Full Minutes

The Advisory Committee on Immunization Practices (ACIP) convened in Auditorium B, Centers for Disease Control and Prevention (CDC), Atlanta, Georgia on February 21 and 22, 1996 at 8:40 a.m. Dr. Jeffrey Davis, Chairman, presided.

The meeting was opened by Dr. Jeffrey Davis, Chairman. Dr. Dixie Snider, Executive Secretary and Associate Director for Science, CDC, welcomed the Committee.

Following housekeeping announcements by Drs. Davis and Snider, each member of the audience introduced themselves. The audience included representatives of vaccine manufacturers, academia, state and federal government agencies, and scientific journals.

The ACIP members were asked to introduce themselves and any member who may have a potential conflict of interest was asked to 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, a person with a direct conflict cannot vote on any issue related to the conflict.

Dr. Joel Ward, Director, Center for Vaccine Research, UCLA, reported that their group has received funding from two pharmaceutical companies, Merck Sharpe & Dohme and SKB, and that the funding represents less than 20 percent of project budget. No other conflicts were reported.

Dr. John Modlin, Professor of Medicine and Maternal & Child Health, Dartmouth Medical School, reported in the past year he has served as an Investigator for North American Vaccines and for Medimune, and also as a Consultant for Connaught Laboratories.

Dr. Ed Thompson, State Health Officer, State of Mississippi, reported that he has no conflicts of interest.

Dr. Barbara DeBuono, Commissioner, State of New York, reported that she has no conflicts of interest.

Dr. Steve Schoenbaum, Medical Director at Harvard Community Health Plan of New England, Providence, RI, reported that he has no conflicts of interest.

Dr. Marie Griffin, Associate Professor, Department of Preventive Medicine at Vanderbilt University Medical Center, reported no conflicts.

Dr. Fernando Guerra, Director of Health, San Antonio, reported that he is currently serving as an investigator in the field trial for acellular pertussis for a north American vaccine company; and that his Department has also in the past received some support from the Merck Company for developing some additional linkages in the computerized immunization tracking system.

Dr. Mary Glode, Professor of Pediatrics, University of Colorado, reported that she is currently involved in negotiations for a contract for a vaccine (not being discussed today) with Chiron, Biocine and other members of her department have done some work with varicella vaccine but she was not involved in that work.

Dr. Jessie Sherrod, Assistant Professor of Pediatrics School of Medicine, MLK, Jr. Medical Center in Los Angeles, reports no conflicts of interest.

Dr. Jeffrey Davis, Chief Medical Officer at the State of Wisconsin reports that he has no conflicts of interest.

As is the normal practice of the ACIP, Liaison and Ex Officio members were not asked to disclose conflicts of interest.

Issues Regarding Use of Acellular Pertussis Vaccines in Infants

Dr. Peter Strebel thanked Dr. Jeff Davis, Dr. Mimi Glode, Dr. Marie Griffin, Dr. Neal Halsey, Dr. Carolyn Hardegree, Dr. George Peter, and Dr. Joel Ward, the Acellular Pertussis Working Group for their assistance in preparing for this presentation.

Dr. Jill Hackel, Lederle Laboratories, discussed the acellular pertussis component manufactured by Tekata, licensed in Japan in 1981, and licensed in the U.S. in 1991 for use as the 4th or 5th dose in the immunization series. The formulation of the pertussis component has 40 micrograms of protein with 86 percent

of it being FHA; 8 percent Pertussis Toxoid; and smaller amounts of Protactin are 69 K and FIM 2; and it's combined with diphtheria and tetanus toxoids produced by Lederle.

An efficacy study was conducted in Germany, and was one of two stratums: there was a stratum that was randomized to receive either the Lederle whole-cell vaccine or the Lederle Tekata DTaP vaccine, and a second stratum which received DT. Two hundred twenty-seven individual sites were enrolled in the study with 4,000 in each vaccine group and an additional 2,000 in the DT group; the average length of follow-up was about 24 months.

The case definition of pertussis disease for this study was defined as, 21 days of cough with another symptom, paroxysms, whoops or post-tusser vomiting, and then one or more of the following for confirmation: either a positive culture or a positive household contact, a significant rise in PT, IGG, or a single-serum sample of IGA that was higher than the value of the general population as determined by the random kinetic curves.

The unadjusted efficacy of the DTaP group was 84 percent, and of the whole-cell group 93 percent, with the adjusted overall values

of 81 percent and 91 percent respectively. We looked for factors which were different between strata and which were related to disease, and what popped out was the number of adults in the family and families who had children who were not previously immunized against pertussis. This was validated in two ways; one is the statistical technique called bootstrapping and the other is a delphi panel. A list of all the demographic variables was given to a group of experts and they were asked which ones were most likely to influence risk of pertussis disease. They did not know which ones were different between the strata, analyzed the results and obtained an efficacy adjustment that basically was identical to the original one performed.

The efficacy calculated in the six-month period after the completion of the primary series was 74 percent in the DTaP group and 85 percent in the whole-cell group. Looking at the follow-up time after the booster, children enrolled in the study between May of '91 and December of '94, had an overall, 84 percent in the DTaP group and 93 percent after the whole-cell group.

To summarize, the Wyeth Lederle acellular pertussis vaccine was efficacious as was the Lederle whole cell vaccine. There is safety data for primary series for more than 20,000 doses in

infants and more than 5,000 doses in children who received all four doses with the acellular vaccine.

Multiple acellular vaccines are likely to be licensed in the U.S. over the next two years. Product license applications have been filed for three products with the FDA. The fourth point is that at the moment the acellular products license for infant use will be in the formulation of DTaP without a combination with Hib or IPV.

There are five issues that need to be answered. The first issue is what should the recommended schedule be? Secondly, are whole cell vaccines a permissible alternative to acellular vaccines for the primary series? Thirdly, is there a need for a fourth dose of acellular vaccine in the series, and if so at what age? Similarly, is there a need for a fifth dose, and if so at what age? Question five, are acellular vaccines preferred for the fourth and fifth dose? At present our statements read that acellular vaccines may be preferred for the fourth and fifth dose. The question for ACIP is, AShould this recommendation be strengthened to say are acellular vaccines preferred?@

Dr. H. Jafari: The two major questions that have surrounded the use of acellular vaccines are: are acellular vaccines associated with fewer and less-severe adverse reactions than whole cell vaccines, and, are acellular vaccines equally or more efficacious than whole cell vaccines?

Except for vomiting, for all of the mild reactions evaluated, