of disease is 55 in 100 patients a year for diarrhea, meaning some of those kids are seen twice.

And the second emphasis about decreased hospitalization is shifted to the increase in

outpatient care in terms of much more intensive outpatient care, so that many of those kids, instead of being seen by a doctor for five minutes and go home, they stay in an infusion center for six hours or eight hours for that day for outpatient care, which basically is coded as a single MD visit but turns out to be very, very costly as well.

So there's a lot of twist to how you make the cost analysis for outpatient care.

DR. DAVIS: Thank you.

Neal, did you have something you wanted to say?

DR. HALSEY: Yeah.

I would actually start out by reinforcing what Chinh Le has said. That's my impression from some of the hospitals in the Baltimore area. We haven't done a formal analysis, but I can tell you that's the clear direction that things have been moving, and I think that the cost estimates may be underestimated because six to eight hours in an outpatient setting is fairly intensive.

The Red Book Committee has undertaken the development of a statement on this in anticipation of a licensure. Jon Abramson is with us, who is

coordinating that for the Red Book. Basically we invited the manufacturer to present data, which we reviewed in detail. No decisions were made at the time of that visit in anticipation of additional information, and especially the new cost effectiveness analysis, which we very much welcome in helping resolve the conflicts over the other analyses that were done.

Some of the information that was shared from our practitioners on the Committee is there is a potential problem of the perceived need for this vaccine, which I think needs to be addressed. If we do have a vaccine, if we do go with universal immunization, we will have -- we really do need to embark on a large-scale education program for practitioners and the general public.

And given a marginal perceived need on the part of the public, the concern about safety will be paramount in the minds of the physicians, and we really need as much information as we can from large scale demonstration projects, or whatever can be started, as soon as possible to allay those concerns.

I don't know if there's anything else that either Georges Peter or Jon Abramson want to add in terms of

what we've undertaken so far.

DR. DAVIS: Those are helpful comments. Thank you.

Peggy Rennels is here, and can proceed with her discussion on adverse events.

DR. RENNELS: At the last ACIP meeting I presented the results of the U.S. multicenter trial of the rhesus-human reassortment vaccines given at a dose of 4 times 10^5 platforming units, and administered at 2, 4, and 6 months of age.

In this trial there were two children who had received RotaShield who were hospitalized during the week post-vaccination for gastroenteritis, and were shedding rotavirus in the stool. There were no such hospitalizations among the placebo recipients. Now asymptomatic vaccinees also shed rotavirus in the stool, so that the meaning of that observation was unclear.

Therefore, I reviewed the rates of hospitalization for gastrointestinal events within seven days of vaccination with RotaShield, which is the preparation for which licensure has been applied.

In all studies carried out throughout the world,

the rate of GI hospitalizations among the RotaShield recipient was 1.2 per 1,000, as compared to placebo recipients of 1.4 per 1,000 for a P value of 0.78. In just the U.S. studies, the rates were also very similar between the vaccinees and the placebo recipients, 1 and 0.9 for a P value of 1. So there does not appear to be any excess hospitalizations among the vaccinees for gastrointestinal events.

Now a line listing of these hospitalizations reveal that they're mostly diarrhea, vomiting, plus/minus fever, dehydration, although there was one vaccine recipient who experienced intussusception post-vaccination.

In a review of all rotavirus vaccine trials by Wyeth of two different reassortments, three different dosage levels, two formulations, and two buffering methods, there were a total of five hospitalizations for intussusception among vaccinees and none among controls. Two of these vaccinees received the RotaShield, the other three received other preparations. All of these cases followed doses two or three of the vaccine, none followed dose one, and they occurred between 6 and 51 days post-vaccination.

Now a comparison of the rates of intussusception among the vaccinees and controls did not reveal significant differences either by Fisher's or Poisson, but I was concerned that with larger numbers a causal association might emerge. So I, with the help of others, have attempted to determine whether these intussusception cases were likely due to the vaccine, or more likely due to chance temporal association.

To try to answer that we asked three questions: First, does natural rotavirus cause intussusception?

A review of the literature revealed there's actually never been a controlled study of this issue. One uncontrolled series did suggest a possible association between wild rotavirus infection and intussusception, whereas two others did not.

And a study by Nichols and his colleagues also looked at the seasonal occurrence of intussusception and found no seasonality, as you see with rotavirus. So his numbers was small, so that was further pursued.

Here's a graph of the seasonality of hospitalizations for diarrhea, for rotavirus diarrhea, and for intussusception, and this is in children aged 3 to 23 months in New York State over a two-year period.

Note the typical marked peak of rotavirus hospitalizations as opposed to the rather even seasonal distribution of intussusception cases. I think this is a powerful argument against natural rotavirus being the cause of intussusception.

Question two is at what age does intussusception occur? In other words, would we expect to see it at age four and six months of age, when we did see it among the vaccinees?

Here's a graph of age incidence of intussusception over a two-year period in children cared for in Northern California Permanente. You can see that idiopathic intussusception is almost exclusively a disease of young children, heavily concentrated in the first year of life.

Also, if you break down that first year of life, or actually the first two years of life by months, you see there's really a peak between about 4 and 9, 10 months of age. And I think this probably explains why we saw cases after dose two and after dose three, but not after dose one. And if the intussusception cases in the vaccinees were due to the vaccine, I would expect for them to follow primarily dose one, the first

infection.

The last and most important question, then, was how does the rate of intussusception in these vaccinees compare to rates in other populations?

Because intussusception is so markedly seasonal and so -- I'm sorry -- is so age-dependent, not markedly seasonal, then it's very important to compare children within the same age groups of vaccinees versus control populations. The rotavirus trials followed children until about three different age groups: Through 6 months of age in the safety and immunogenicity trials, to approximately 12 months of age in the one-year efficacy trials, and through approximately 24 months of age in the two-season efficacy trials.

So I chose to compare intussusception in those age groups of vaccinees with a comparison group being the Northern Kaiser Permanente. All of the cases in vaccinees occurred within that first 6 to 7 months of age. If you just compare that age group, you see that in Kaiser Permanente the rate of intussusception for 1,000 children was 0.6 compared to 0.5 in all rotavirus vaccinees, and compared to 0.2 in the RotaShield

recipients. So in fact it was a bit lower in the RotaShield recipients than in the Northern Kaiser Permanente children, but the differences were not significant.

Now if you're unhappy with having only one comparison population, I was made available two other comparative populations, but only broken down by years. But what I did in order to utilize that was just look at the vaccinees who had been followed through at least 12 months of age, and compared them with these other populations. Once again, the background populations between 0.5, or 1,000 to 0.81, as opposed to in the vaccinees 0.28 to 0.42. So again a little bit lower in the vaccinees, but not significant.

So in summary, the post-hospitalization vaccination rates for gastrointestinal events was very similar in the vaccine and control groups, and that intussusception does not appear to be associated with rotavirus diarrhea by literature review or by lack of seasonality, and that the rate in the vaccinees of intussusception was actually a little lower than the background rates.

So I conclude that hospitalizations, including for

intussusception, are most likely due to chance temporal association. But post-licensure surveillance for possible rare vaccine reactions through the Vaccine Safety Datalink, through VAERS, will be very important for this new vaccine, as well as for any new vaccine.

Thank you.

DR. DAVIS: Thanks, Peggy. That was very nicely done. Very nice summary of that important vaccine safety issue related to this vaccine.

I'm going to have Roger come on back up here, and if we could have the lights back on, I want to wrap this up for today.

DR. GLASS: I think that's really the end of our presentation. We've tried to give you the background on disease burden and on the cost effectiveness, which are all being promoted in on this untoward complication that was at least raised.

I think for the next meeting of ACIP we'll go into the specifics of the recommendations and try to challenge you more with decision-making and discussion of the hard issues and fine points, and we would wish that we would get back any feedback before that time.

Neal.

DR. HALSEY: I just wonder if the decisions that you're hinting at are universal immunization or not. And it would really be very helpful to know the cost of the vaccine, should it be approved, before making that decision. That was my opinion at the Red Book Committee, that I would want to know what the cost is before we recommended it for universal use. And I wonder if one of manufacturers is free enough to comment on that.

In addition, I would reinforce what John Livengood said about the adverse events. Even if we don't see excess hospitalizations, there will be perceived adverse events. There will be increased telephone calls to physicians about things that do occur. And so there will be some indirect costs associated with perception and/or reality.

And I would caution that every time we have taken a vaccine to universal widespread use, there is usually something that's found out within a couple of years that we didn't anticipate at the time. So I think it might be to err on the side of a little caution and include in your indirect costs some assumptions about some adverse event costs that would be there.

DR. GLASS: Appreciate that comment, Neal. That goes back to my first line, Neal, of don't shoot first and ask questions later.

I don't know if someone from the industry wants to address this, or --

DR. DAVIS: Peter Paradiso from Wyeth-Lederle.

DR. PARADISO: I want to thank Neal for asking that question.

[Laughter]

DR. PARADISO: He has asked before.

I think we've seen a lot of new data today on cost effectiveness studies, and we're interested in following up on those and talking with Roger about that. We have not set a price for the vaccine, and I'm not going to stand here and tell you what the price is; and there are marketing people here who would kill me if I even made a suggestion.

But clearly, I think that you can see that we're going to prevent hopefully a lot of cases of hospitalization, and more importantly a lot of cases of overall rotaviral disease.

And my own prediction is -- one of the things that we see in our -- to price about is even more

effectiveness of vaccines when we actually get out in the field. And if you were to prevent 50 percent of overall infections, I think you're going to see more benefit than we predict from these efficacy trials, where you don't get the population kind of benefit.

And we're looking at, as Roger said, more effectiveness kind of studies to help get at some of those issues. But I think what we're seeing is a fairly substantial disease burden, and as we get closer to licensure we'll have hopefully more to say about these issues.

Thank you.

DR. DAVIS: Thanks, Peter.

I think we want to tie it up. Two extremely quick comments, if anybody really has to make them.

DR. GLEZEN: I just wanted to make a quick comment in relation to Neal's suggestion, that maybe some members of the AAP weren't too impressed.

Texas Children's Hospital in Houston is the largest children's hospital in the country. It takes care of a large Medicaid population, and runs at capacity throughout the winter. It often has to go on drive-by status when we have flu and RS, and they do

diagnose rotavirus there routinely,

And they have approached me about the prospects for a rotavirus vaccine because they are now in process of planning new hospital space, and the prospects for a rotavirus vaccine to them are very intriguing because that would reduce their need substantially.

So I think this is a very important problem. I don't think it should be underestimated.

DR. DAVIS: Thank you for that comment.

Last, Rob Breiman.

DR. BREIMAN: Thank, Jeff.

Roger, I'm a little concerned about whether 7,000 fully immunized patients is really enough to be able to evaluate whether or not you have clinically important but relatively rare adverse events. And in sort of following your concept of not shooting first, what sorts of ideas are thought of?

Neal had mentioned the concept of a demonstration project. I'm not sure if you were talking about in phase three or post-licensure, but do you have ideas about how you could get a better sense of important adverse events before the vaccine is actually out for routine use?

DR. GLASS: For rare adverse events it would be hard because they're rare, just like intussusception. On the other hand, the idea of taking a full catchment population -- all the data we've used for national hospitalization represents the slice of hospitalization with relatively poor data on ambulatory care, emergency room visits.

The joy of taking a population like the VSD of Bob Chen's and the Kaiser Group is that for that birth cohort we can do everything. It's already set up to do everything. So all we have to do -- we're from a group that has very little research money -- and all we have to do is to try to encourage them to screen for rotavirus, all hospitalizations, some fraction of ER visits, some fraction of outpatient visits, to be able to get a good fix in that population first of the cost benefit and what the vaccine would be worth to Kaiser and to their population, then to look at adverse effects if we could introduce the vaccine into that population.

The other issue is the issue of Texas Children's, where you have a large inner-city population where the rates of hospitalization for diarrhea are more than

twice what they will be in the Kaiser, and where this vaccine would be of even greater benefit. How to organize -- Texas Children's did one of the first good rotavirus surveillance projects ten years ago.

To be able to reimplement that and get a better fix on how important rotavirus is today -- our national data says that 15 years ago 9 1/2 percent of hospitalizations were due to diarrhea. Our current data, the latest data from '95, suggests that 13 1/2 percent are due to diarrhea. So while total hospitalizations have gone down, the fraction has gone up.

What that means for rotavirus is that if 40 percent of those diarrhea cases or more are due to rotavirus, that's about 4 or 5 percent of hospitalizations for children under five, and in a place like Texas Children's that could make a major impact.

DR. DAVIS: Thank you very much.

I think we're going to close the floor right now. We could be fine-tuning the statement, too. If people have additional comments they can return them to Roger, because that was circulated.

We will resume at 11:15.

[Whereupon, a brief recess was taken from approximately 10:53 a.m. until 11:35 a.m.]

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DR. DAVIS: I know that some of you are here because of the issue regarding varicella. That came up yesterday, and I've had a lot of discussions with a lot of people. And what we want in the future for this issue, since we voted on an option, we're going to let that stand.

There are other options. There's at least one other option that we need to consider in the future, and there's a variety of data that we requested as a Committee that we still need in order for everyone to have the information for decision-making not only in the future, but for justification.

There's a little bit of the cartoon that Roger Glass showed about you were supposed to ask the questions first before you shoot. And I resonated with that, because I do feel that there is information that as a Committee could have been developed in a more step-wise process that could have benefited our Committee.

I do feel that the vaccine is important, that it is important for the children in this country to have vaccine available, and that we need to have as seamless a vaccine delivery system as possible with everyone having access. So I think in terms of the people that will now benefit, there's no question that there will be a great deal of benefit there.

But I do want to ask that a working group be developed to delineate the impact of what we voted on, and also to seriously consider additional options which we did not vote on that were more costly. I think with that, we will then move on to the next topic.

We'll move on to the vaccination of health care workers. And Ray Strikas and Walt Williams will be leading this discussion.

I want to congratulate both of you for all of the hard work that you have put into this statement. This is a good example of an evolving process that has made use of all of the recommendations available to you in ACIP documents and in draft statements. So I thank you, and we'll move forward here.

DR. WILLIAMS: Thank you. Good morning.

The updated recommendations on immunizing health

care workers were sent to you for final review prior to the meeting. As noted in the cover memo of the draft, it has been updated to incorporate all of your comments, and I'll specify those that were identified as most important during the last meeting, as well as comments from CDC reviewers in other areas that impact important recommendations.

The recommendations now have been made consistent with recently published or updated recommendations on hepatitis B, pneumococcal infections, meningococcal disease and outbreaks, measles, mumps, rubella, which is still under your review, and pertussis.

This morning I will briefly outline the content of the statement, identify the changes made in response to your recommendations, and seek your concurrence to proceed to publication. Minor edits are planned. As with every document, every time you read it you can think of other ways to improve it.

The edits that have been considered on the draft that you now have include adding descriptive subheads in certain sections to improve readability and ease of use, and also moving chunks of text that are now included in the recommendations to the rationale

section, particularly those sections on pertussis, meningococcal disease and outbreaks, and vaccinating persons with HIV. It will not mean adding any new text. It would mean taking chunks of the text in those recommendation sections and putting it into the rationale section where appropriate.

One note, as this first slide indicates, these are recommendations of the ACIP as well as the Hospital Infection Control Practices Advisory Committee. That group met during the last five weeks -- I forget the date, exact date -- and reviewed specifically the recommendations for immunizing health care workers. And there are several things I'd like to point out toward the end, in the table, where they have recommended a substantive change.

The recommendations again are those of ACIP and HICPAC, and they are intended to apply to the health care workers working in other settings other than hospital environments, and there is a list of settings that are specified in the recommendation.

The diseases for which immunization is strongly recommended are listed here. The section on measles, mumps, and rubella is consistent with the current

version of the MMR recommendations that you are deliberating, and throughout that process we'll make sure that text and recommendations in this document remain consistent with the MMR statement until it's published.

The section on tuberculosis and BCG vaccination was shortened considerably, as recommended by several reviewers. It more specifically identifies prevention activities versus vaccination as the primary way to control tuberculosis infection in U.S. hospitals.

The section on other diseases for which immunoprophylaxis is or may be indicated, all of the information on hepatitis C has been moved from this section to a separate section that has that title, Hepatitis C. This was recommended by Dr. Hardegree and others.

The information that was included previously in the, quote/unquote, recommendation section has been moved to the text, so all of the information on hepatitis C now appears under a separate subhead, Hepatitis C, with information that would be considered useful for health care workers related to prevention of transmission of that disease.

The section on other vaccine-preventable diseases, the recommendations on use of pneumococcal vaccine is consistent with the recently published recommendations. There was only a short reference to use of pneumococcal vaccine, and the issue that was of most importance had to do with revaccination of persons considered to be at highest risk.

The section on immunizing immunocompromised health care workers has been updated. The section on corticosteroid use is consistent with the guidelines in the 1997 Red Book, as recommended by Dr. Halsey. That information appears in text as well as a table. It has been updated in both places.

The section here as well as in the table 4 on use of MMR in persons with HIV infection was updated per Dr. Katz' recommendation to be consistent with recent observations related to the use of measles vaccine and potential harm in persons who are severely immunocompromised.

The Other Issues section, there were no major comments during the last meeting about this section. It remains essentially unchanged.

The tables, again there were five tables:

A table basically summarizing the published ACIP recommendations as of January 1 of this year. It has been updated to note publishing of new recommendations on use of acellular pertussis vaccine as well as pneumococcal and others.

Table two, immunizing agents and schedules for health care workers, is a laundry list of the immunizing agents or indications, and major precautions.

Table three, recommendations for postexposure prophylaxis for percutaneous or permucosal exposure to hepatitis B virus is consistent with the current iteration of that draft statement.

Table four summarizes ACIP recommendations for immunizing health care workers with special conditions, including HIV. That table is consistent with published recommendations on use of immunizing agents in persons with all types of immunocompromise. And again, the section on MMR use was updated per Dr. Katz' recommendation.

The one table where there had been changes suggested by HICPAC is the table on work restrictions for health care workers, and that is table five.

In general, the HICPAC felt that any person who has active disease, active vaccine-preventable disease -- measles, mumps, rubella, pertussis -- or who is considered susceptible and has been exposed should not be in the hospital. The prior language indicated relief from direct patient care. They feel that that should say relief from duty, and that those individuals should not be in the hospital until they are clearly not able to transmit disease.

I mention that to the Committee now because it's important that if there is any problem with that change in the recommendation, it's resolved at this point.

DR. DAVIS: Thanks, Walt. That's a very nice summary.

We can have some discussion. Any comments?

Chinh Le.

DR. LE: Thank you. I think this is a very welcome document, and I'd like to make a couple of suggestion to update, especially the section on hepatitis C.

I think hepatitis C is a very fast evolving disease, and right now on page 25 and 26, basically what it says is institutions should consider

implementing policies and procedures for follow-up of health care workers after percutaneous or permucosal exposure of hepatitis C positive blood.

Follow-up procedures might include baseline testing of the source and baseline and six-month follow-up testing of post-exposed person for hepatitis C, for anti-hepatitis C and liver function test, and so on.

I'd like to point out the very excellent draft by the National Institutes of Health, which was March 27th, Management of Hepatitis C. And basically I think it's a very nice document looking at how you would document acute infections with hepatitis C.

Basically is says that after initial exposure hepatitis C RNA can be detected in the blood in one to three weeks, and then antibody to hepatitis C virus almost invariably become detectable during the course of illness. Fifty to seventy percent of patients would have looked -- of patients at onset on symptoms, and approximately 90 percent of the patients after three months of onset of infection.

So to me that six months' delay recommending hepatitis B follow-up serology for exposed health care

workers seems a little bit outdated. And I think the data is even more important when there is a paper on infectious disease where there were two workers who were exposed to hepatitis B by percutaneous blood, infected blood, and then was followed by the RNA method, found to be positive by the RNA method by about a month and a half after needle exposure, was treated with interferon, and cleared of uremia.

Obviously this is very early initial data, and we're not making strong recommendations. So that is the procedure. But this really opens up a very important issue, that hepatitis C is a very common concern in hospital employees, and waiting six months delay to make a diagnosis is probably outdated.

DR. WILLIAMS: Do you have suggestive wording?

It seems like that would be an easy thing to -- especially since it may be evolving, it may be advantageous to put in some wording that just says baseline and follow-up testing at appropriate intervals, and just cite the papers that you've referenced rather than specify a specific month. It seems that that may be an evolving issue, as testing for infection or evidence of infection may improve over

time.

DR. LE: I'm going to give you those two articles. I'm sure I can trust your judgment to just rewrite --

DR. WILLIAMS: If I could, I'll get those citations from you at the end of the session. And we'll change the wording to say source of anti-HCV and baseline and follow-up testing at appropriate intervals, and cite those two references. And I think that will indicate to readers that the interval may be as short as one month, as you're indicating, or as long as X month, and anywhere in between. And as new data become available, obviously that testing interval can be modified.

DR. DAVIS: Thank you.

Jane, and then Pierce.

DR. SIEGEL: That issue was discussed fairly extensively at HICPAC. And the hepatitis group felt very strongly that a lot of that was very experimental, and advised caution in how it was worded and how directive the recommendation should be. So I just think we have to keep that in mind.

DR. WILLIAMS: To be more or less directive?

DR. SIEGEL: Less directive than Chinh is

suggesting, and a little bit more vague, because a lot of the early treatment is purely experimental.

DR. LE: I absolutely agree that the early treatment is experimental, but the diagnosis of hepatitis C could be made earlier, following this INH draft. And in the anxiety of the worker, I think it should be attempted to make earlier. Plus the fact that the RNA test is widely used now by most gastroenterologists in --

DR. SIEGEL: Well, the hepatitis group had some very strong feelings about how that should be worded.

DR. WILLIAMS: Do you think the wording that I just sort of proposed gets at making it less --

DR. SIEGEL: I think that probably addresses it. And I do think it's important to state that the source patient must be tested at the time of the occurrence.

DR. WILLIAMS: Well, that is clearly specified.

DR. DAVIS: Okay. That's good. Thank you very much.

Pierce Gardner.

DR. GARDNER: Walt and I were just looking at the table about work restrictions on health care workers, and I spent some time -- did some work in this some

years ago. I was a little concerned about the mumps recommendation for postexposure folks.

The data used to be that there were enough subclinical cases that cohorting didn't work very well. Nosocomial mumps is not a very important problem, and I guess I -- this statement that susceptible personnel are relieved from direct patient contact for a two-week period struck me as something that's new since I looked at the data some time ago. And I wondered if there's real data to indicate that that's an important thing to do?

DR. WILLIAMS: That actually has been the recommendation since about 1983, and it's been published numerous times and discussed in different fora.

DR. DAVIS: Yeah, Pierce last looked at it in 1982.

[Laughter]

DR. GARDNER: I guess that's right. It's been a while.

DR. WILLIAMS: The comment that I made in the preamble was that right now the work restriction that is proposed by HICPAC is instead of relief from direct

patient contact for postexposure susceptible personnel would be to, quote, exclude them from duty, and the period of exclusion would be the period that you just indicated.

And that's based on the incubation period and information for all of these diseases, information on potential shedding of virus prior to onset of clinical symptoms. And HICPAC as well as ACIP has always tried to provide the widest margin of safety, recognizing that different studies may indicate shedding of virus one or two days prior to onset of symptoms of --

DR. GARDNER: I guess my concern is that the consequence and amount of nosocomial mumps is not very much, and this seems like killing a gnat with a sledge hammer, I guess.

DR. WILLIAMS: Elizabeth, I hate to put you on the spot, would you comment?

Elizabeth Bolyard is working in the hospital infections program with the HICPAC on that specific guideline, and has been my primary contact as far as trying to make sure these two documents are consistent, and may be able to comment further regarding their discussions.

DR. BOLYARD: I agree that mumps is not a problem in hospitals, and I think because we don't see that happen very often they would rather take the margin of error and not expose other people should the person come down with it. But we really have not seen many exposures in health care institutions, so mumps is probably the weakest of the whole group. If we're going to exclude rubella and the others, we should include the mumps in that, too.

DR. DAVIS: Fair enough. Thank you.

Any other comments? Chinh Le.

DR. LE: I need some clarification on table five as well. It's a little bit confusing to me in terms of exposure after zoster.

The way I read the table it says zoster, if the index patient has localized zoster, the susceptible personnel postexposure should be relieved from direct patient contact, is the way I read this; meaning if my clinic assistant or my receptionist registers a patient who comes in with zoster, and let's say she's not varicella seropositive, she should be relieved from direct patient contact.

My understanding about zoster transmission is that

if it is continuous and localized, is not aerosolized, it's a contact-type of precaution; and if there's no direct touching of those lesions I don't see why the health care worker has to be released from patient contact because of face-to-face exposure with somebody with zoster.

DR. WILLIAMS: In general, that's true.

There are at least one or more published reports of distant transmission of varicella from patients with zoster, and at least one of those is cited in this document in reference in the text. And it basically says in general what you're saying is true, but because of potential airborne transmission from a patient with zoster, again the discussion was that to provide the widest margin of safety personnel who are susceptible, if exposed, this would be the precaution to take.

Our hope is that with aggressive identification of susceptible personnel at the front door, and offering vaccinations to those who are found to be susceptible by history, that this situation can be obviated.

DR. DAVIS: Thank you.

Dave Fleming, did you have something you wanted to say?

DR. FLEMING: No. I'm sorry, I was just reading the table.

DR. DAVIS: Okay, thanks very much.

Yes, Chinh Le?

DR. LE: One more comment about hepatitis B.

The recommendation is persons found not to respond to primary series should be revaccinated with a second three-dose vaccine series. There is a very nice article in *JID*, March 1997, giving single dose of 40 micrograms, meaning given as a dose of 40 micrograms of antigen, and having 100 percent response rate for the people who did not respond to primary series. I thought that should be included as one of the potential possible recommendations.

DR. WILLIAMS: I will raise that issue with the hepatitis branch. I think in general they have felt that the best course of action would be to offer a three-dose series, complete three-dose series with testing for immunity following that. And that is the language that's in the current hepatitis B new ACIP recommendations.

I would leave it to the Committee in finalizing that document to resolve whether this new information

might also be included as an option.

DR. DAVIS: Clearly, one of the issues is just the hepatitis B document, given the fact that COMVAX [phonetic] information is also being included in there, and there's quite a few -- it's loaded as it is right now. That needs to get resolved and published.

And I think when we're really talking about a substantial new use of a vaccine with a substantial increase in the amount of antigen that's administered, even though it's in a single dose, that would probably be something that the full Committee here would have to consider, and it would be a major change.

It's additional information, and I'd be a little reluctant to do that at this point in time, even though it is a recent article and it is very interesting. It is something that the Committee probably ought to consider. But I think a high priority right now for us is to get that hepatitis B statement published as well.

Anything else? I'd like to bring this -- okay, Jane, this will be the last comment. I want to bring this to a close.

DR. SIEGEL: Just one other comment. Do you want to consider having just a small section about the

pregnant health care worker? Although it's addressed in the individual immunizations, frequently the questions come up, what vaccine can you give a pregnant woman and that sort of thing; and just setting it aside as something that could be easily accessed.

DR. WILLIAMS: The table four specifies vaccinations. There's a vaccine-specific table on vaccinating people with, quote, special conditions, and pregnancy is included there.

And the discussion was that -- we previously had a section in the text on pregnancy, and the feeling was that that table should be adequate. So we've streamlined the document and removed the stuff that was in the text, and I think all of the information that you're requesting is in the current draft in table four.

DR. DAVIS: I'm going to ask everybody just to review this document very carefully and get your comments back to Walt within the next three weeks.

DR. WILLIAMS: Again, we were hoping that, unless there were major issues, that we would get the concurrence of the Committee with these minor changes and edits that I've described, that we would move

forward to publication. This is, I think, the third round of comment.

DR. DAVIS: Well, it is the third round of comment.

Let me take a couple more comments, given that. Rob Breiman and then Stan Gall.

DR. BREIMAN: I also had some questions about table four and that column on pregnancy. For one thing, should there be any recommendation in terms of what trimester? Is this a broad recommendation for use of these vaccines at any time during pregnancy?

DR. WILLIAMS: What we have advised throughout the document -- again, this is intended to be a summary of published recs -- is that people should consult a specific document on that vaccine, because there in detail is the information on use of the vaccine and pregnancy and which trimester and all of that.

So rather than try to incorporate all of that in this table, we cited the appropriate statements, made the broadest recommendation with regard to use in pregnancy, and hope that individuals, if they have a detailed question, would follow through with looking at that specific recommendation.

DR. BREIMAN: And I guess that same logic would apply to things like BCG and vaccinia use in pregnancy, where it seems like you would have to have very, very special circumstances.

DR. WILLIAMS: Right.

DR. BREIMAN: But I'm sure that's explained somewhere.

DR. WILLIAMS: It's explained in the greatest detail as far as this Committee and those specific documents, and rather than make this extremely long we've tried to concisely present that information; and hope, again, that individuals would refer to those documents if they had questions.

DR. DAVIS: Stan.

DR. GALL: The pregnancy statement, or the pregnancy list here -- for instance, influenza, it says use if indicated. We've already -- in the current new *MMWR* booklet says it should be administered in the second and third trimester. So this should be changed from use if indicated to recommended type.

DR. WILLIAMS: Recommended.

DR. GALL: Also, oral polio. Oral polio is not

indicated in pregnant adults, so that should probably be a C rather than an R, or a use if indicated. I think you need to look at that a little more carefully so it's in line with the real world.

DR. WILLIAMS: The influenza comment is quite on target. It's an evolving issue for this Committee regarding the use of influenza vaccine in pregnancy. That was just an omission. But that has been an open issue up until the last meeting.

Oral polio vaccine, the recommendation, use if indicated, really is referencing potential use of oral polio vaccine in outbreak situations, which is very rare. We will --

DR. GALL: Also, in adults that are pregnant, they need to use inactivated, enhanced inactivated, not oral. That's, I think --

DR. WILLIAMS: But again, the recommendation for controlling outbreak circumstances does suggest consideration of oral polio vaccine. So again, without trying to put a lot of detail in this document, we'll again check the wording to make sure that it is consistent. But there is a potential use of oral polio vaccine in certain populations during an outbreak if

you want to assure rapid immunity and decrease the risk for transmission to other individuals.

DR. GALL: I understand. But there hasn't been any polio around for a long time, number one. Number two, oral probably is safe, because Sabin was given during the 1950s and there's been no adverse effects. But since there's no polio in North America or South America or where this document is going to be used, it would seem to me you would want to change that.

DR. ORENSTEIN: I think there's a difference between a totally unvaccinated pregnant woman traveling to a polio-endemic area and someone who had received prior doses; and I believe the current ACIP recommendations until actually recently would have had OPV preferred, and now have an OPV as virtually an equal alternative to IPV for the pregnant woman who is traveling and needs an extra dose.

UNIDENTIFIED: I would agree with that, Walt.

DR. WILLIAMS: But again, this table is consistent with current published recs.

Your comments regarding risks for transmission of polio in the Western Hemisphere was considered by the Committee, but was a section in the prior text five

iterations ago that actually discussed polio and decreased transmission.

And there were firm recommendations from almost all the Committee, too, because of the points that you're making regarding low risk in the Western Hemisphere or no risk except for international importation, that that section be totally deleted from the document. And it was, and the only reference to use of polio vaccine at all appears in the tables, table four and table five -- I'm sorry, table one and table four.

DR. DAVIS: John -- I really want to pull this to -- I'm going to call this right now.

I think we're in affirmation. Let me just word it this way: I'll ask the Committee, are you comfortable with the status of this document, short of minor fine tuning?

[Show of hands]

DR. DAVIS: Okay, so you have the go.

I still feel as though there are a couple of minor little fine points that the Committee doesn't -- we don't have to see it again. We will trust your judgment.

DR. WILLIAMS: What I will plan to do is once the edits are made, is to consult with you directly regarding those edits, and with your concurrence we'll go to publication.

DR. DAVIS: That would be fine. And then if there's anything that I perceive as being problematic, we'll get back to the full Committee. But we trust your judgment. You're doing a great job on this, you really are; and it's hard work.

And thank you for HICPAC, Jane, and your committee. I think this is an excellent joint activity here.

The next presentation will be on Lyme disease vaccine update.

And I do want, by the way -- I said three weeks; get them in two weeks so we can really speed this along.

This will be Lyme disease vaccine update, a good bit of information today. Dave Dennis will introduce the topic. Dave's from CID, Fort Collins, and there's quite a few other people that will be providing some inputs.

So, Dave.

DR. DENNIS: Good morning. Thank you for the opportunity to speak with you briefly.

Two years ago Lyme disease vaccine was presented to this Committee as a heads-up. At that time one manufacturer had begun phase three field trials, the other manufacturer had them on the planning board.

A lot has happened since that time. The two manufacturers have both utilized a single protein recombinant outer-surface protein A lipodated vaccine in their field trials. Both vaccines have been shown to be immunogenic and safe with a phase one and phase two trial results, including studies of vaccine of people who had previously had Lyme disease.

The vaccine has been found not only to develop a humoral immune response, but most interestingly, probably the primary action is a novel action in which the organism is killed in the mid-gut of feeding ticks because they imbibe the antibody and be complemented.

Now the status of the evaluations at present are that the phase one, phase two studies are completed, have been reported upon. Phase three studies have been completed involving about 20,000 participants. And they have not yet been reported, but there are plans

for both manufacturers to present results to FDA before the close of the year for consideration for licensure. The FDA has approved upon request the use of the vaccine in the placebo group of one of the manufacturers.

There are a number of issues left to address, of course. The safety and efficacy not only of the phase three trial results, but perhaps long term. In particular, there are concerns about dosage schedule and whether or not boosters are going to be required. And as well, the question of using children has not been addressed because the trials just dealt with persons greater than 15 years of age.

This morning, both the Connaught and SmithKline Beecham will present. SmithKline Beecham will be presented by Dr. Dennis Parenti, and the Connaught status of their evaluations will be presented by Dr. John Zahradnik. I'll briefly address targeting of the vaccine based on immunologic factors, and Dr. Martin Meltzer will address modeling for cost benefits in Lyme disease.

Dennis.

DR. PARENTI: Good morning. On behalf of

SmithKline Beecham I would like to thank the Committee for the opportunity to discuss our Lyme vaccine study.

This morning what I'd like to do is to discuss the study design and methodology for our pivotal efficacy trial, and hopefully lay the groundwork to come back in the near future to discuss the study results with you in detail.

Before I delve into our pivotal efficacy trial, I'd just like to have one or two slides to bring you up-to-date as far as background material is concerned.

The SB vaccine is recombinant DNA-expressed lipoprotein OspA. It's expressed in E.coli transformed with Borrelia burgdorferi strain ZS7. ZS7 is part of the sense-restrictive genospecies which is endemic in North America. It's 30 micrograms per dose, absorbed onto aluminum as an adjuvant.

In 1994 we started a dose-ranging study, a phase two dose-ranging study in an endemic area of New England. At that time we realized that as we were dosing that the Lyme season was going to be coming upon us pretty soon, and decided that we would try to get an early opportunity to access the efficacy of the vaccine, kind of a proof of concept.

I'm not going to show the data from that study, but what I do want to do is show some of the lessons that we learned from that early study.

It became obvious in the study that it was very critical that we had case definitions and documentations of Lyme disease, and that the CDC case definition is very adequate, obviously, and very good for surveillance, but clearly would not be good enough for an efficacy trial. In order to have a high sensitivity of detecting cases, an awful lot of suspect cases would have to be worked up.

Also, in order to have a good specificity for the confirmation of cases, you really had to document them very well. We felt that it was important to photograph EM lesions, for example; to biopsy all the EM lesions for culture and PCR; again, to document it as best as could be.

It was important to get acute and convalescent sera on all suspect cases. We also felt that it was important to obtain baseline sera on subjects, and to obtain sera at the end of each transmission season. And we made a decision to utilize the Dearborn Western Blot criteria.

Let me delve into our pivotal efficacy trial, Lyme 008. This is a multicenter, randomized, double-blind, placebo controlled trial conducted in 31 sites in New England, mid-Atlantic, and in the Midwest. We enrolled 10,937 subjects. The vaccine was administered on a 0, 1, 12 schedule.

The first two doses were administered in early '95, and then after that we followed patients via postcard surveillance throughout the entire first summer through the entire tick season. They received five postcards over the summer. These postcards basically reminded subjects of the symptoms of Lyme disease, and if they had one of these symptoms it reminded them to contact the investigators for an evaluation. It also queried them about safety data.

At the end of the first year subjects came back at month 12 -- I'm sorry, they had had baseline blood work drawn prior to being dosed. And at month 12 they returned and had blood drawn for end-of-year Western Blot testing and received the third dose.

Again, through the second year, through the second summer they received postcards from us, surveying again for Lyme disease symptoms, reminding them of those, and

for safety data. The study was completed in mid-November of '96, after 20 months, basically conducted over two tick seasons.

Let me just review the inclusion/exclusion criteria, pretty brief and pretty straightforward. In order to get into the study, basically you had to be healthy, between the ages of 15 and 70, and at risk for acquiring Lyme disease, which meant that you had to live in an endemic area and have at least some chance of exposure to ticks and Lyme disease.

The exclusion criteria, patients were excluded if they had chronic or recently treated Lyme disease, if they were receiving chronic antibiotics or immunosuppressed, or if they received other investigational vaccines in addition to the usual study exclusion criteria about not having hypersensitivity reactions, pregnancy, et cetera. Prior Lyme disease was not an exclusion.

Let me just show you some of the scheduled visits and some of the numbers of visits that we had so you have some idea of the compliance. The first visit, again patients had baseline blood work drawn before they were dosed, and we started with 10,937 patients.

One month later they returned for the second dose, and as you can see we lost a few subjects. The third visit was just a safety visit one month after the second dose.

Visit four is the one-year visit, and at this visit they received a third dose. And as you can see, over a one-year period we lost a little less than 400 subjects. Visit five was a visit that was for the immunogenicity subset only. Visit six was the end-of-study visit at month 20. As you can see, at that point in time we had lost about 800 subjects, approximately 7 1/2 percent dropout over two years.

These are the scheduled visits, and let me just show you some of the unscheduled or the study procedure visits. Again, I had mentioned that all subjects had sera drawn both at baseline at the end of the first year, and at the end of the second tick transmission season. I described the postcard surveillance that we had.

Now if they had developed symptoms of Lyme disease, all subjects were asked to contact the investigator, make an office appointment, and they were asked to come in for both acute and convalescent sera

for Western Blot testing.

The protocol also defined specific procedures that had to be done depending upon its subjects symptomatology. So for example, if they had a rash, we had asked all the subjects to come in, and asked the investigators to measure the size of the rash. We had provided all of the investigators with a camera, so we asked them to take photographs of all the skin lesions.

We also trained the investigators on how to take skin biopsies, and we asked that all skin lesions except for the ones that were on the face be biopsied and sent for culture and for PCR testing. And, similarly, if you had arthritis and had a swollen joint, the procedures for tapping the joint, sending joint fluid for PCR, et cetera, were all outlined in the protocol as well.

The laboratory data for the study, all the suspect acute and convalescent sera were performed at one lab. That was the lab of Dr. Allen Steere, who was our coordinating investigator. The lab technicians read the Western Blots. Dr. Steere and all the investigators were kept blinded to the presence or absence of the 31 kD band.

As I mentioned before, we utilized the Dearborn criteria. I'm not going to review that criteria right now. I think the important thing is that for acute sera conversion, not only could we assess positivity and negativity of IgM, but more importantly that it was in reference to their baseline specimen.

Let me give you some idea of how many people were evaluated in the course of our study -- a lot of them. The first year, approximately 1,100 subjects were evaluated. That's approximately 10 percent of the population had some symptoms suggestive of Lyme disease and came in for an evaluation.

I should mention that we emphasized to the investigators that we really wanted to have the widest surveillance possible, we wanted subjects worked up even with the remotest possibility that it might be Lyme disease. So they were very, very aggressive in working up subjects for Lyme disease. In year two again, almost 900 subjects. Again, almost 10 percent of the population were worked up.

Let me very briefly show you some of the lab data that these suspect visits generated. As I said, we asked that skin biopsies be performed on all subjects

and sent for culture and PCR. Let me just give you some idea of the number of culture positive cases that we had. In the first year we had 49 positive cultures versus 56 in the second year -- and I apologize, I should have put the denominator here. This is out of approximately 120-so skin biopsies, and this is approximately 150.

The asymptomatic seroconversion was defined as having a positive IgG at the end of the first year when your baseline specimen was negative. For the second year it's defined as having a positive IgG when your end of year one specimen was negative. So at the end of the first year we had 14 asymptomatic seroconverters, and in the second year a similar number.

If we take all the subjects who had lab-confirmed cases by culture, PCR, or by seroconversion, we had 109 cases in the first year and 130 in the second year. I think that pretty much agrees with the CDC data that 1996 was a little bit busier than 1995. We had approximately 25 percent increase in cases as well.

I'm going to switch right now from lab results and just discuss safety monitoring very briefly. The

safety database for our pivotal study is generated from the solicited reactogenicity diary card data that we had. We collected unsolicited events recorded at each contact during year one.

I've already mentioned the postcard surveillance. Subjects received eight postcards during the course of the study, and of course investigators were asked to report SAEs, serious adverse events, whenever they occur.

With regard to solicited reactogenicity we utilized a subset of 938 subjects at one site. I should mention that this same subgroup served as our immunogenicity population. They filled out diary cards for three days following each vaccination, and we queried about the local and general symptoms, the local symptoms being redness, soreness, and swelling; the general symptoms of arthralgia, fatigue, headache, rash, and temperature.

Currently we have 24 months follow-up on all the vaccinees and all the placebo recipients. We continue to follow the vaccinees via postcard surveillance, and will have ultimately 36 months of follow-up on this cohort. And we're hoping to have approximately 170,000

subject months of follow-up on our vaccinees. Currently, our placebo recipients are receiving vaccine at the current time.

In summary, Lyme 008, we believe, is a well-controlled pivotal efficacy, safety, and immunogenicity trial. We believe that we have sufficient high quality data to support submission for a PLA. And we believe that Lyme 008 will make a major contribution to the understanding of the epidemiology and clinical manifestations of Lyme disease, especially in the area of asymptomatic infection.

Thank you.

DR. DAVIS: Thank you.

I think what we'll do is move forward with the next presentation, and we'll have a discussion on all of this at the end.

DR. ZAHRADNIK: I thank you for inviting me here today. I was told I needed to take five minutes to present this, so it'll be at a little bit faster clip than the last one.

I can say that many of the things that you heard as far as the efficacy study were very similarly performed in our study, the criteria, et cetera, as

will make the comparison of studies, I think, that much easier for you.

I'll briefly go over the study with you. This was a randomized, double-blind, placebo controlled two-year observation period; multicenter, utilizing 14 sites within the Northeast and the Midwest.

The vaccinees received either 30 micrograms of OspA or a placebo. It was a half cc dose intramuscularly. There were 10,306 adults who enrolled in this study. They received two doses of vaccine given one month apart. Bloods were taken at baseline and post-dose two in a subset of these volunteers. If clinical symptoms of Lyme disease were reported, acute and convalescent blood specimens were obtained.

An addendum was added to this study, and this was the administration of a third dose to all eligible subjects, who received this on the anniversary date of their first dose. They received whatever they had received in the first two doses. Approximately 75 percent of the subjects enrolled in this portion of the study. The follow-up for blood and Lyme disease was similar.

Inclusion criteria for this study included

individuals who were 18 years of age or older and who were in good health at the time of enrollment, and individuals determined to be at high risk for acquiring Lyme disease.

The primary end point, of course, was to evaluate the efficacy of the OspA vaccine in preventing Lyme disease. The primary analysis of efficacy data included definite cases of Lyme disease.

Now these were patients who had positive serology using the Dearborn criteria, either IgM or IgG immunoblot, and they were either early acute localized disease -- that is, [inaudible]. They were early or acute disseminated disease.

They had multiple EM lesions of five centimeters or greater, with or without signs of systemic dissemination which would include cardiac or nervous system disease; or it was a single EM lesion with cardiac or neurologic disease; or it was a late Lyme disease which was defined as musculoskeletal or neurological disease.

Secondary analysis included probable cases of Lyme disease -- that is, those who had early localized disease, the EM lesion without any laboratory evidence

of infection. And what we classified as possible cases of Lyme disease, those individuals who presented with atypical symptoms: Fever, fatigue, headache with neck stiffness, arthralgia, myalgia, chills, or backache that weren't characteristic of viral syndrome, and laboratory evidence of infection.

The subjects were followed for adverse reactions actively on a monthly basis through the Lyme season, and quarterly in between the Lyme season via a postcard system during the entire 24 months of the study.

The subset of subjects had all local and systemic reactions collected for 30 days after each vaccination. Any serious or unexpected adverse experiences or events that were deemed vaccine related or were not related were reported to us by either telephone and/or fax.

Any rheumatologic or neurologic adverse events were referred to a rheumatologist or a neurologist for evaluation when appropriate. Reports were sent to us and then to an intermediary group who forwarded them to the DSMB for evaluation in a blinded fashion.

The study population resided in an endemic area of either Connecticut, Massachusetts, New Jersey, New

York, or Wisconsin, and employment and recreational activities put the subject at risk for exposure. Amongst these subjects the mean age was 46.1 years, the range was 18 to 92 years. They were 59 percent male and 41 percent female.

Now I'm going to present to you two brief slides which summarizes, and only does that, the results of this study. The efficacy of this study in those subjects who were less than 60 years of age was 100 percent after three doses. In those who were greater than 60 years of age, the efficacy was 75 percent after three doses of vaccine.

This vaccine was generally safe and well tolerated. There were no statistically significant difference between the vaccinees and placebo controls regarding the incidence of serious or unexpected adverse events.

We continued to follow these subjects for safety and for the development of Lyme disease, and are interested in evaluating this disease in the future in a pediatric population.

Thank you.

DR. DAVIS: Thank you.

Let's see, right now it's 12:30, and I'm not sure in terms of -- the cafeteria, is it open until 1:00? I'm just trying to figure out how to best use our time.

I think what we can do, let's take some questions right now regarding the -- I'm not sure.

Martin, how long is your cost benefit?

DR. MELTZER: Ten minutes.

DR. DAVIS: It's a ten-minute presentation? I want to have opportunities to ask questions and have discussion about this, and work around the -- what we could do is have -- because I think we need time for that, we need time for discussion, and we should work around the schedule downstairs.

What I think we could do is resume in 45 minutes with asking questions and hearing Martin Meltzer's cost benefit analysis, and Dave has five minutes, too. So I think to bring everything to closure we'd be pushing the envelope a little bit.

So we're going to resume in 45 minutes. So it's 12:30 right now. We will resume sharply at 1:15.

[Whereupon, a lunch recess was taken from approximately 12:30 p.m. until 1:21 p.m.]

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DR. DAVIS: Please be seated. I realize that we're very short in terms of people, but there clearly is no shortage of interest in this vaccine. I believe our Committee members are now entering, so I think we can begin.

If everyone can be seated we'll resume our discussion of the Lyme disease vaccines. You've heard presentations from representatives of SmithKline Beecham and Connaught regarding their vaccines, and we heard information regarding phase three trials for each.

And what we wanted to do was to have the opportunity for Martin Meltzer to present his cost benefit analysis on these vaccines. It's really modeling the costs and benefits. And I'll turn it over to you now, Martin.

Did you want to say something first, before?

DR. DENNIS: Yes.

DR. DAVIS: Okay, just go ahead up there. I'll turn it back to Dave Dennis.

DR. DENNIS: I want to just very briefly address targeting the vaccine from some of the epidemiologic issues that we are addressing as persons who are

responsible for the national surveillance of Lyme disease.

Some of the factors that have to do with Lyme disease vaccine and its consideration for use is, one, Lyme disease still is considered a rapidly emerging disease. It's a disease of place and behavior. It's transmitted by ticks, and these ticks have very specific ecologic determinates. So it's a selected foci, both from an ecologic standpoint and also from a geographic standpoint.

Most risk to persons in the United States is peri-residential. There is also recreational, occupational factors that increase a risk of persons being exposed to the infection. It is really almost considered a family disease in the endemic communities, and persons considering vaccine will consider this as something that they will consider for use in their family.

Prevention tools that we have now, personal protection are the major ones, and of course awareness of tick-infested areas and avoidance of those areas, wearing the proper clothing, insecticides, tick checks for early detection and removal of ticks. We

promulgate these, but without ever having had really solid data in hand that they are making an impact on the prevention.

Early detection of Lyme disease symptoms and treatment, because we know that this disease in its early stages is easily treated and without sequelae if it's detected very early on.

Prophylaxis of tick bite is a question that's unanswered right now, but there are more people presenting to physicians with questions about tick exposure and tick bite than there are persons presenting to physicians for suspected Lyme disease. So it's a big cost issue.

Tick control measures, we don't really have a way to deal with control of ticks. We can reduce their numbers in very limited areas, but this is a tool that we don't have a very -- we don't have a very strong tool in our tool box for tick reduction.

And then, of course, the question of vaccine. And if there is a highly efficacious and safe vaccine at reasonable cost, it will be an important potential prevention tool for us in public health.

This is just a curve to show you that the

incidence of reported cases of Lyme disease in this country has continued to increase. There were more than 16,000 cases reported last year in highly endemic areas. There's considerable underreporting, and we wouldn't be surprised if there were actually three to five times the number of cases as is registered in the national reporting system occurring each year in the United States.

Most cases present with early disease, erythema migrans or erythema migrans and some other objective manifestation. These people should be easily treated with a very low frequency of occurrence of sequela. About 25 percent of patients present with arthritis or arthritis and neurologic disease, and then a lower percentage of other late-stage manifestation.

The disease, although reported from almost all states, really occurs from indigenous exposure in 20 or so states clustered in the Northeast and mid-Atlantic, upper North Central, and to a much lesser degree in Northern California. There are large areas of the country, including the Southern United States, the Great Plains, and the Western United States, that the risk is either very small and never has there been a

confirmed case, or there is no risk and these cases being reported are either misdiagnosis, misclassification, or people who have been exposed elsewhere.

So if we look at the states that have rates greater than the national average of about 6 per 100,000 this past year, eight states account for 90 percent of all cases, with rates highest in Connecticut of about 100 per 100,000.

And if we look at the distribution by counties -- this is just the rates without any qualifications to them -- you can see that cases are reported from throughout the United States, but the really hot areas, of course, are in the Northeast, the upper North Central, Wisconsin and Minnesota, and to a much lesser degree in northern coastal California.

These reports of cases here, as I say, there has never been a confirmed human case of Lyme disease from indigenous exposure in the Southern United States or in the Great Plains or Rocky Mountain areas. There is a potential for exposure to infected ticks in this area, but the risk is very small because of environmental consideration. And again, if you hone down on the

areas where more than 90 percent of cases of Lyme disease reported in the United States occur, in the Northeast and upper North Central you would see it's rather limited.

If you look at a map of the country in which you exclude all counties that have rates less than the mean of 5 per 100,000 and exclude all counties that have had only five or fewer cases reported, you're just left with these areas that are really targeted as high-risk counties; and again showing the regional, those high risk counties. So there's only about 90 counties that account for 90 percent of cases of reported Lyme disease in the United States.

It's a tick-borne disease, and so it's driven by the biology. And we know that the exposure to infected ticks is most intense here and here, to a much lesser degree here (indicating). Although there are infected ticks of the species that can transmit to humans here, they don't readily feed on humans in the Southern United States. They have very low infection rates of the ecology, and as I say, we've never confirmed a human case of Lyme disease from exposure in the Southern United States.

One other important aspect of targeting has to do with age. This is a bimodally incidental disease in humans. There's no gender difference, but by age there's peaking in the early childhood, with the highest rates in the age group five through nine years, and then a drop off in late adolescence and early adulthood, and then it peaks again in the mid-years of life.

Some of the considerations about the vaccine use, we know that there's going to be a big consumer-driven demand for this vaccine. Of course, it will be promotion by the manufacturers as well. But this was a disease that people lined up to participate in the vaccine trials, and some had to be turned away.

It's going to be a vaccine in which its use is going to be based on personal decision-making, probably by the head of the household and whether or not he or she thinks that themselves and their children are at risk and should be immunized.

There are HMO and third-party payer considerations having to use as the potential distribution of vaccine. Certainly patient advocacy considerations, because Lyme disease patient advocacy groups are very active in

patient education and providing recommendations on prevention. There also is important political considerations, because some counties have such a concern about Lyme disease that they have had considerable political persuasion.

And then, of course, what is the public health response going to be? The ACIP recommendations, practice guidelines from professional societies like the American College of Physicians, et cetera, are going to be important.

One last slide talking just about some controversial aspects. The methods of action, as I said, it's both humoral response as well as a response against the organism in the tick. However, because of the way the organism selectively expresses OspA, there's no booster of immunity on repeated exposure to infected ticks because the parasite coming out of infected ticks does not express OspA.

Is there a risk for subclinical infection? And in particular is there a risk that there may be persisting infection that's not manifest by symptoms, and so people would not be treated and develop late-stage disease without awareness of their infection?

We don't know what the duration of protection is. We know that the humoral immune response is rather affinescent [phonetic]. We are concerned that immunizing is going to confound the serodiagnosis. It certainly will confound the serodiagnosis using the ELISA or IFA procedures that are the first test in the two-step procedure recommended at Dearborn.

Will it increase complacency for tick exposures? Not only do we have a concern about Lyme disease, but we have concern about other diseases that these ticks transmit, like ehrlichiosis [phonetic], babesiosis, perhaps Powassan virus. And, of course, there are other ticks that people don't recognize as deer ticks that transmit things like Rocky Mountain spotted fever, tularemia, et cetera.

Will it result in reduced government-funded research if there is a vaccine that's considered to be efficacious? And most particularly, what are the cost benefits and what is the cost effectiveness when this vaccine is applied either for individual use or community intervention?

Thank you.

DR. DAVIS: Thanks, Dave. That was a very nice

summary, certainly framing some of the issues, and that's a nice segue into the next part of the discussion.

This is Martin Meltzer from NCID, who will provide a cost and benefit model.

DR. MELTZER: Good afternoon.

In evaluating the economics of Lyme disease vaccines, there's a couple of decisions I had to make early on. One was the methodology, and I chose using a decision tree approach -- which I'll elaborate on a little later on -- for the simple reason that I wanted to answer the question, is it worthwhile to vaccinate -- a vaccinate yes/vaccinate no type of approach. And a decision tree allows you to do that very simply.

Second of all, as you look at the results and as we go through the discussion of the methodology and the results from that, we had to make several assumptions about many variables in the decision tree. David went through a list of the unknowns, the data points that we're not fully sure of. And so what we really have at this stage is a series of sensitivity analysis as opposed to a definitive answer.

The approach I took in terms of timeline, the data

that you're about to see is a one-year timeline. Essentially I've assumed that people will need a yearly booster dose of the vaccine, so what we have is an annual threshold dollar value for vaccination.

That doesn't mean to say that all costs and benefits are valued just for one year. There are some of the long-term sequelae that I valued over up to 15 years -- that is, if you fail to get vaccinated in a given year, you may end up with a case of Lyme disease that will result in sequelae lasting up to 15 years.

Some further details: The perspective. The perspective I've taken here is what are the costs and benefits of vaccinating an individual from society's point of view? In other words, does it pay for society to vaccinate a given individual under a set of given scenarios?

For Lyme disease itself, I've assumed just four outcomes. The first is case resolved. Essentially you go to the doctor; you're correctly diagnosed with a case of Lyme disease; you're treated, and that treatment is successful.

There are then three categories -- rather than actual outcomes, that would probably be a more correct

technical way to look at these -- one is that you have sequela that you can classify as cardiac. The others are neurological and arthritic. There are, of course, in long terms of sequelae for Lyme disease, many more conditions. Cardiac doesn't cover all the problems related with cardiac problems.

The reason that I have not broken down the long-term sequelae into a more thorough explanation and detailing out is that we lack a lot of data, particularly on the cost of these sequelae. In other words, I can't go into the category labeled cardiac and list five or six different conditions that are cardiac-like because of long-term sequelae Lyme disease and attach costs to treating that. There are no data on those. So I was limited at this time of the analysis to just having three categories.

Here is the decision tree. Essentially you start off with vaccinate yes/vaccinate no. In either case you can still get Lyme disease. If you get Lyme disease there is no outcome in terms of medical or clinical outcome, of course.

If you do get Lyme disease, you then have to answer the probabilities. What are your probabilities

of getting diagnosed early, correctly, and having successful treatment? And if you are treated, what is then the probability of that treatment being successful? Or if it fails, what is the probability then of getting one of the long-term sequelae, one of the three categories that I mentioned earlier?

The crux of the economic evaluation is as follows: Recall at this stage I have no idea what the cost of the vaccine will be. The vaccine is, of course, in phase three trials. The manufacturers have not gone to licensure. So I cannot put in the model any real dollar value of the cost of vaccination. And any cost that I put in would be speculative, at best, and always open to argument.

I thought it also at this particular stage more useful, especially from a public health perspective, to look at the threshold cost of vaccination. The model generates values of each arm, whether you vaccinate or don't vaccinate, and I compare those and I consider the threshold value for vaccination.

The threshold basically tells you that amount above which -- the dollar amount above which it is not worthwhile vaccinating in economic terms, the costs of

vaccination are greater than the benefits, the cost savings. Below that threshold it is obviously that the benefits are greater than the cost of vaccination, and from an economic point of view you would be well advised to vaccinate. At the threshold the cost and the benefits are exactly equal.

Note that I say the term "vaccination costs." This is not just the cost of the vaccine in the ampule. This is the cost of the vaccine, administration of that vaccine, travel to an from the site of vaccination, any lost productivity associated with time off taken to travel to and fro from the site of vaccination, and any treatment of adverse side effects.

We had some discussion just before lunch from the two representatives of the drug companies regarding side effects, and that was very interesting.

In terms of cost of sequelae -- and I have to say that I think this is perhaps the weakest part of the dataset that we have, when we consider the economics of Lyme disease -- what does it cost to treat a case of Lyme disease, particularly when patients go into the long-term sequelae?

There is one study that I'm aware of in the

literature that considers it -- Magid, et al. -- and that's a very, very small database. I think the authors in that paper readily acknowledge that. And all that paper covered was one year's cost of treating patients in the three groups, cardiac, neurologic, and arthritic, and the cost of having a case resolved.

We considered that particularly in a case of neurologic and arthritic, the long-term consequences are in fact are going to last far longer than a year. And we took the cost found by Magid and extrapolated another 15 years, and then discounted those costs back at a rate of 3 percent, which is the rate you use when discounting costs of the societal perspective.

Getting on to results, in the model the costs here are for one year. Here's the timeline that we consider for each particular outcome. Lyme disease, for example, cases of two to three weeks, probably be closer to the three weeks. The total cost in the model there for a case resolved is $161.

In the case of arthritic, Magid, et al. published a figure of just about $2,250, just under, for one year's treatment. We felt that to consider that many cases that treating the long term sequelae that are

labeled arthritic from Lyme disease is going to take longer than one year. And we put 15 years, took that $2,228, ran it over 15 years, and then discounted it back to the initial year. The same thing for neurological. Most cardiac conditions, I am told, are resolved within a year or less.

The results: The first scenario that I ran, I considered a couple of elements here. One is the probability of getting Lyme disease. Here I have three probabilities, 0.5 percent, 1 percent, and 3 percent. On the X axis I'm considering here the effectiveness of vaccination, of the vaccine, and we had some data on that before lunch.

And what I have here is the impact at different probabilities of Lyme disease over the range of the effectiveness that I've considered, and the red line is the base case cost of sequelae, which is essentially these figures that I've put on just now.

And then I also considered, and I said, well, given the database and the costs of sequelae and how uncertain it is, what would be the impact of taking the costs of sequelae and multiplying them by 1.5 or by 0.5? In other words, 50 percent plus or minus 50

percent, to give me a very wide range.

There are two points that I'd like to address here. One is note how the threshold costs -- this red line -- increased with the probability of getting Lyme disease. Intuitively, I think this is obvious. One would expect the benefits of vaccination to increase, the higher the risk of getting Lyme disease.

Also note that as the probability of Lyme disease increases, so does the importance of understanding the cost of the sequelae. The difference, the distance between the base case and either plus 50 percent or minus 50 percent, increases as you increase the probability of getting Lyme disease.

The interesting point of this graph is the relatively flat lines that you get as you increase the effectiveness of the vaccine in the model. In other words, relative to the probability of Lyme disease, in terms of economics, the effectiveness of the vaccine is not as important as the probability of contracting Lyme disease.

The Y axis is the threshold. Take the red line, that is the threshold. Anytime the cost of vaccination is below the red line, you would say that it is cost

beneficial to be vaccinated against Lyme disease. Anytime that the cost of vaccination is above the red line, you would say that the economics do not justify the cost of vaccination.

Remember, I said economics. There are other considerations at any given time as to why you would use a vaccine. But in terms of that, you would say that it costs more to vaccinate than the savings you generate from the cases of Lyme disease that you would avert from using the vaccine. So it's a threshold value.

For example, just say your probability of Lyme disease is 1 percent; the effectiveness of the vaccine is 80 percent. The threshold cost is around $75. Anytime the cost of vaccination on a yearly basis is more than $75, under those conditions, you would say that it is uneconomic to vaccinate.

Again I emphasize, it doesn't mean to say you don't vaccinate. Just understand that you cannot justify it purely on economic grounds.

DR. SNIDER: What's the probability of time period? That's accumulative probability over what period of time?

DR. MELTZER: One year. This is all in the one-year time frame. Every year, because at this stage we have no data on how frequently you're required to have a booster shot, and we have assumed at this stage that every year you have to go through the same decision process as to whether to vaccinate or not to vaccinate.

DR. ORENSTEIN: Can I just ask what that means in terms of dollars? The cost of vaccination is the cost of vaccine, cost of administration, essentially time off to go for an appointment. In terms of the numbers there, your example of $25, it looks like, on the .005 thing at 70 percent efficacy, what is that $25? Is that just vaccine cost?

DR. MELTZER: No. As we mentioned, the cost of vaccination, all those elements that you outlined there -- the cost of the vaccine, the cost of administration, the cost of going to the doctor or wherever you get to the site of the vac, any lost productivity, and the cost of treating any adverse side effects.

DR. DAVIS: Are you basing this on a three-dose series, or on a two-dose series, or --

DR. MELTZER: It's just the cost of vaccination.

FDA might license this vaccine and require -- I don't know, it doesn't matter -- a certain number of doses to be given.

DR. DAVIS: Okay. So my question had to do with the total cost of the vaccination, so this is -- and that's what --

DR. MELTZER: It's a whole series, because I have no data as to what, (a) either what the cost of the vaccine will be; and (b), I think we heard some data this morning about how many booster shots -- how many shots were given. But what the FDA will license is obviously a point that's still to be discussed between FDA and the manufacturers.

Then there's one other part that really bothered me as I did the analysis, and I decided to look at this using Monte-Carlo analysis, which uses probabilities and the distribution of probabilities. And what I was after here was what might be very important in terms of economics, it's the probability of getting the sequelae.

Because some of the sequelae obviously generate a lot of cost, and it might be well worthwhile vaccinating to protect those very small percentage of

people that then go on to long term sequela if the costs and the probabilities together give a very high probability of a lot of money being spent.

So what I have here is a graph that considers three different levels of cost of sequelae, three probabilities of getting Lyme disease. And the red line and the dotted lines then consider distributions of the probabilities of getting those long-term sequelae.

Let me just zoom in on what the maximum and minimum. The minimum cost, risk and cost, assumes a 0.5 percent chance of getting Lyme disease, and assuming that the costs of treating the sequelae is only half of those figures that I originally put up. The maximum risk and cost is assuming that the risk of getting Lyme disease is 3 percent, and that the cost of treating sequelae is one and a half times the cost that I originally put up.

There are two points to note. First is that as the risk of getting Lyme disease increases, we notice again that the impact on the threshold of getting sequelae, the cost of the -- the probability of sequelae becomes more important. The distance between

the media, the red lines and the dotted lines, increase. We also noticed that regardless of if you're talking minimum scenario or maximum scenario, the lines, the thresholds, decline as you increase the probability of correctly diagnosing and treating Lyme disease.

What we have in this graph here is two technologies. One is the vaccine, represented by the threshold cost of vaccination on the Y axis; the other is the technology of correctly diagnosing and treating Lyme disease in the early stages. What this graph says is that there is still some economic value, even when you have a vaccine, of the concern at correctly diagnosing and treating Lyme disease in an early stage.

Just wrapping up here, public health implications from the study, I think that there is enormous costs and benefits, specifically on the economic side, in targeting the use of the vaccine by risk of getting Lyme disease.

There's clearly a large difference -- if you look at the two Y axes -- between the minimum risk and the maximum risk. One side we're dealing at the less than $50 range as a threshold, and when you turn up to the

maximum costs and the maximum risks you're over the $300 mark, getting close, in fact, to the $450 in certain scenarios.

That last graph also clearly demonstrated, I think, the value of continuing to work on improving the correct diagnosis and treatment of early cases of Lyme disease. I think no matter even if there is a technology to prevent Lyme disease, no vaccine is ever going to be 100 percent effective in all age groups. That was shown this morning. Therefore, there's still some need for correct diagnosis and treatment, and that does pay off in improving that.

The second set of conclusions is that in terms of economics we can rank some of the variables that went into the model in terms of their impact on that threshold of vaccination. First is the number one impact in this model is definitely the probability of Lyme disease. As your probability of Lyme disease goes up, so does the value, the economic incentive, to use the vaccine.

The cost of sequelae and the accuracy of correct diagnosis of early Lyme disease are what I consider a second tier of importance in terms of variables driving

the results. The effectiveness of the vaccine, at least within the ranges that I studied, and the probability of sequelae are less important than the other two variables already mentioned.

I do want to emphasize here that in all my studies and all the numbers and graphs that I've shown, I have made no consideration of intangible benefits that might be associated with vaccination. Fear and loathing had definitely a value in society. What I have is research imperatives, the way to get -- the lawyers call it pain and suffering.

And economics -- and we have a study underway of the willingness to pay for vaccine. We have a study that's just been completed and is on my desk awaiting results. We've asked 1,000 people in an area where Lyme disease is endemic, how much would you be willing to pay for Lyme disease vaccine, assuming it has a given percentage of effectiveness? And we varied the levels that they were offered, and the dollars amount that they were offered if they would be willing to pay, and also the varied levels of effectiveness of the vaccine. These results will be analyzed and published hopefully within the year.

I do want to emphasize, particularly to this panel, that just because somebody says they are willing to pay, say, $150 a year for a Lyme disease vaccine, do not interpret it to mean that they will actually pay $150. There is a valuation, and it's very, very important, but there is always a difference when you come up and expect them to pay.

And for this particular methodology, I would say the economics is not fully reconciled, and my feeling on methodology as to how to make sure that what people state they're willing to pay in value is actually what they are willing to pay. But it does give some valuation, and this valuation would be in some sense additional to what the costs and benefits in purely financial terms would be.

Second of all, the cost of sequelae is clearly an area, from my point of view as an economist, that we need a lot of work on. And we have got a couple of studies going on where we are trying to address this. And there is some proposals due for additional funding, and we're hoping that some of those proposals that will come will include segments addressing the costs of Lyme disease and its treatment.

The model at the moment -- and I do emphasize that I'm fully aware that it is rather simple -- the one value of simplicity is it makes recalculating as more data becomes available or as hypotheses are generated to recalculate and test the results.

That is all.

DR. DAVIS: Great. Thanks very much. That was a very creative analysis, given the fact that there's no specific cost of the vaccine and the cost of immunizing against this disease, and is a very interesting approach. I appreciate your putting that together and presenting it to us.

Chinh Le, and then Dave Fleming.

And also, I know we haven't had an open discussion for the manufacturers as well, so if you have questions for the previous presenters that's open as well.

DR. LE: I have a question about the vaccine, and I have a comment about the cost analysis.

Practicing in an area of relatively low risk for disease, for Lyme disease, which is in Northern California, but a tremendous amount of anxiety about the disease, I think I have a different perspective about the cost analysis.

First about the vaccine. We know that there's quite a bit of heterogenicity of different Borrelia strains even within California, other places. And I wonder whether the vaccine by the two manufacturers here have been tested to cover the multitude of strains that are in the U.S. or in Europe?

I think that has quite a bit of impact, if somebody gets immunized with a strain selected in Connecticut and she goes to California, that that vaccine will be protective or not. I don't know whether you would be able to do any field study within California because the incidence of the disease is so low, and I wonder whether you have animal data showing that the vaccine is protective against various strain of Borrelia?

DR. DAVIS: Any response to that?

DR. MELTZER: I can address it from the economics models. One can make two basic hypotheses straight off, I think.

One is that there is no effect, even though they're not homogeneous, the stains are not exactly homogeneous from coast to coast, in which case the results of the model would be exactly applicable. The

other is that one might suggest that one strain makes, because of differences in strain, the vaccine is less effective against, say, the strains on the West Coast than on the East Coast.

Again, though, I note within the range of efficacy of the vaccine that I studied, the difference in terms of economics is not so great. The technical basis for the vaccine and heterogeneity are.

DR. DAVIS: Howard Six.

DR. SIX: We did look at that, and all of the Borrelia strains that have been isolated in the United States with maybe one or two exceptions, but essentially all fall into a class called B-31, which is a family.

Both we, and I think SmithKline, are using representatives of that family. The OspA is from a prototype of that family. The best data that we can give you is that if we assume that in the efficacy trial people were challenged with whatever strains were in nature, and so we're measuring protection against those.

Better data is from dogs. We have vaccinated with a single OspA molecule coming from the B-31 family, and

then challenged with ticks that have come from the wild. In those challenged studies we used 12 to 14 ticks. Seventy-five percent of them were carrying Borrelia which came from the wild.

We didn't do the heterogeneity assays for all of the strains that we could get from the ticks, but in those challenge studies and in the dog model initial challenges are 100 percent protective. And if you go out for a substantial period of time, they are still above 95 percent efficacy. Each dog was challenged with eight or nine wild-type strains of Borrelia, so we think that the coverage is there.

DR. DAVIS: Thank you, Howard.

Dan, did you have any -- or Dr. Parenti?

DR. PARENTI: I was just going to say that we agree. We have similar pre-clinical data. And I think it's well known that in the U.S., in the North American strains, if you do sequence homology using OspA there is more than 99.5 percent conservation of the OspA.

DR. DAVIS: Thank you very much.

Dave Fleming and then -- did you have a thought just on the tail end of that question?

DR. LE: Well, I want to make comments about the

cost analysis.

DR. DAVIS: Okay, do that. And then Dave Fleming, and then Marie Griffin.

DR. LE: I just want to ask whether your cost analysis was done on what the actual cost for recommended regimen of treatment.

For example, amoxicycline [phonetic], 21 days cost so much; cefuroxime [phonetic], 21 days cost so much. And that into it, assuming you're making a cost analysis on a recommended regimen of therapy, or you're making cost analysis on what's really happening in the community.

Because I can tell you, in the community the treatment is all over the place. People treat with tremendous amount of antibiotics, all kinds of stuff. It is absolutely crazy out there in terms of cost analysis.

The second thing is the efficacy of the vaccine. This is a very funny disease, as you know, with Lyme disease, because of the psychology and anxiety behind it. And there is a scientific efficacy, which is whatever you prove in your study, 90 percent, 100 percent or whatever, and perhaps a perceived efficacy

by the client eventually versus -- for example, if you got a vaccine and still get febrile illness from ankylosis [phonetic] and so on, and blame the vaccine for being not effective.

And if this vaccine is consumer-driven, you should be aware of the population that you're aiming at. It's an extremely difficult population to deal with. And especially when Lyme disease -- perhaps some of [inaudible] Lyme disease may be immunologic, autoimmune, whatever, arthritis or whatever, it could be autoimmune, whether the vaccine itself will be blamed later for any kind of aches and pain down the road.

I think those are very, very big potholes that I foresee. I would love to see a good vaccine, no question about it. But I think this is the most difficult vaccine to evaluate because of the psychology of the disease that we're dealing with.

DR. DAVIS: Thanks.

DR. MELTZER: First, I'll reply to your first question. The cost of treating Lyme disease is basically modeled on the recommended doxycycline for three weeks.

You are quite right, however, that there is a great deal of differentiation amongst practitioners and patients as to how long Lyme disease is treated. We're hoping that when we collect this dataset for both a retrospective and a prospective study that we'll get a better idea of how wide that range is.

Second of all, in terms of what people expect a vaccine to do, and are they getting a vaccine just for Lyme disease or do they think they're getting a vaccine that will protect them against all infectious diseases that could be transmitted by all tick bites, that's where you get the sort of willingness to pay.

And I would very carefully state that the methodology that we have employed will not be able to tease out that point, because I'm not so sure that we could even begin to get that kind of data without educating the public to a lot larger extent that we are able to in a telephone conversation, as to what exactly the current vaccine -- essentially, they gave us a value for Lyme disease vaccine.

Whether they were valuing all these things that you mentioned, and whether they took into consideration that they might get another tick-borne disease that

they would still blame on the vaccine, is an unknown question. I think that's a very difficult task to get a handle on at this moment.

DR. DAVIS: I think we'll get on to these other two questions. Dave Fleming, and then Marie Griffin, and then we'll need to cut the discussion.

DR. FLEMING: I just wanted to confirm that in your low incidence estimate you were using as a figure 5 per 1,000?

DR. MELTZER: 0.5 percent, which is -- yeah.

DR. FLEMING: In most states in this country that would be hundreds to thousands of times greater than any conceivable cohort that you could construct in most states. And so I guess I would encourage you to, when you present these estimates, also present an estimate of incidence that would be achievable in most states.

I think the point that needs to be made is that the vaccine is likely to be very cost ineffective in most places in this country, and to see that graphically with incidences, that reflect incidences that we could construct in most states, would be helpful.

DR. MELTZER: You are absolutely right. David's

presentation at the beginning clearly delineated that there were very small portions of the country where the average, county-wide average, anywhere begin to get close to even 1 percent, the rest 3 percent.

There is the point I wanted to make, though, that certain individuals in any given community are much likely at a very higher risk than the average. For example, foresters, people who go on routine camping trips, or have very large lawns that are routinely infested with deer carrying the tick.

DR. DENNIS: That range, 0.5 to 3 percent, that's based on special studies in very high-risk communities. We don't know of any community that would have a higher risk than 3 percent per year. There may be Shelter Island or something that would have 4 or 5 percent per year. So those are very specific high-risk communities.

DR. FLEMING: So maybe we could come up with different words for that low-end estimate --

DR. MELTZER: Right. The point there is clearly that even at 0.5 percent many communities are nowhere even approaching that. And if you look at the figures, the threshold is getting pretty low anyway; and the

implications, I think, are obvious.

DR. DAVIS: Thank you.

Last question from Marie Griffin.

DR. GRIFFIN: You estimated a one-year efficacy. How is it going to change if it's effective for five years?

DR. MELTZER: There you will introduce, spread out the cost, essentially, and the benefits. And I'd have to go in and recalculate the distribution of the time, of the cost and the benefits, and then discount back for that. And that would change the threshold levels.

But I'd also want to say that I'm not saying it's one-year efficacious. I'm just saying that the requirement might be that we've assumed a booster every year. I don't think it's exactly synonymous saying that it's not efficacious for more than one year. I have not seen any data of the degradations of levels of antibodies in human models over time to really get an idea of what the vaccine would do due to vaccinations. So much would depend, of course, on FDA licensure, what that is.

But if you do have a longer term, I'd have to go into the model and recalculate and basically string out

the cost and the benefits over the time. So the cost might be up front, but you won't need to be vaccinated. It is a reasonable question and a reasonable hypothesis, and fairly easy to do.

DR. SNIDER: Just for clarification, then, on that point --

UNIDENTIFIED: [Inaudible], whether it was used on a yearly basis for that 15 years or not.

DR. MELTZER: No, the thresholds would change, actually, because the cost of both arms would change over time if you do that. Less effective, of course, would be the [inaudible] vaccine, but the threshold would change a little bit.

DR. SNIDER: But in terms of what you did in your analysis, did you assume that people were vaccinated each year, and you included in your vaccination cost the cost of vaccinating each year?

DR. MELTZER: No. This is just a year by year. Every year you have to go through essentially the same analysis -- what are your risks of Lyme disease, what are the cost of treating sequelae, and all those items.

It's a year-by-year analysis, with the downside

being that if you did not get vaccinated and you got one of the long-term sequela, you contracted Lyme disease and you ended up with a long-term sequela, you would end up with up to 15 years of costs treating some of those sequelae.

DR. DAVIS: John Modlin had a comment, too.

DR. MODLIN: Just a very quick comment. We didn't see any age-specific data incidence data on Lyme, only total incidence data. My understanding is that this is a disease that peaks in the school-age population, for children. Is that not the case, that it's sort of the 5 to 9, 5 to 15 year age group that has the highest incidence?

And if that's the case, quite frankly, we're now well into phase three trials with the vaccine. It's an inactivated vaccine and should be very safe to use in kids, and it would be easy enough to know. It doesn't make a lot of sense to me, quite frankly, to be getting this far along without testing the vaccine in the age groups that have the highest incidence of the disease.

DR. MELTZER: That's a point I want to iterate. From the point of view of the modeling, when I was looking at the risks of getting long-term sequelae, I

used the expert opinion on the risk for 18 years and older for most of those evaluations, those two age groups, because I have no knowledge of what the effect of this vaccine and all the other parameters with people under 18. I had to take the risks --

DR. DAVIS: It certainly will be very important to introduce this vaccine into a pediatric population and be able to evaluate it.

Yes, Carolyn?

DR. HARDEGREE: This issue of going into younger children has been brought to the Vaccine and Related Products Advisory Committee at least on two occasions, and they have wanted to see some safety data in the adult population in a larger number of subjects and see some of the efficacy data before this was extended into the lower age groups. This has been discussed a couple of times.

DR. DAVIS: Thank you.

DR. SIX: They specifically asked for two years of follow-up, 24 months of follow-up of the vaccinees for safety data before we went down in age. That primarily drove the efficacy trials to be two-year trials.

DR. DAVIS: Thank you. That was Howard Six.

UNIDENTIFIED: That was Howard Six, who said they are looking for two years of safety data before moving into the younger age groups, for the record.

DR. DAVIS: All right, I think we ought to close.

Thanks very much, Martin and Dr. Parenti and Dr. Dennis, Dr. Zahradnik, Dr. Six.

And we'll move onto the next topic, which will be Respiratory Syncytial Virus IVIG. There are new preparations of RSV-IVIG. And Dr. Larry Anderson from CID will introduce this topic, and then you can proceed with introductions of Mr. Top as well.

DR. ANDERSON: What we will do, and hopefully do it fairly quickly since it's getting later on in the afternoon, is to first -- the purpose really is to put before the ACIP the idea of developing recommendations, and then briefly outline some draft recommendations that are really just a starting point. Hopefully what will be accomplished is that the ACIP will agree to move forward, initiate a working group that we would then work with in developing more refined recommendations.

I'll give a brief overview. Dr. Frank Top from

MedImmune, Inc. will give efficacy data and status of IVIG and some information on new products that conceivably may become available, and Linda Han from my group will give a very brief outline in what we've done in developing a starting point for proposed recommendations.

Respiratory syncytial virus occurs as outbreaks every year in temperate climates, in the winter and spring primarily, with the peak incidence of disease incurring in 1- to 11-month infants. In this particular slide the yellow is RSV isolates in the United States over time. And notice the marked increase around January to February every year, and with that an associated increase in lower respiratory tract mortality in infants 1 to 11 months of age.

If you look at hospitalization, which is the prime measure of RSV illness or severe illness that we will be looking at in efficacy data, the most common risk factor of severe disease is young age, with the 1 to 6 month being the prime target for hospitalization for RSV disease.

In this you're looking at bronchiolitis, which is kind of the classic disease associated with RSV

infection. It also can cause pneumonia, and most commonly causes an upper respiratory tract infection, though in primary infection approximately 20 to 40 percent of infants will have physical exam evidence of lower respiratory tract involvement. It also can be involved in otitis media, and in the very young infant a more atypical presentation of apnea.

In addition to causing disease in infant and young child, more recently we've also appreciated that RSV can be a significant contributor to lower respiratory tract illness during RSV season. And this is a study done in collaboration with bacterial diseases groups here at CDC, and a group in Ohio looking at community-acquired lower respiratory tract illness. And based on serologic evidence, about 4 1/2 percent were noted to be infected.

However, both in the infant and young child and in the adult, there are certain groups that are particularly at risk. Children with underlying respiratory or pulmonary disease, cardiac disease, or immunosuppressed status, or premature were at increased risk. In the adult population a group that has recently been noted to have a very high risk, at least

in some settings, is severely immunosuppressed, such as the bone marrow transplant patient.

Now RSV has been long noted to be a major cause, probably the single most important cause, of serious lower respiratory tract disease in infants and children worldwide, and this just summarizes some data the Institute of Medicine published in 1985 showing rates of hospitalization under five, estimated at 90,000 a year, hospitalization or medical costs of $300,000, and estimated deaths of 4,500. This gives some baseline, and then global figures as well.

The RSV-IVIG was licensed in January of this year, and the American Academy of Pediatrics developed a really very good set of recommendations that were published in April 1997. And the document that we've put together, the recommendations, are based really on the very excellent work that they did.

Despite that, I think it's also worthwhile for the ACIP to develop recommendations in addition. Certainly RSV is a major pathogen in patient groups not covered by AAP in the recommendations. And that's really more in line with thinking of possibility of new preparations becoming available with monoclonal

antibodies and the possibility that it might be used in older children, particularly the adults, possibly the immunosuppressed patients, such that I think it's well worth the ACIP to begin moving into this area.

In addition, I think the ACIP can provide some guidance in thinking about studies that might be helpful in proving and refining recommendations for Respigam or other RSV-IVIG products. And finally, I think it's traditionally been a role of the ACIP to look at this type of biological product.

I'll stop here and turn it over to Dr. Top.

DR. TOP: Thank you very much, Larry.

My purpose today is to tell you a little bit of the data behind the basis for the FDA's approval of RSV-IG for prophylaxis of children with bronchopulmonary dysplasia and prematurity; and then secondly, to update you on a second-generation program we have in terms of RSV monoclonal antibody that may also have implications on use in prevention in some of the risk groups that Larry was talking about.

The idea that antibody might protect against RSV infection was championed by Val Hemming and Greg Prince in a series of experiments in cotton rats. These

experiments showed that antibody, a neutralizing antibody to RSV, protected against RSV replication in the lungs and in the upper respiratory tract of cotton rats.

These experiments were done by infusing immune globulin at various titers into the animals, drawing sera for antibody titers the next day, challenging the animals with RSV, harvesting the lungs and nasal titers of the animals four days after, and then determining for each animal the antibody titer in this direction here, and the total amount of virus in the lung.

And I think what you can see here is a sharp dose response curve in which pulmonary virus is reduced by 99 percent at a serum RSV titer of approximately 1 to 300 to 1 to 400. The same dose response curve pertains to the nose, but note that the 99 percent protective point is about an order of magnitude greater, approximately 1 to 3,500.

The goal really of the clinical studies was to determine whether an antibody titer somewhere between 1 to 300 and 1 to 400 could lower lower respiratory tract RSV infection. And we would have predicted that would have also resulted in an upper respiratory tract

infection, and basically that's what the clinical studies have shown.

RSV-IG is made by screening donors by microneutralization assay, selecting the top 5 to 10 percent of those donors with RSV neutralizing antibody, plasmapheresing them, pooling their plasma, and then making their immune globulin in a way that is standard and is used for other immune globulins.

There is a viral inactivation step, solvent-detergent viral inactivation method involved in that to remove envelope viruses. The methods used to produce RSV-IG are really the same as licensed methods for our other product, Cytigam [phonetic], and is very similar to other immune globulin products.

This shows the results of comparative laboratory evaluation of 8 lots of RSV-IG with 13 lots of conventional immune globulin by a number of different laboratories, and in neutralization assays Respigam was about six times more potent than IVIG against A strains of RSV virus and approximately four times enriched in terms of neutralizing activities to B strains.

Interesting enough, there did not seem to be any enrichment in this process in terms of ELISA antibody,

either as measured to whole virus or as measured to F- and G-proteins And so the process, the neutralization screening test, seems to select out donors that have antibody with potent biological activity but not just attachment activity.

The next slide shows the comparison of RSV-IG to IG-IVIG in cotton rats, and shows that where at a dose of 0.5 grams per kilo in cotton rats very little protection from background is obtained with immune globulin, more than a two log [phonetic] protection is obtained with IVIG. The comparison of these two indicates that RSV-IG has about ten times the activity, the potency in the cotton rat model, as does conventional IVIG.

In the first clinical study of RSV-IG we studied 250 children with bronchopulmonary dysplasia, congenital heart disease, or prematurity.

One group was randomized to receiving 750 milligrams per kilogram of RSV-IG, which was a dose believed to raise and maintain the serum-neutralizing antibody titer above 1 to 300 throughout the course of the winter respiratory season. A second group got 150 milligrams per kilogram, and this group proved to have

trough titers usually in the 60 to 70 reciprocal range. And then there was a control group.

There was really little statistical or medical benefit from the 150 milligram per kilogram group, and I won't talk about that any further. The group that received 750 milligrams per kilogram had a nearly 60 percent reduction in the incidence of hospitalization due to RSV-IG.

In days of hospitalization per 100 children there were less ICU admissions in the high dose treatment group than in the control group, and less total ICU days in the hospital. In this group itself, two children in the control group required mechanical ventilation as opposed to zero in the treatment group.

In a second pivotal trial to assess the safety and efficacy of RSV-IG, we studied children with bronchopulmonary dysplasia and prematurity. This was a randomized, double-blind placebo control study conducted during the '94-95 RSV season, and it was a multicenter study.

Inclusion criteria included a diagnosis of bronchopulmonary dysplasia or BPD. The children had to be less than 24 months of age. They had to have a

diagnosis of bronchopulmonary dysplasia, and they had to have an oxygen requirement within the last six months before enrollment. We also studied a second group of children who were premature in that their gestational age was less than equal to 35 weeks, and that they were less than six months of age.

We did not study children with immunodeficiency, previous reactions to IVIG, mechanical ventilation at entry, recent RSV, or severe renal impairment.

This cartoon basically shows the design and conduct of the study. First infusions were given to the children between November 15th and December 22nd in 1994.

Children were randomized into one of two groups. One group received 750 milligrams per kilogram of RSV-IG monthly during the course of the season for a total of five infusions. The control group received 1 percent albumin on the same schedule.

The last infusion was April 15th, 1995. We continued to follow the children for another month for efficacy parameters, and for another 30 days thereafter for serious adverse events.

Five hundred and ten children were randomized in

this study. Two hundred sixty of these were in the placebo group, two hundred and fifty in the treatment group. The children came from 54 centers in the United States.

The incidence of RSV infection was reduced from 35 in the placebo group to 20 in the treatment group. This was a reduction of 41 percent. Days of RSV hospitalization per 100 randomized children were reduced from 129 in the placebo group to 60 in the treatment group, for a reduction of 53 percent.

The same was seen for days of increased oxygen need in the hospital, a 60 percent reduction, and the number of days in the hospital in which the investigators judged the child to have moderate or greater RSV, 54 percent.

An additional finding -- and this is a finding that we have consistently observed in the other randomized trials that we have done -- is that the immune globulin itself has an effect not only on RSV infections, but also has some effect on non-RSV disease. So the upshot is that the treatment group had a 38 percent reduction in the total incidence of respiratory hospitalizations.

Sixty-nine children had those in the placebo group as opposed to 41, and a 46 percent reduction in the total days of respiratory hospitalization per 100 children. Seventy-seven percent of the hospitalizations in the control group in this study were indeed for respiratory hospitalizations. And that is important, I think, to consider in cost benefit analyses later on.

The drug proved to be safe and well tolerated in these children with BPD and prematurity. The safety profile was quite similar to other IVIGs. Eight percent of the children, almost all of those children were children with bronchopulmonary dysplasia, received diuretics around the time of the one infusion. That is a high figure, since these children usually have visits at this same time for their BPD diagnosis, and in many cases their doses were adjusted by their physicians for reasons other than AEs.

One to three percent of infusions resulted in significant adverse events. These were largely fever, respiratory distress and allergy. One percent of infusions couldn't be completed due to an adverse event. Permanent discontinuation rate of infusions was

similar, however, in both groups. Generally, the serious adverse events seemed to be fluid related or fever related, and could be controlled by reducing the amount of infusions.

These two randomized control trials served as the basis of licensure of RSV-IG, and for the recommendations that the Committee of Infectious Diseases and Committee of Fetus and Newborn of the American Academy of Pediatrics have recently made.

We have further plans to advance our studies on the prophylaxis of RSV infections to children with congenital heart disease, and also to patients who are immunodeficient, particularly patients with bone marrow transplantations and other things.

However, we have also been working on another way of attempting to prevent RSV disease, and that is instead of using immune globulin, per se, we have been working on an RSV monoclonal antibody directed against a conformational epitope on the F protein, which is conserved across strains.

This particular monoclonal antibody has neutralized all of the A strains and B strains that we have tested over a period now of ten years. And in

preliminary studies in animals, doses that result in serum levels of 25 to 30 micrograms per milliliter have reduced RSV replication in cotton rats by about 99 percent, and all animals with titers -- or rather, concentrations of 40 micrograms per milliliter or greater were protected by at least 99 percent.

We have done quite a few studies of this monoclonal antibody, and just very briefly I will take you through them. This is a randomized, double-blind placebo control-dose escalation trial of the monoclonal antibody in high-risk children with BPD and prematurity, in which we studied three doses in an escalating fashion, 3, 10, and 15 milligrams per kilogram IV monthly, for up to five injections.

Adverse events and serious adverse events were balanced among the 493 groups in this study and the placebo. The one child that died in this study was in the placebo group, and died of disseminated adenoviral infection. We found no clinically significant changes in AST or ALT, BUN or creatinine, CBC or platelet count, or urinalysis after giving the MEDI-493 monoclonal antibody, and there were no significant differences among MEDI-493 groups in any of the

chemical changes.

Monthly IV MEDI-493 infusions of 3, 10, and 15 milligrams per kilogram were safe and well tolerated in this study. The half-life of this drug was between 17 and 23 days, which is right in the ballpark of IVIGs.

Doses of 10 and 15 milligrams per kilogram every 30 days maintained mean levels of 25 to 30 micrograms per mil, and the higher dose maintained greater than 40 micrograms per mil for the majority of patients, and therefore is the dose that we've chosen for further studies.

We found no specific induction of antibodies to the MEDI-493 in these children after giving it IV. We've subsequently completed two other studies of IM use in children, and two studies of IV use in treatment in children. The safety profile has been very good, as it was in this study, and we have run across no examples of immunogenicity.

Consequently, last November we launched a randomized, double-blind placebo-controlled multicenter trial of a 15 milligram per kilogram dose of MEDI-493 versus placebo in 1,500 children in the U.S., Canada, and U.K. This involves 139 centers. Again, the

indication here is for prematurity and for BPD.

This study should be analyzed within the next three months or so, and its outcome will clearly lead us into further directions in terms of cardiac, congenital heart disease patients, and bone marrow patients, depending on its outcome.

Thank you very much.

DR. DAVIS: Thank you, Dr. Top.

Let's have some discussion now on what we've heard.

Larry?

DR. ANDERSON: I think we have one other speaker.

DR. DAVIS: I'm sorry, I didn't see another speaker on the agenda, so I apologize.

DR. HAN: I'd like to just take a few minutes to summarize our proposed recommendations, which are largely based on those published by the American Academy of Pediatrics in 1997.

The Food and Drug Administration has approved the use of RSV-IGIV for prophylaxis against RSV disease in children less than two years of age who were born or at 35 weeks of gestation, or who have bronchopulmonary dysplasia, or BPD.

Approximately 500,000 children in the United States meet these criteria each year. Administration of RSV-IGIV costs approximately $6,000 per child per season, and is associated with considerable practical difficulties.

Ideally, RSV-IGIV prophylaxis would be reserved for specific high-risk groups. Our recommendations, however, apply to general high-risk groups.

In this situation it is important to make individual cost benefit analyses for each patient, taking into account the severity of the patient's underlying condition, the number of risk factors present, and other factors such as the availability of intravenous access sites, patient access to treatment, and the likelihood of patient exposure to RSV.

With that said, I'll now review some proposed recommendations for the use of RSV-IGIV. Recommendations are made for each of several high-risk groups on the basis of RSV morbidity and mortality data which are presented in the table at the end of the document.

These risk groups include children of BPD, children born prematurely, children with congenital

heart disease, and people with compromised immune systems. The document also considers RSV-IGIV use in nosocomial outbreaks, and then makes some additional recommendations regarding timing and duration of prophylaxis and administration of live vaccines.

I'll begin with the recommendations by risk groups. In the next few slides the statements in quotations are taken directly from the proposed recommendations.

Among children with BPD, RSV-IGIV should be considered for those who have required supplemental oxygen within the last three to six months. Recent oxygen requirement has been associated with increased risk of severe RSV disease, probably serving as an indicator of the severity of underlying lung disease. Other factors should also be considered, including the child's overall pulmonary status and clinical condition.

Among children born prematurely, RSV-IGIV should be considered for those born at 28 to 32 weeks of gestational age during the first 6 months of life. Infants with extreme prematurity, less than 28 weeks of gestation, may benefit from RSV-IGIV prophylaxis for

the first 12 months of life. These recommendations are based on the observation that RSV hospitalization rates peak within the first six months of life and increase with decreasing gestational age.

RSV-IGIV has not been shown to be safe or effective in children with congenital heart disease, or CHD, and in fact may even have a deleterious effect among children with cyanotic CHD. Children with cyanotic CHD should not receive RSV-IGIV. Children with acyontic CHD, on the other hand, may benefit from RSV-IGIV if they also have BPD or other risk factors for severe RSV disease.

People with particular forms of severe immune system compromise have a very high risk of death from RSV infection, and theoretically could benefit from prophylactic RSV-IGIV. RSV-associated mortality rates among bone marrow transplant recipients, for example, may exceed 50 percent. However, RSV-IGIV has not been shown to be safe or effective in these patients, and the amounts that would be needed in adults and older children would be expensive and probably difficult to obtain.

In the controlled nosocomial outbreaks, the first

priority is strict compliance with recommended RSV infection control practices. However, during such outbreaks RSV-IGIV may also have a role in preventing disease in hospitalized children who would otherwise meet criteria for prophylaxis -- that is, children who have BPD or who were born prematurely. Considerations for RSV-IGIV use in this setting include the medical condition of the child, the likelihood of infection, and the duration of the child's exposure to RSV.

There remains the question of whether there is a role for the use of RSV-IGIV prophylaxis in outbreak settings in patients with severely compromised immune systems.

Finally, there are several areas that could be explored in the future. Some objectives of potential future studies would be to define the risks of RSV disease among specific subgroups, to estimate the cost of RSV disease in specific risk groups, and to assess the safety and efficacy of RSV-IGIV prophylaxis in additional groups of patients.

There is also going to be the development of some new products, such as monoclonal antibodies for intramuscular administration, which may reduce the

expense and difficulty associated with prophylaxis.

Thank you. Are there any questions?

DR. DAVIS: Thank you very much.

Are there questions for any of the presenters?

Dave Fleming.

DR. FLEMING: Do you at this point have any even crude estimates of what the risk level might be in those groups that you presented, and therefore some crude estimates of cost effectiveness of these recommendations?

DR. HAN: That information is, as best as we could do, summarized on the last page of the recommendations.

It's a fairly comprehensive table with the various risk groups and the various estimates from what studies have been done -- estimates on hospitalization rates, estimates of duration of hospitalization, frequency of ICU admission, duration of ICU admission, et cetera. And what crude cost estimates have been done so far are crude and preliminary, and basically account only for the cost of ICU admission, hospital admission, and mechanical ventilation, which seem to be the three most expensive things.

There is also -- I'm sorry about that. It's the very back page of the kind of thick -- it's on the back of that packet that says draft, on the very last page. It's the last three rows, the third from the bottom. It's mostly just a comparison between the risk groups.

So for instance, among children with BPD, the cost per hospitalization, if you take the hospitalization, the duration of hospitalization times whatever, $500, $700 a day for hospitalization, and then you add in the percentage who are going to require ICU admission and multiply that by $1,700 per day or so, and then add in the mechanical ventilation rate; and then there's some base fee for physician services, pharmacy, radiology, et cetera. It's not a very good estimate, but I think it puts you in the right ballpark.

The next row down is the number -- assuming a 50 percent efficacy of RSV-IGIV -- the number of people who must be treated to avoid a single hospitalization. And that's based on the hospitalization rates that are down there. It's on the second row.

And then you can sort of say, all right, if it takes about $6,000 to prophylax one patient for one

season, then how much would it cost to prophylax all the people that would need to be prophylaxed to prevent one hospitalization. We need to work on those figures.

But it's not going to be cost savings, but the cost effective analysis that has been done so far demonstrates relative cost effectiveness.

DR. DAVIS: Chinh Le?

DR. LE: I'm new on this committee, and maybe you can clarify this for me. Is it the duty of this committee to review and make recommendation on all biological agents which come out?

DR. DAVIS: No.

DR. LE: I don't know what this document adds to what the Academy of Pediatrics has already published. And if staff time, labor, cost is an issue, and we are just kind of spinning exactly the same wheel as the AAP has done, and to be honest with you, with all respect to this committee, when pediatricians come up for advice they look at AAP and they don't look at ACIP.

I'm not sure what is the value of us making a rubber-stamping of the AAP. Unless we have an argument about what the AAP is doing, it's basically rubber --

the AAP does not need to be rubber-stamped anyway. But I don't understand why this really needs to take our time, if it is not a duty that we have to look at all biological agents.

DR. DAVIS: There are licensed biologics that we have no statements for. And Dr. Anderson presented a variety of reasons why he thought the ACIP might consider this. I think in large part --

DR. LE: None of the reasons on that slide strike me as any reasonable reason to spend an amount of time with it.

DR. DAVIS: Maybe Neal and Georges Peter would have something to say here.

DR. PETER: Well, I encouraged Larry Anderson to pursue this question because this committee has made recommendations on the use of immune globulins -- for example, the recommendations for prevention of hepatitis A prior to the introduction of the vaccine.

If indeed the recommendations here are similar to those of the Academy, we feel affirmed. But I think the feeling we had in the Red Book Committee was that this issue is a moving target, and indeed we would gain experience, new products would become available.

And you know as well as I do that RSV is probably the most major infectious diseases for which we've previously not had means of prevention. And I think this committee and the public health sector should be involved, particularly given the costs and the burden of disease.

So even if they do affirm and agree, nevertheless, the involvement to this group, I think, is important.

I don't know if you --

DR. DAVIS: Neal.

DR. HALSEY: Well, I'm not sure I share exactly the same perspective.

I'm delighted that you didn't come up with any dramatic differences. I can tell you that we struggled at great length to get data that would allow us to make the distinctions that we did. We have not endorsed the use of the product for all of the categories for which it is licensed, children above 32 weeks' gestation in particular, and those above 12 months and some above 6 months for prematurity only.

RSV has been a very contentious issue within the pediatric community, especially because of the conflicting data on ribavirin. This was not an easy

statement to develop, I can assure you.

If you were certainly going to use the product at all in adults, then there absolutely would be a definite need for a statement by this committee because the Academy wouldn't issue such a statement. But I would find it pretty impractical to use -- the dose of RSV-IGIV that you would need for adults would be very large, and I didn't hear Dr. Top describe any planned studies in adults, even those there is disease. There's no question it's an important contributing cause of disease, but monoclonals might be a potential role there.

I don't have any strong feelings one way or the other. Chinh Le is right. There's a lot of work involved in developing one of these, and --

DR. LE: I think the AAP did a superb job in putting the confusing -- into helping the pediatricians out there already, it seems like.

DR. HALSEY: But I would add that the one thing that we didn't have which you have done already somewhat, is some of the additional cost effectiveness data, which you have more people who are skilled at that, and that's very helpful to see those.

We struggled with but could not lean upon well-established studies, some conflicting data from those studies that were completed at the time. We finished the development of this statement late in 1996. So cost effectiveness is one area that you have more expertise than we do.

DR. DAVIS: John Modlin.

DR. MODLIN: This is a product, of course, that's come along just at a time when most hospitals are trying desperately to reduce the cost of their formularies. I know that this is a major issue for hospitals that have really borne the brunt of trying to pay for this, because almost all of these infants for whom RSV-IG is indicated for are graduates of intensive care nurseries for the most part, and are still followed in hospital ICU follow-up programs.

So I think the degree to which this committee does have some representation from and does represent some of the interest of hospitals, it may make some sense to keep a close tab on what's going on with this product even if we don't generate our own separate document, our own separate recommendations.

Dr. Top indicated both MedImmune and other

companies are preparing monoclonal antibody preparations. I guess the efficacy of those preparations is yet to be determined. But I think this product represents really the ground floor of the efforts to passively protect these infants against serious RSV infections.

And so even if we don't generate our own statement, I think this is something that the committee is going to require revisiting from time to time. There's no question, as well -- Larry touched upon it -- but I want to emphasize the fact that there is now within the last two or three years a growing awareness of the importance of RSV infections in certain adult populations, and there's no question that there will be additional efforts to try to prevent disease in immunocompromised adults.

DR. SNIDER: I want to clarify for Chinh Le the answer to the question, because Jeff's response was only partial. The answer to your question is that no, as we put down in our draft of policies and procedures, the ACIP is not obliged to issue recommendations.

The other part of the answer, though, is that CDC issues recommendations with advisory committees and

independent of advisory committees, and so because of the nature of this product it seems appropriate to me to bring it before ACIP for consideration to make a determination. And then CDC, the program has an option also of issuing recommendations with, alone or in concert with other PHS agencies or whatever, on this topic.

So those are other options available to the program, so it's important to get a reading from ACIP as to whether it wants to go the route of issuing recommendations so this program can consider whether it wants to not issue recommendations or issue recommendations through another route.

So that's why it's important, I think, to bring it to the table for discussion.

DR. DAVIS: I think we need time to read through the information that we have since it was just presented to us for the first time, and if this is going to be a major commitment of resources I think that the committee members need that time at this point to decide.

Right now we have five committee members here, and there will be others that will need to be working on

it. I don't know how -- I could poll the people that are here right now. I feel personally that I need a little bit more time to consider the relative merits of our doing this, and so I think maybe we should leave it at that.

We're obviously as a committee interested in getting more information, and I think we can use the information we have now to make decisions regarding how we as a committee will proceed.

DR. SNIDER: I don't know how Larry feels, so I'll let him speak for himself. But to my way of thinking, though it might be useful if the committee could reflect for a while, but get some input from everyone as to whether this is worthwhile going forward with prior to October, so that people could start moving along.

What's your sense, Larry?

DR. ANDERSON: Well, I think we brought this up to the ACIP because I think it's a biologic that's important. I agree that AAP has done really a very good job, and it certainly would respect the concept that the AAP document is sufficient.

I think in the long run the ACIP, I think, is

likely going to want to develop some kind of recommendations, because I think at least there will be consideration of use for this product in adults, or variations on this product. And therefore I think at some point in time it will be important to the ACIP, and I thought it was important to bring it up at this point in time.

I'd certainly, obviously, defer to whatever you folks think.

DR. DAVIS: I appreciate all the work that went into the presentation for today. I'll ask the committee members to correspond with us regarding their desires on this, but please review the information that you have. And continue to provide us with information that might be valuable in informing us.

And I would certainly concur that at some critical time we will need to move forward with this. But I do feel individually we need more time as a committee to have all the information read and thought through, and consider the framework of what's already out there.

The next presentation is regarding influenza in children. And we have multiple presenters, Dr. Keiji Fukuda from the influenza branch, Paul Glezen, liaison

to our committee, and Dr. Leighton Read from Aviron.

DR. FUKUDA: In a few minutes Dr. Paul Glezen, who is well known to you, and Dr. Leighton Read from Aviron Corporation are going to be giving two presentations that are related and which have profound implications for the ACIP, and really for the country in general.

Paul is going to be talking about the impact of influenza in kids, and really this is going to lead into the idea of the possibility of recommending general vaccine immunizations for healthy kids for influenza. Dr. Read is going to be talking about a live attenuated vaccine for influenza which may be licensed in the next few years.

And when you take these two things together, really what it is is a lead-in into the idea of recommending universal influenza immunization, which would be an unprecedented venture. And because of that, what I'd like to do is give a little bit of background to put these talks into context.

Now currently ACIP recommendations are targeting at three groups, and really at the first group. Current ACIP recommendations really focus on vaccinating people who are at high risk for

complications, severe complications of influenza. They are also targeted towards people who are likely to transmit influenza to people at high risk, and this includes health care workers and family members. And finally they're targeted towards people who are in socially critical jobs and whose absenteeism in large numbers could really prove crippling for the country.

Now the current licensed vaccine which is used is an inactivated trivalent vaccine, and in general it's been a quite safe product. And since the advent of better manufacturing procedures in the '70s, the incidence of side effects has been low when compared with placebo.

It's clearly an imperfect way of protecting people against influenza; nonetheless, it's been relatively effective clinically. In healthy young adults most studies show that its effectiveness ranges from about 60 to 90 percent. In the nursing home elderly the degree of effectiveness is much lower, around 30 percent.

However, it does protect against the more severe complications of hospitalization and death by about 47 to 95 percent in that group. Clearly this strategy in

that group of people has been shown to be cost effective. Its cost effectiveness in other groups is a little bit more controversial and a little bit less certain.

What we're really entering into now are two major issues which will be facing ACIP over the next year or two. The first issue is whether ACIP should broaden its recommendations for influenza immunization to target healthy infants and children, and related is healthy adults. This is not a topic which will be discussed today, but it's clearly a topic which is related to what will be discussed. The second major issue is what would be the role for a licensed live attenuated trivalent influenza vaccine.

Now vis-a-vis the issue of broader recommendations, there are several issues that the ACIP will have to grapple with. But the first one is what would be the indication for such recommendations, and I think it would be important to clarify whether we would make -- if these recommendations were made -- for the prevention of illness and complications in those people who receive vaccine, or whether it would be to prevent and control epidemics and pandemics on a larger social

level, or whether it would really be done more for reasons of cost benefit, whether one would argue that it would reduce absenteeism in companies.

Although this is not directly the concern of the ACIP, an issue which is particularly germane to broader recommendations is whether current manufacturing capacity meet the demand created by broader recommendations. Both live attenuated vaccine and inactivated vaccine rely upon eggs for production, and so a simple question is simply are there enough eggs to produce that much vaccine?

Another issue which is of concern to us is if broader recommendations could potentially create the situation where recommendations for vaccinating healthy people could divert vaccine supply away from people who are at high risk for complications.

Some of the more difficult issues to think about vis-a-vis universal recommendations have to do with long-term potential consequences. One question which comes up is whether exposing people to annual vaccines from childhood year in and year and year out would somehow alter their immunologic responsiveness in some way which cannot be foreseen.

A second issue has to do with the viruses themselves. The evolution of influenza viruses in large part depends on the prevalence of antibody in populations, and so one question which has come up is whether by inducing high antibody levels in a large population, whether one would somehow alter the evolution of these viruses.

Related to live attenuated influenza vaccine, again there's several issues to come up or to be discussed. But some of the more important ones revolve around potential safety issues. These vaccines have been around now for at least three decades, and in general the safety record on them is excellent. However, it's one thing to study the safety of a vaccine in several thousands of people, and it's another thing to imagine their annual use in a couple hundred million people.

And so some of the issues which come up are whether it would pose any risk to immunocompromised children and adults, or what risk; whether in fact the vaccines are genetically stable enough to use on a year-in, year-out basis, and what the risk is for reassortment of the vaccine virus with wild-type

viruses.

In terms of effectiveness in dosing, some of the issues that ACIP will have to grapple with are what are the relative indications for use of an inactivated vaccine versus the live attenuated vaccine, and then whether interference between the components contained in the vaccine could somehow lessen the effectiveness, and then whether there's any potential for interference with other vaccines and how that would affect dosing schedules.

Anyway, these are some of the issues which come up in thinking about these vaccines, which potentially offer a very exciting new phase in the control of influenza.

And so I'm going to turn the podium over to Paul now, and then he'll be followed by Leighton.

DR. GLEZEN: Thank you, Keiji. Appreciate it.

I appreciate those of you who have stuck around for this, and I hope that we can answer some of the provocative questions that Keiji has given, but also put this in perspective.

There are three perspectives, I think, to think about. One is control of influenza in this country;

two, pandemic preparedness; and three, to think about the global aspects of controlling influenza and how we're going to meet the needs of larger populations.

These are the topics that I suggested for today: Risk of influenza in healthy and high-risk children; improved coverage of high-risk children with current inactivated vaccines; and then the possible indications for a live attenuated virus vaccine in healthy children.

The first part of this presentation will be largely new data which we've generated at Baylor, sponsored by NIAID, and then I'll go onto some aspects of control on epidemic influenza also sponsored by NIAID, as well as all the vaccine studies that we'll talk about.

This just shows the infection rate and illness rate for children in the Houston family study, in our studies from 1976 to 1984, so this is the annual rate. And you can see that the infection rate and illness rate are highest in school-age children, a little lower in children under two, and of course in adults.

So I particularly want to point out that the highest rates year in and year out -- and this annual

rate, you can see the infection rate is almost 50 percent every year, with one of the three prevalent influenza viruses. This sort of data has been replicated in many different sites and in many different years over the last 30 or 40 years.

What I've done here is to summarize a very large amount of data that we've accumulated over the last 20 years in Houston to look at the age-specific risks.

First, the top histogram is P&I mortality; the middle histogram is hospitalizations for acute respiratory disease; and then the lower histogram, age-specific rates for medically attended illness, as we measured in an HMO in Houston. As you all know, P&I mortality, of course, is highest in the elderly. But as you can see, there are appreciable numbers of death in people from 45 to 64, and perhaps some in children under 5.

When we look at hospitalizations, we can immediately see that the risk changed considerably. Again, the highest risk is in persons over 65, but the rates for people under 65 are pretty high, and we see very significant rates in children under 5 years of age. And in some years, depending on the virus that's

circulating, these rates are indeed as high as the rates for the elderly, particularly in years when we have influenza B and H1N1, primarily.

Medically attended illness, of course, the highest in children, preschool and elementary school-age children, and the rates level off in older children and adults.

Now the study that we've done recently was designed to specifically look at the impact of acute viral respiratory infections in high-risk patients. We did this in the setting of a defined population, and we used four large clinics in Houston: Two from the Kelsey Siebolt [phonetic] System -- Pasadena, which serves mainly a blue-collar area, largely HMO patients, and the larger West Clinic, which is a mix of HMO and fee-for-service in a little more affluent area; and then two of the Harris County Hospital District clinics -- Casa de Amigos, that serves an area largely populated by Hispanics, and the Martin Luther King by low-income black populations.

Now this shows the number of patients hospitalized at the hospitals that served these patients in a four-year period from 1991 to 1995. And one of the

points I particularly want to make about this is that, first, most of these are high-risk patients, particularly over five years of age.

The majority of these had underlying chronic conditions. For the younger people it's asthma, and for the older people it's chronic obstructive pulmonary disease, diabetes, hypertension, and coronary artery disease. And this is quite a change from our earlier studies, our earlier surveys of hospitalization during flu epidemics, in that a much higher proportion of patients have underlying conditions.

There may be two or three reasons for this. One is that discharge diagnoses may be more accurate now simply because third-party payers are requiring that diagnosis be more stringent; and the other good possibility is that criteria for admission are much more strict than they were 15 years ago when we did a lot of these surveys, in that patients who are relatively healthy don't have underlying chronic conditions and don't end up in the hospital at all. So that's an important change.

But the one thing that I wanted to point out particularly is that when you look at actual numbers of

patients hospitalized, the elderly constitute a relatively small fraction. Even though their rate of hospitalization is high, when you look at total numbers hospitalized, it's not all that great.

Now Houston contains a relatively young population compared to the United States as a whole. But even if you doubled this number, the elderly would only constitute about a third of high-risk patients hospitalized for acute respiratory conditions.

And then you can see that we were able to attribute an influenza infection to 35 percent of these admissions. RSV, influenza, and parainfluenza were the most important agents that we associated.

Now to get a better look at the etiology, we tried to get paired blood specimens on all of these patients to test, but in this type population it's difficult to get them back for the convalescent blood. So we were only able to get paired bloods on 403 patients, but we were able to test for neutralizing antibody rises to RSV, the prevalent influenza viruses, and the three parainfluenza virus types. In addition, we looked at coronavirus antibodies, and you can see we did find a fair number of those, and most of those are in adults.

Now with this you can see that influenza then becomes the leading virus infection associated with these hospitalizations. And I want you to remember now, we're looking at year round. We're not just looking at epidemic periods. This is year round hospitalization of patients from a defined population.

And it accounts for about 15 percent, at least an influenza infection was associated with 15 percent of all the admissions. RS was close. Parainfluenza, surprisingly, was associated with a large number, and particularly a surprising number of adults.

If we look on down this just a little more, this shows the association of influenza infections by age. So that of the children hospitalized during that period, most of these being high-risk, about 12 percent under 5 had an influenza infection, but 21 percent of children 5 to 17 years of age had an influenza infection.

So I want you to think about that a minute. That's 21 percent of all the children hospitalized over a period of four years, their hospitalizations were associated with an influenza virus infection.

The frequency of virus infection was related to

age in adults, too. And for influenza, again it was about 20 percent of young adults, about 14 percent of middle-aged adults, and about 10 percent of elderly adults, that we could establish an influenza virus infection related to their hospitalization.

So just to recapitulate, I want to emphasize that children under five have high hospitalization rates for acute respiratory conditions during influenza epidemics. And I want to add to that that influenza infections are commonly documented in children hospitalized for conditions other than acute respiratory, so not included in our estimates here are children with encephalitis, myocarditis or pericarditis, myositis, renal failure, or unexplained fever in early infancy. So there are a considerable number of hospitalizations for conditions other than acute respiratory that have to be considered when we think about the risks.

Now as I pointed out, 21 percent of school children hospitalized over a four-year period with acute respiratory conditions have influenza virus infection. Three-fourths of these children have asthma, a condition with increasing hospitalization

rates and mortality. So particularly in inner-city populations, it's a matter of great concern that we do something to try to decrease hospitalizations of children with asthma. And I think that better coverage with influenza vaccine would be a step forward in this regard.

Our own sample, we only found about 7 percent of our children had had flu vaccine. We had one vaccine failure. In the survey we just did at Temple it's about the same. And I think that national data would probably show the same results, that our efforts at this time to provide influenza prophylaxis to these high-risk groups is really lacking.

And the other thing that I wanted to emphasize, that two-thirds of all high-risk patients hospitalized with respiratory conditions are less than 65 years of age, so there is a large population under 64 that we need to be thinking about and I don't think are getting vaccine at this time.

Now we have proposed at least a small study to try to remedy this situation. And at the site at Scott & White [phonetic] Clinic in Temple we've written a proposal utilizing their computerized registry. They

were actually the pilot for the Texas computerized registry that they call ISIS.

I don't know how this compares to the systems used in other parts of the country, but from what we heard yesterday the working capabilities of these don't seem to be too great. But anyway, we will use this. It has the ability to generate recall letters, and there's an auto-dial computer connected with this which we can use also to help.

They will perform influenza surveillance to define the influenza epidemics each year, and then they have linked medical records that's linked between the ambulatory and the hospital beds. And we will use that to identify the children with asthma for the program and to determine the morbidity.

So it's the purpose to not only improve the immunization coverage of this group, but we will have the ability to evaluate the effect of this and to look at morbidity both in the ambulatory setting and the hospital in this relatively large pediatric population. There are over 13,000 kids that get care there, and they should be selected to have a high incidence of asthma since it's a tertiary referral center.

Well, now I'd like to move to the more general concepts and put this in the context of pandemic preparedness, et cetera.

As you know, three or four years ago an ION committee published a report on *Emerging Infections: Microbial Threats to Health in the United States.* Influenza is presented in this and mentioned throughout the volume that they published as a report as the prototype emerging infection.

And here's a quote: Influenza vaccines are underused. Only a fraction of those at increased risk of fatal outcome are vaccinated. Influenza thus remains essentially an uncontrolled disease.

And yesterday in our study of varicella, I think they neglected to add influenza to their list of uncontrolled epidemic diseases in the United States that are vaccine preventable. And this is something I think we should work toward remedying.

Dr. Lederberg, who of course was co-chair of that ION committee and editor of that volume, was interview by a science reporter from *The Scientist,* and I picked up this quote because I thought it was particularly pertinent. After they asked him about all the other

esoteric and sort of rare diseases, Dr. Lederberg said:

"My particular nightmare is a revisit of the lethal flu of 1918, which claimed about 500,000 American lives and 25 million worldwide. The biological caldron that churns out our new flu variants is working as ever, and we are especially vulnerable in the unique state of human culture which combines unprecedented human population density, hygienic stratification, and unmitigated travel."

That's quite a quote, but I think it summarizes, I think, the problem that we're facing.

Now maybe in response to that, but certainly pertinent, was the reactivation of a Federal working group on influenza pandemic preparedness. And they've also published a report, *Prevention and Control of Influenza in the United States: Preparing for the Next Pandemic.*

And I'd like to emphasize this -- I don't know whether this was done on purpose or not -- but I think that the best way to demonstrate that we are able to control pandemic influenza is to control epidemic influenza as it occurs here every year in the United States. So I think that ought to be a goal.

I think it's great to write reports and set up procedures and things for these events, but I think unless we have some superstructure and some systems going, it's going to be very difficult to meet this threat.

If you look, for instance, at the effort in 1976, we weren't able to start the immunization program until the middle of October. But most of the pandemics of this century have peaked the last week of October, and we're going to have to be ready to move much more rapidly than that if we're going to have any chance of confronting this sort of a problem.

Now this is pneumonia and influenza mortality in the United States from 121 cities for the period from '93 through '97. So this shows excess mortality for last winter, and I think you can see there's a very large peak and a relatively broad peak with two humps, and the first peak probably represents the H3N2 disease and the second peak the influenza B that followed it.

But that's a lot of mortality, and considering the fact that we distributed about 80 million doses of vaccine last year, I have trouble finding the evidence that we really have accomplished our primary goal,

which is to reduce mortality in the elderly.

One of the reasons for this, I think, we glean from a study that Ann Falsey reported in *Journal of Infectious Diseases* a couple of years ago. This was a study that was connected to the Medicare demonstration project that HCFA sponsored. And this was in Rochester, and they tried to do virus diagnosis for RS and flu in the elderly population that was hospitalized in their hospital.

The thing that I want to point out about this, they documented influenza infection in 210 of about 2,000 patients. This was roughly 10 percent of the patients they studied. And the thing that disturbed me was the fact that 129 of those, or 61 percent, had been vaccinated with the currently available influenza vaccine.

So despite the fact, as Keiji said, we know that the vaccine is effective. It significantly reduces the risk of hospitalization and death. But unfortunately there's still a lot of slippage there, and I have to consider these vaccine failures.

Now this doesn't tell us how frequent vaccine failure is, but if we look at the mortality data for

this year and whatever, considering that we probably have already achieved, I'll bet, the goal for the year 2000 covering 60 percent of the elderly, it doesn't appear that we've been able to greatly reduce the mortality, and there's still an awful lot to go.

So I think that this compels us to start looking at other strategies and things that we might do to reduce this overall risk. And just to capitulate here a little bit, influenza vaccine significantly reduces hospitalizations and deaths in high-risk elderly. And despite the benefits, though, excess mortality is high.

One hundred percent coverage of high-risk patients would not affect epidemic influenza. Chronically ill patients with less than optimal response to the vaccine would still be at risk, as shown by this study of Falsey, et al.

Well, what are some other things that we might consider as an approach to producing some control of epidemic influenza? This is the approach that we suggested, and we would like to try to test. And it's based on the fact that school children have the highest attack rates of influenza, that children are the

spreaders in the community and are the introducers in the household, and that children are accessible for rapid uptake of vaccine.

We don't have time to present the supporting data for this, but I would like to invite you to look at the paper that I published in *Epidemiologic Reviews,* 1996 -- there's only one issue a year -- on page 64 where I summarized this, and at least cite the studies that I think would support this conclusion.

So therefore, universal immunization of children has a potential to directly reduce morbidity in those children, of course, but to dampen epidemics and hopefully then reduce the risk that high-risk patients in the community will be exposed.

Now these are examples of herd immunity that we can cite. One is a study by Monto and Tacumsey [phonetic] in 1968 where he immunized school children with one dose of the inactivated vaccine, and he showed that adults in that community had less illness than in Adrian [phonetic], a neighboring town. These were mainly parent-age adults that they screened.

There was a study the same year by Warburton in Australia. This is in the Northern Territory where

some communities were immunized and others weren't, and he cited this as an example of herd immunity because he saw good protection in the communities that were vaccinated.

There's a recent study from the USSR, this using the Russian live attenuated vaccine in school children, and showed that where they had good coverage in the schools that teachers and staff had significantly less influenza than schools that were not covered.

And then in a very recent *JID* there was the instance of nursing homes in the United Kingdom where it was shown that immunization of caretakers was a more effective way of reducing mortality in the elderly patients than immunizing the patients themselves; though if you looked at all the measurements of morbidity, the nursing homes where they had both immunization of the patients and the staff had lower morbidity.

Another way to look at this is to look at -- this is again from the Houston family study -- we looked at the risk of infection in infants during the first year of life, and related that to the number of siblings that these children had. And you can see that with the

increase in siblings the risk increased progressively.

So therefore, if you turn this around and then you immunize these children, then obviously you would reduce the risk that their younger and more vulnerable siblings would be infected. So this is the concept that I'm trying to put forward.

Now to do this we have a proposal standing at NIH which we have at least some hope that will be funded within the year. This plan is to try to assess the potential of immunization with influenza vaccine to affect herd immunity.

The purpose is to initiate studies that will define the proportion and characteristics of persons in the community who should be vaccinated in order to control epidemic influenza; and the hypothesis being that it's impossible to immunize everybody every year, and so what's the critical population which will demonstrate the effectiveness?

Now specific aims are to demonstrate not only that you will protect the children vaccinated, but it will reduce the risk for unvaccinated contacts in the same age cohort, for younger and older contacts in the same household, and for younger and older community contacts

regardless of immunization status.

To accomplish this we propose to use the live attenuated cold-adapted influenza vaccine. Now Leighton is going to tell you more about this product in a minute, but in the studies that we've done in Houston using the bivalent cold adapted, bivalent A, we've shown that the attenuated vaccine gives better protection in 3- to 10-year-olds than does the inactivated vaccine. These are head-to-head comparisons. It gives broader and longer-lasting immunity; it's certainly easier to administer; and it's more acceptable, of course, for children than taking a shot.

Now could it be given in the face of an impending epidemic? We've had some experience with that, and we've had more this year. And I think the answer will be yes. And could it be used for epidemic control? That's what we would like to test.

Just to graphically demonstrate the acceptance of this vaccine given by spray, this is just -- it looks like a tuberculin syringe, but it has a rounded tip. And from the age -- I guess this kid is about five years of age -- but I think you can imagine what the

scene would be if that had a needle on the end of it. This child wouldn't be sitting. And you don't see any white knuckles here. His mother is sitting over there very calmly, and he's ready to accept his vaccine. So I think this illustrates very well the ease with which we think we could use this vaccine to reduce serious morbidity.

So just to finish up, I'd like to first urge improved coverage of high-risk children with inactivated vaccine, and I think that should reduce hospitalizations.

And there is one point that I want to make right now which is very important: What we are proposing right now would in no way change the current priorities for the use of the inactivated vaccine. They would remain the same, and we would still be urging immunization of high-risk persons with the currently licensed inactivated vaccine.

But we think that the use of the live attenuated vaccine in healthy children will benefit not only them but the community. And annual immunization may be necessary in the first three years, but not necessarily forever in these kids.

So that finishes my part, and now Leighton will tell you a little bit more about Aviron and the live attenuated vaccine.

DR. READ: Thank you, Paul.

That was a very interesting quote from Dr. Lederberg, but I think we all can thank him for coining the phrase "unmitigated travel."

[Laughter]

DR. READ: Since this is our first opportunity to appear at the ACIP, I'd like to give you a little bit of an introduction to the company.

And then I'd like to take a few minutes to give you very briefly a history of the cold-adapted live attenuated influenza vaccine, and then a little bit about information about how we assessed it at the time that we were contemplating a commitment to this program, and then the some of the steps that we've taken at Aviron in collaboration with the NIH in our CRADA since we brought the program on board at Aviron, and then to give you some sense of our timetable going forward as we move towards regulatory filings and hopefully launch of a product.

Aviron is a company that I started in 1992 with

three distinguished virologists, Bernard Royceman, Richard Whitley, and Peter Polazzi [phonetic]. And we had a very clear focus on prevention as our business strategy, and we were also interested in developing products that were focused or that were intended for very broad use rather than niche or very particular high-risk groups.

The founding technology contemplated bringing the tools of genetic engineering to the very well-proven strategy of preventing disease with live attenuated virus vaccine. So as illustrated in this cartoon, the concept included ideas such as deleting virulence proteins by deleting the genes which code for proteins that may be involved in virulence, a strategy that we followed in building a number of genetically-engineered candidates as live attenuated vaccines for HSV-2.

Another approach would be to interfere with the replication of the virus by genetically engineering changes in the polymerase, an approach that we and others have tried in producing genetically-engineered attenuated candidates for the prevention of influenza, and an approach that we are contemplating in the process of developing for respiratory syncytial virus.

A third strategy, in some ways the mirror image of the first one I mentioned, would be to take a vaccine candidate that might have been produced through classical approaches such as serial passage, and then apply genetic engineering to add something back in.

This is an approach that we're taking in order to produce a genetically-engineered live attenuated vaccine for the prevention of CMV infection and the consequences by beginning with the Towne [phonetic] strain of CMV vaccine, and adding information back in that was deleted in the process of its creation by serial passage.

Aviron's product portfolio today, then, includes these genetically-engineered vaccine candidates for the targets that I've just mentioned; a subunit vaccine based on a glycoprotein on the surface of the Epstein-Barr virus, which is, we understand from our partners at SmithKline Beecham, intended to go into human trials later in 1997; and then two programs at a much later stage of development, both of which were licensed into Aviron, in both cases with a considerable amount of data from human trials, both cases from the National Institutes of Health.

So we're going to focus today on the cold-adapted influenza vaccine. This product, as many of you know from the literature and from other presentations, was created quite a few years ago. It was originally created in 1967 by John Massaab at the University of Michigan, originally under support from the United States Army.

The vaccine was created by serial passage of a virulent influenza virus under progressively cooler conditions, and the product that was created was an influenza strain that had properties of cold-adapt. It was cold-adapted, and then it grew at 25 degrees centigrade better than wild-type flu. It was temperature sensitive, and had a cutoff for growth around body temperature. And also, it had a very reproducible phenotype of being attenuated in ferret models.

The Army's priorities changed, and the National Institutes of Health stepped in with a program of support for clinical trials, which really represents an extraordinary record of information and an extraordinary collection of information in terms of immunogenicity, safety, and even efficacy for this

vaccine.

This effort was largely led by people in the Division of Microbiology and Infectious Disease at NIAID, but there was also considerable interest and support from people in the Laboratory of Infectious Disease in the Intermural Program at NIH. And that support continues in the form of our CRADA today. From 1991 to 1993 Wyeth-Ayerst had a CRADA with the NIAID in connection with this product, and for two seasons Wyeth-Ayerst conducted immunogenicity studies in children.

Their research priorities changed, and the product was advertised in the *Federal Register.* Aviron spent almost a year conducting due diligence on this opportunity. We reviewed a 60,000 page collection of the various I&Ds [phonetic] from the studies that had been sponsored by NIH and Wyeth. We had a chance to talk to many of the investigators that worked on this program, people at the CDC and NIH, and we decided that this was an interesting and important opportunity for public health as well as a commercial opportunity.

This history of trials includes over 70 published clinical trials, as I said, ranging from safety to

immunogenicity to efficacy. The efficacy studies include challenge studies, spontaneous field trials in which an immunogenistic cohort was then followed through a following flu season, and there was evidence of protection; and finally, at least one large prospective double-blind placebo-controlled field trial. Nearly all of this data was collected on monovalent forms of the vaccine, a single strain of influenza A or influenza B, rather than the antigens represented by the trivalent inactivated vaccine.

At the time that Aviron stepped forward and committed to this program, I want to report to you our assessment of the product based on that literature. There isn't the time today to try and make a case based on the data for the points on this slide, but our assessment at the time included evidence in the literature to support the attenuation of this live virus; its genetic stability, especially in a setting where the virus could reproduce -- for a number of days a virus replication would occur in very young children; that the virus was non-transmissible -- for example, in the setting of day care where one child would be vaccinated, there was evidence that it was not

transmitted to others.

There was considerable evidence for safety. The recipients of this vaccine total over 7,000 individuals ranging from 2 months of age to 103 years of age with no reports of serious adverse events that were clearly associated with the vaccine. In addition, it was well tolerated.

There was a considerable body of information on immunogenicity, including antibody responses in the serum, in the nasal mucosa, and cytotoxic T-cell responses; and as I said, information on effectiveness from challenge studies and field trials.

There was also a very clear set of issues that needed to be addressed in taking this product from its status in 1994 to a product that was ready for widespread use in the population:

There was still a need for further information on the safety and efficacy of a trivalent preparation of the vaccine containing antigens which would match those in the inactivated flu shot.

Work was needed to improve the predictability and the speediness of the reassortment process by which the vaccine is updated every year.

In addition, additional work was needed on process development in order to have a manufacturing process that would be predictable and safe.

We felt like there was more that would be needed to be known about correlates of protection. Influenza immunity has been the subject of a great deal of research already, and we believe that, like with many vaccines that are currently on the market already and widely used, they are still a subject of important work in trying to better understand how these vaccines work. We think that that will be the case for the cold-adapted influenza vaccine.

Finally, it was very clear that we would need to understand better and be able to make a clear-cut case for the value of the product in terms of pharmacoeconomics.

Since 1994 Aviron has made a number of accomplishments in moving forward on this program, often very much as part of our CRADA with the National Institutes of Health. In terms of formulation we have created a trivalent internasal formulation in the form of a spray device. As you saw in the slide that Dr. Glezen showed, this is a small glass syringe with a tip

designed to produce a large particle aerosol.

Our objective here is to simply provide the liquid vaccine in a format that's more convenient than drops and hopefully would provide a little bit better delivery to the nasal mucosa, which is the target organ for delivery here, and also one that would facilitate in the appropriate circumstances even self-administration.

Our clinical trial program includes studies if safety and immunogenicity in almost 300 adults and a study in 356 children. Ninety-three adults were studied in a challenge efficacy trial which resulted in a positive result. We have completed enrollment in a 1,600-patient study, phase three pivotal field trial, focused on the pediatric population I'll say a little bit more about. And we also now have underway a consistency lot trial in 500 children.

We've made progress in the production of this vaccine. Our partner in manufacturing the vaccine is Evans Medical in England. As many of you know, they produce one of the influenza vaccines that's marketed in the United States, the inactivated vaccine.

And we've also made progress in improving both the

classical approach for reassorting the vaccine, updating the vaccine, as well as adding genetic engineering and a recombinant approach that complements this very well. I think in the interest of time I'm going to skip a discussion of the recombinant approach and tell you a little bit more about the clinical trial that has just recently been completed.

This was a study in children from 15 to 71 months of age who were vaccinated this last fall. They received a vaccine that matched the trivalent inactivated vaccine that was recommended for use in the fall in terms of the three antigens, the two strains of influenza A and the influenza B.

The study was conducted as part of our CRADA with NIH at ten sites, six of which are vaccine treatment and evaluation units under contract to NIAID. In this study, 1,314 of the children were in the two-dose arm and received either two doses of vaccine or placebo in a two-to-one randomization strategy; 288 of the children were in the one-dose group.

The primary endpoint of this study will be the reduction of culture-confirmed influenza in the treatment versus the placebo group and those who

received two doses of the vaccine.

Our plans going forward are to continue the consistency lot trial. And in the third quarter, really July or August of this year, we expect to unblind this pivotal trial that I've been discussing with you. So we've decided to save a presentation of either the historical data or Aviron's data until we have the results of this trial and can put the information in appropriate context. So look for this information at a future, perhaps the next, ACIP meeting if we're invited to present at that time.

In the fall of 1997 we're going to mount additional trials which almost double the number of patients that have been involved in our trials, almost 3,000 subjects to date; and more than 3,000 are contemplated in the coming year in an adult effectiveness trial focused on endpoints such as absenteeism and health care cost:

A high-risk adult trial, in this case to document the safety of combining the current inactivated vaccine with our trivalent intranasal spray; a trial to establish the safety of this vaccine in a particular high-risk group, children with asthma, severe and

moderate asthma; and we're also in discussions with folks here at the CDC regarding a day care study, as well as a study which the Veterans Administration is contemplating, looking at the use of cold-adapted vaccine plus the inactivated vaccine in high-risk patients.

Our target for filing, regulatory filings for United States, is approximately a year from now, in which we would then hope to have availability of the product for widespread use for the flu season of 1999-2000.

Our goal for this product is to provide an important adjunct to the methodologies that are available today for the control of influenza. We see the potential, if the data will allow us to make this case to the FDA and to you, to provide a product that is a practical approach for the annual protection of children.

We also believe that this product will allow the dramatic growth that we have seen in the use of the influenza vaccine in healthy adults to continue by allowing people who are not interested in exposing themselves to the needle, or people who find the

logistics associated with the current flu shot to be barrier to immunization, this product, because of its delivery mechanism, could expand the number of healthy adults who are protected, moving us in a direction of better coverage.

Finally, we think that this product could offer an adjunct in combination with the inactivated vaccine to provide better protection for adults who are at high risk of complications. We saw data in Paul's talk that the job is not being adequately done by today's vaccine.

So as we think about these broad opportunities, it includes the opportunity to protect children for their own sake, for the morbidity, mortality -- not mortality, but the morbidity and the hospitalization that's seen in young children. We think there is an opportunity to avoid parental lost work as a result of childhood influenza.

I showed this at a meeting of investors and somebody said, she's not talking to the pediatrician; she's on a conference call.

[Laughter]

DR. READ: People do stay home from work when

their kids have influenza. As you know, two-thirds of the kids in this country live in a family with either one working -- one parent or both work. Certainly adults transmit influenza to each other in meetings such as this, and then there's an opportunity for disease to continue to propagate through the population.

I think that this cartoon series here is actually the reality of the influenza epidemic. If you examine the peak of the epidemic in the age groups that were just depicted in this little slide series, it follows the sequence precisely. And clearly there's more that will need to be known about cause and effect in the herd immunity protection.

So just to conclude, I'd like to thank you very much for your attention, and ask that you do begin the process of considering the possibility that we should move towards universal immunization for influenza on the basis that this is a vaccine-preventable disease; and the gap between what we could be doing and what we are actually doing is as wide or wider than for any other vaccine-preventable disease in the United States.

Thank you very much.

DR. DAVIS: Thank you. Appreciate that information about Aviron and the product and development. Certainly we'll be very interested in learning more about the performance of this product as information is going to be returned.

I think we should have some general discussion, given the fact that we've had quite a few presentations now from Drs. Fukuda and Glezen and Dr. Read. Are there any questions for any of those speakers from any of our committee members?

This is primarily for information only, and there are some other issues that were carry-over issues from prior discussions of influenza, primarily with regard to the statement and the emphasis on programs that currently are beneficial, and to put them into a more prominent position in the statement. And we're very sensitive to this, and we'll work on this.

I see Dave Fedson's hand up.

DR. FEDSON: These are very exciting reports, and the people who made the presentations and those who work with them really deserve congratulations.

I really have two questions, probably mostly directed to Paul Glezen.

First, notwithstanding the important health benefits in children and many of their contacts with childhood immunization, Paul, do you have any thoughts on the Japanese experience during the 1980s? At least the late '70s and early and mid-1980s, when approximately 80 percent of children in Japan are said to have received influenza vaccine each year, and yet the Japanese public health officials felt that there was no impact on transmission of the disease in the population and public confidence and professional confidence in the program fell to the point where the program was discontinued in the early 1990s; and now hardly anyone in Japan, young or old, receives influenza vaccine.

This is an experience that has never been published, at least for readers of the English language. But I wonder if you have any thoughts or any contacts with Japanese investigators that might illuminate the sort of contrary experience of the Japanese.

And the second question is really, Bob Chen and Walter Orenstein reminded us recently in their nice review, I think probably in the same issue of

Epidemiologic Reviews that your paper appeared, that as the vaccine -- as coverage of the vaccine increases in a population, increasing proportions of the cases observed are going to be observed among people who are vaccinated.

So can we say in the population, for example, where 74 percent or so of the elderly or high-risk people are vaccinated, of the cases that occur, that this doesn't really reflect the phenomena that Bob and Walter were describing in their paper?

DR. GLEZEN: I'm sorry, I'm not familiar with that paper.

DR. FEDSON: It's in the same issue of *Epidemiologic Reviews,* I think, in which your paper appeared.

DR. GLEZEN: I'm sorry, I didn't get beyond page --

[Laughter]

DR. FEDSON: Am I correct in that, Walter? Walter will give you a free copy of the issue of *Epidemiologic Reviews* --

DR. DAVIS: He's got reprints.

DR. FEDSON: I think we can let Walter speak on

behalf of his own paper.

But in fact, the observation has been made many, many times that as vaccine coverage increases, an increasing proportion of the cases of disease which do occur occur in people who have a history of vaccination. And this is what you expect. So it's not necessarily an indication that the vaccine is not working, I guess is my point.

DR. GLEZEN: Right. But I think in those situations you're seeing very few cases, though, that are vaccine failures. Here, unfortunately, we're still seeing epidemic excess mortality, and I don't think we're seeing that at all.

DR. FEDSON: Well, but we really don't have, under these circumstances we don't have a measure of what we would be seeing if nobody was vaccinated. And when you look at the population-based studies in recent years --

DR. GLEZEN: Yeah, that's true.

DR. FEDSON: -- at the effectiveness of influenza vaccine in older populations of community-dwelling elderly people, the vaccine still has -- inactivated vaccine still has a substantial measure of protection.

DR. GLEZEN: But I would have to guess this year was another 40 or 50,000 excess mortality year. It's not showing any diminution. Now we may have more elderly, the population at risk may be increasing, but I don't think that rapidly. So I'm afraid I'd have to say I can't be real optimistic about it. I'd like to see more progress, but I don't think we're going to make it yet.

In relation to Japanese experience, unfortunately, of course, this was instituted without any studies to demonstrate its effect. In the years that they carried this out -- I've tried to review some of the data, and there were a few papers published, and unfortunately it's been a long time since I've looked at it.

But the questions that I had, number one, their method of doing HI tests differed, but I had some question about the potency of the vaccines they were using and how well matched the were with the epidemics at that particular time.

One of the frustrations of reading Japanese papers is that they tend to use their own designation for viruses and don't relate them to the WHO prototypes. So it's difficult for me in reading the data, and maybe

Nancy may have a better understanding of this than I, but it's very difficult for me in reading papers from Japan to assess whether or not they are using the appropriate vaccine for the virus to circulate.

Another obvious factor is the fact the population density of Japan is 13 times that in the United States, and this could make quite a difference. And one possibility is that if they hadn't immunized the school kids in those years they would have had epidemics that were much worse. We don't know either way. But they certainly have lost interest in this approach.

But I also want to emphasize that I think the live attenuated vaccine would be more effective than the inactivated vaccine, particularly in the younger children, elementary school, those that have the highest attack rates and probably are important for spread.

So all I am asking is the opportunity to test this hypothesis and prove it one way or the other.

DR. DAVIS: Walt.

DR. ORENSTEIN: I think the point that David was making on the issue of vaccine efficacy is, obviously, if you have 100 percent vaccination coverage, then 100

percent of your cases are going to have a history of vaccination.

What was of concern to me in the data is that I think it was something like 61 percent of your cases had a history of vaccination. That's similar to the national vaccination rate, and I don't know what the rate was in that community, which is the key rate.

DR. GLEZEN: About 75 percent. Rochester had the best coverage of any of the demonstration sites.

DR. ORENSTEIN: So that implies there was some degree of --

DR. GLEZEN: And it was significantly -- the immunization rate was significantly higher in the high-risk proven cases. They had 74 percent immunization, whereas the flu cases only had 61 percent. So that was significantly different in that study, and it does demonstrate some protection.

There's one other point I want to make related to Keiji's comment about worrying about vaccine supply. The use of live attenuated vaccine could well improve vaccine supply, because at least from estimates that have been made so far, you can make 10 to 100 doses of a live attenuated vaccine for every one of the

inactivated that we currently make.

We know right now that a large proportion of the vaccine which we distribute in the United States is going to healthy people, not to the high-risk targeted people. So I think if we had a live attenuated virus, we could perhaps make available a lot more inactivated vaccine for high-risk patients.

But that's not enough. We have to start developing structures for delivery of an inactivated vaccine to high risk, particularly those under 65.

DR. DAVIS: John Livengood.

DR. LIVENGOOD: That was in some ways exactly what I was going to ask about, because clearly we're doing a much better job with the Medicare-eligible population, which is essentially everybody over age 65, than we are with younger high-risk adults and high-risk children.

I hear the concerns that if we went to a universal recommendation that we might no longer have adequate vaccine for the high-risk groups, who we clearly have the highest priority for.

But I was wondering whether or not if there were a process at the ACIP to look at this, that sort of

signaled that perhaps this would be the direction in which they were likely to go over the next several years. That would send a signal to the manufacturers to produce more vaccine if they saw that there was going to be a market that was considerably larger.

So I don't see that as an insurmountable obstacle, say, over the next several years. Clearly, if you were to take a vote next year and say everybody should be immunized in the fall of '98, that would be somewhat difficult to see how we could do it.

But if you were to begin through a working group or through examination of these issues over the next year or so, perhaps in preparation for new products or some of these types of things over the longer haul, it might send a type of signal and not get us caught in some type of a bind at the point in which you're ready to consider doing that, that there wouldn't be enough vaccine to go around.

DR. DAVIS: I think that's a point well taken.

Certainly I know I've had some discussions with some folks in influenza branch about those types of issues, and clearly a very active working group that would begin before our next meeting and would move

issues along not only for the next statement, but also for preparing it for subsequent statements, this would be very important. And the number of participants in that working group process, of course, would have to be fairly substantial.

Stan Plotkin had his hand up, and then Walt Orenstein.

DR. PLOTKIN: Just to say that I'm all for sending signals, but manufacturers are well aware of this. Everyone would like to get out of the embryonated egg into cell culture or a competent technology, and there are many projects along that line. So the message has been received.

DR. DAVIS: Thank you, Stan.

Walt Orenstein. This will be the last comment.

DR. ORENSTEIN: I wonder if I could ask Dr. Read to just summarize what the benefits of what the live product would be over the inactivated product.

You mentioned the issue of non-injection, perhaps production might be easier. But it wasn't clear to me in the presentation, aside from the lack of a needle, of what other potential benefits there were. And are you doing comparative trials with inactivated vaccine

to see if there are any differences in the phase three study you mentioned?

DR. READ: The phase three study is a vaccine trial versus placebo. We have conducted a comparative study with the inactivated vaccine in the challenge setting in adults. The bottom line is both vaccines were highly effective compared to placebo, and the study wasn't powered to show a difference between the two vaccines.

There's a considerable amount of information on the relative efficacy of the two vaccines. Perhaps the largest datapoint is the five-year study from Vanderbilt, which was a comparison of bivalent live intranasal influenza vaccine given by drops, with trivalent inactivated in the arm. The third control group received monovalent B in the arm. That complicated design is because the influenza B master strain wasn't ready when that study was begun by Kathy Edwards and Peter Wright and their group.

In the four years that influenza A circulated where one could make a comparison -- this is a large study; this was roughly 1,500 patients a year, a total of 5,000 participated with dropouts over five years --

in the four years where influenza A circulated, both vaccines were highly significant versus placebo. There was no statistical difference between the live vaccine or the inactivated in any of the four years.

The inactivated vaccine efficacy as measured by culture positive influenza was generally in the 70s, 70 percent. The cold-adapted vaccine was a little bit more variable, ranging from the high 50s to 85 percent. So two years the live vaccine was better, two years the inactivated vaccine was better, no statistical difference.

Our view of the potential advantage of the product, we think that the delivery advantage is a very significant advantage. This is a product that now doses are available for 80 million Americans, with very many of those being given. There's obviously a tremendous amount of consumer or individual decision-making going on, so even small changes in the presentation of the product or its accessibility logistically could have a huge impact in uptake rate.

As Paul mentioned, there's evidence that the live attenuated vaccine is more effective in young children. I'm not prepared to make the case to you today that

that's that case, but there are studies which the Baylor group has conducted, among others, that make that case. That's the group in which you see the highest amount of shedding of the vaccine virus after immunization, and therefore you might expect the highest level of immune stimulus.

Other advantages are the theoretical advantages related to the fact that it's a live vaccine, which produces a very clear-cut musocal IgA response that is seen to a much less extent, if at all, with the inactivated vaccine. There's also very clear differentiating responses in terms of cytotoxic T-cell responses, also something you might expect for a live vaccine that replicates intracellularly in comparison to an inactivated vaccine give in the arm.

I hope that answered the question.

DR. DAVIS: Thank you.

I want to thank all of the presenters for their very interesting presentations, and for a lively discussion among the people that were here. Thank you very much.

Next and last will be a topic, continued Hemophilus influenzae type B carriage among Alaskan

native children, despite high coverage with PRP-OMP vaccine. And we have -- Oren Levine is here, and Brad Perkins, and Dr. Galil. I had asked Oren if he would be willing to present this on relatively short notice, and he was kind enough to do this. So let's proceed.

DR. LEVINE: Thank you for the opportunity, and thank all of you for waiting this out. We're going to try to be exceptionally brief.

We wanted to take this opportunity to present some preliminary analyses from a study that we have just completed, carried out in collaboration with the Indian Health Service, the Alaskan Department of Health, and the Arctic Investigations Program.

This study came about when, about this time last year, we received a phone call from Rod Singleton, the Immunization Director for IHS, who had observed several cases of Haemophilus influenzae type B disease following a switch in the vaccine that was routinely administered to Alaskan native kids from PRP-OMP, which had been the routine vaccine since 1991, to a schedule that used Tetramune as a strategy to reduce the number of injections.

So right now what I would like to do is just have

Karen Galil describe for you briefly the investigation and the results; and then I was just going to take a minute afterwards to kind of put those into perspective about what we know about conjugate vaccines.

So I'll pass this to Karen.

DR. GALIL: Following the introduction of routine infant immunization with PedVaxHIB in Alaska in 1991, there was a decrease in the incidence of invasive disease from that time until 1995. On January 15th, 1996, the vaccination schedule was changed and Tetramune became the vaccine that was routinely used for Hib immunization.

As you can see from the graph, there was a four- to five-fold rise in the number of cases that were detected following this change. During an 11-month period in 1996 and 1997 following the change in the vaccine regimen, there were ten cases of invasive Hib disease. All of these occurred amongst Alaska Native children. Nine of the children were under 12 months of age, and 7 of them were partially immunized with Tetramune.

We hypothesized that there had to be continued carriage of Hib in this very well- vaccinated

population, so in response to the request by the Alaska Department of Health, the Arctic Investigations Programs and Indian Health Service, we did a cross-sectional study of Hib carriage in the Yukon-Kuskokwim Delta of Alaska.

We performed oropharyngeal swabs on Native or part-Native children who were aged between one and five years of age in five villages in the YK Delta, and in the regional center of Bethel. If you're not familiar with this area, it's an area in southwest Alaska which is formed by the delta of the Yukon and Kuskokwim rivers, which Oren will point out for you.

Oropharyngeal swabs were taken from these children, and they were plated immediately onto Hib antiserum agar plates. All colonies which looked suspicious, meaning that they had a halo on the plat, were confirmed using gram stain, X and V factor dependency, and slide agglutination.

We swabbed a total of 498 children, which represents 70 to 90 percent of the eligible children in each village, and we found 42 confirmed carriers, which represents a carriage rate of 8.4 percent. Vaccination rates amongst the carriers and amongst the non-carriers

was similar. Of the 42 carriers, 42, or 95 percent of them, had received three doses of a Hib conjugate vaccine. One child had received two doses, and one child had refused all vaccination.

Carriage varied by village from 3.6 percent to 13.3 percent. Villages B and E and Bethel, which are starred, had cases of invasive disease. There was substantial carriage rate for all the age groups that we looked at, and it varied from 5.6 percent in 1-year-old children to 13.3 percent in those who were 5 years old.

In conclusion, we found Hib carriage rates in the YK Delta similar to those that were found by Joel Ward and others in two studies conducted before vaccination was instituted in this region. There was substantial oropharyngeal Hib carriage in all of the age groups studied. And although PedVaxHIB protects against invasive disease, we did not find any evidence of protection against carriage in this population.

Oren will discuss this.

DR. LEVINE: Thanks for that very brief, hopefully informative description.

I just wanted to point out a couple of things that

are important to consider when we try to explain what occurred, and why there was an increase in the number of cases following this switch.

For those of you familiar with the epidemiology in this population, it's a special population where a high proportion of cases, over 40 percent of cases, occur before the age of six months, unlike in the U.S. or other industrialized populations where less than 20 percent occur within the first six months. Therefore vaccines need to be capable of protecting shortly after the first dose.

The kinetics of the Hib conjugate vaccines that are licensed, all of which have demonstrated efficacy for preventing invasive disease, do differ somewhat. And PRP-OMP differs, the PedVaxHIB or PRP-OMP vaccine, differs in the sense that after the first dose of vaccine at age two months almost 100 percent of children respond with an antibody concentration greater than 1.5 micrograms per ML of antibody, the putative threshold for short-term protection. With HbOC, for example, two doses are needed in order to get that kind of level, so that in this time period kids with HbOC vaccination don't have protective levels.

So what we have surmised or proposed as an explanation for what happened is that there was continued carriage among older children in this population despite widespread vaccination with PRP-OMP since 1991, that when the switch occurred there was a period of prolonged susceptibility in the age below six months, this age group that's historically at high risk of disease, and that there was transmission from those older kids to the younger kids.

The reason this is important is that we have evidence that Hib conjugate vaccines do provide herd immunity in some populations. The evidence that they provide herd immunity comes from two major empiric observations.

One is a decline in incidence among children too young to be vaccinated. The first hint of this was a decline in the incidence among infants following the licensure of Hib conjugate vaccine for toddlers before it was ready for use in infants. And then since licensure for infants, the incidence among those kids still too young to be immunized, kids less than two months, has continued to decline.

In addition, in earlier times when our

immunization coverage rate was not what it is right now, we still were able to see over a 98 percent reduction in disease incidence with only about 70 to 80 percent coverage during the early periods of vaccination.

Now we have a couple of different studies, or types of studies, that show us that Hib conjugate vaccines reduce carriage, and that it's this reduced carriage which presumably is interrupting transmission and resulting in herd immunity.

One type of study is the comparison of vaccinated to unvaccinated children in immunogenicity trials, but these are typically conducted before routine immunization, and therefore none of the population effects that occur from widespread vaccination in a population can be measured. Typically, because they're nested in immunogenicity studies, their focus is on short-term effects.

The second type of study is a comparison of carriage in populations before and after introduction of vaccination, and so those are going to include direct and indirect effects. But they are also going to have the problem of not having contemporaneous

controls, so they're going to use historic data.

This slide is just a quick slide to summarize the studies or data that we have of evidence of reduction in carriage from Hib conjugate vaccinations. Before the study in Alaskan natives there was a study among Navajo that Mathu Santosham and Ino Takowa [phonetic] from Finland collaborated on, which should have given us some hint that the protection against carriage was not going to be complete in this kind of a population.

In that population they only saw a 42 percent reduction in carriage among children 1 to 4 years old. The baseline or background carriage among kids of the same age but who had not been vaccinated was 7.1 percent, and that's important to keep in mind because that's a level typically higher than what we have seen prevaccination in the U.S. and in other industrialized countries.

Other vaccines have given varying rates or efficacies of protection. But in general, in industrialized populations like Finland, Iceland, the U.S., and England where they find carriage rates are about 3 to 5 percent, and other vaccines besides PRP-OMP have been used, between 90 to 100 percent in

three of the studies and 46 percent in one of the other studies.

The HbOC, England's study, is a study that looked at four years after vaccination and saw no difference in two small groups of 60 infants in terms of carriage. And again, that may have been an early indication that perhaps there would be waning immunity against carriage, but that's still not entirely clear.

There is a number of remaining issues that need to be resolved in terms of Hib vaccines, their impact on carriage, and hopefully their potential to continue giving herd immunity effects.

One is we still don't know exactly how Hib conjugates diminish carriage. We don't know whether this parental immunization leads to production of mucosal antibody, whether high levels of serum IgG, as some have hypothesized, are actually transudated to mucosal surfaces and interfere with colonization, or whether simply the priming and T-cell memory leads to a rapid response that's capable of clearing infection once they are mucosally challenged.

We don't know how long immunity will last. We don't know if there are differences between the

vaccines and their ability to protect against carriage. And we don't know what the impact is going to be in all populations that they are used in, whether genetics, environmental conditions, or, as perhaps some of the data suggest from existing studies, that in populations with high levels of carriage of intense transmission the effect of Hib conjugate vaccines against carriage may be somewhat attenuated.

And so I just wanted to finish with a couple of suggestions that would come from our preliminary analyses, and that is for Alaskan natives, American Indians, or other populations with similar epidemiology, PRP-OMP should be used for the first dose of Hib vaccine as long as there is evidence of substantial carriage among older children, and that evaluation of the impact of other vaccine regimens on carriage in Alaskan natives and American Indians should be carried out.

DR. DAVIS: Thank you. Very, very interesting, and appreciated your willingness to do this on short notice and prepare such a nice presentation.

Questions? Dave, and then Chinh Le. Dave Fleming.

DR. FLEMING: Well, I know the number of cases is small. Are you planning or have you looked at cases in non-Native Americans that have occurred during that 2- to 6-month age range to see whether or not vaccine is a predictor of disease?

DR. LEVINE: There weren't any in the Alaskan natives.

DR. FLEMING: No, I meant in the U.S. population as a whole, whether or not the small number of residual cases the we're seeing in infants two to six months of age might be predicted by which vaccine they received.

DR. LEVINE: Kris Bisgard might be able to comment on that. We have looked at the cases that are occurring, continuing to occur. PRP-OMP unfortunately is still a very small part of the market share in the lower 48, and I'm not sure that there is substantial enough numbers to look at that. But maybe you want to comment on that, Kris.

DR. BISGARD: We've looked at those, at our vaccine failures, and have completed a primary series, but not just on a whole -- if they received one dose, like many of these did, we haven't looked at that.

DR. DAVIS: Thank you.

Chinh Le, and then Georges Peter.

DR. LE: You had a transparency that compared the titers of the RPR-OMP versus the Hib titer. Could you put that up again for me, please? Because I think that graph is a little bit incomplete. What it is, it's a graph of 100 percent of the children at 4 months of age with RPR-OMP --

DR. LEVINE: On the Y axis here we have the proportion of infants who have antibody titers above 0.15.

DR. CHINH LE: Yes. I think to make the story more complete you should really go 12 to 15 months to see what happens.

And what happens is with the RPR-OMP you will see a decrease between 6 to 12 months of titers versus the HbOC very persistently up high. I just happen to have a paper from *Pediatric Practices Journal* in June '97 -- this is with COMVAX and so on -- and again, when you look at 12 to 15 months with the RPR-OMP, only 29 percent of children have titers greater than 1 microgram, and 80 percent have titers of 0.15 micrograms.

The point being, I think with OMP vaccine you get

a very high titer with the dose being given at 2 and 4 months of age, and then at 15 months you have that cohort of infants who have declining titers. And whether that correlates with increase colonization rate at that time may be one of the possibilities.

We have used in Northern California Kaiser exclusive the Hemophilus OC vaccine for, I don't know, five years; and we have yet to see a single case of breakthrough or disease in infants like two, four months now.

DR. LEVINE: I think I would point out that the epidemiology of disease in Southern Californian and Alaskan natives is a little bit different, and the key feature is not really the decline of titers between 6 and 12 months, but can you prevent them in the period when they are at high risk between 2 and 6 months? And that's the feature of PRP-OMP that HbOC doesn't have.

The reason I showed those titers was not to make a point in relation to impact on colonization, because I'm not sure, as I said, that we know that serum IgG levels in any way correlate with impact on carriage. But that the kinetics of the response being what they are, you've got early protection, and in this

population that's important because with older kids carrying the bacteria those kids are potentially at risk for disease.

DR. LE: Do you have serological data on the 40 kids who were carriers? Do you have titers?

DR. LEVINE: Do we have titers? No, we don't. In fact, drawing titers from carriers when you know the they are carriers wouldn't be particularly informative, because they all would be extremely high because they're carriers.

DR. LE: Just to see the lack of correlation or correlation.

DR. DAVIS: Georges Peter.

DR. PETER: Is PRP-OMP used in Native American children? I had thought that is was, and I don't know if it still is, and that's another population.

Second is the point that you just made, is the epidemiology of Haemophilus influenza disease in Alaska has been very different from that in the United States. And for example, PRP-Td, when given beginning at four months of age, was very successful in Finland; and yet in Alaska it was highly unsuccessful. So I think the epidemiology, as you make the point, is an important

consideration.

DR. LEVINE: Actually, anecdotally I understand that the Navajo, for example, having spoken with Mathu Santosham and some of the folks that work with the Navajo in the Southwest, indicated that about three to four years ago they attempted to make a switch to Tetramune. When they did that they had some breakthrough cases, and have since gone to a combined schedule with PRP-OMP given as the first dose and Tetramune given as the following doses.

Now programmatically that raises some issues that may be troubling to program managers, but immunologically there's at least some evidence from the mix and match studies that that's in fact the best approach immunologically.

Now all of the vaccines and all these combinations elicit antibody levels considered well above protective levels for preventing invasive disease, and at this point there's no question about the efficacy of either of the regimens to protect against invasive disease when kids are fully vaccinated.

DR. DAVIS: I think it certainly underlines the issue of what the underlying strategies are for -- we

have general underlying strategies for our country, but there are specific underlying strategies in specific populations, depending on the focal epidemiologic features and the immunologic behavior of the vaccine in these populations.

That was very interesting. I know that you're still working on this, but we really appreciated the opportunity to hear about this very interesting phenomenon.

I think at this point we are at the -- I think our carry-over business from yesterday was resolved, so I don't -- unless anybody else has any unfinished business it's time for public comment, which is a traditional time for our diminishing public to provide their input.

And I guess with that, seeing none, I will adjourn the meeting. I want to thank everyone for their participation, and appreciate it.

[Whereupon, the meeting was concluded at approximately 4:27 p.m.]

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C E R T I F I C A T E

G E O R G I A)

DEKALB COUNTY)

I, Kim S. Newsom, being a Certified Court Reporter in and for the State of Georgia, do hereby certify that the foregoing, consisting of pages 1 through 288, inclusive, was reduced to typewriting by me personally or under my supervision and is a true, complete, and correct transcript of the aforesaid proceedings reported by me.

I further certify that I am not related to, employed by, or attorney or counsel for any parties, attorneys, or counsel involved herein; nor am I financially interested in this matter.

WITNESS MY HAND AND OFFICIAL SEAL, this 20th day of July, 1997.

_____

Kim S. Newsom, CCR-CVR
CCR No. B-1642

[SEAL]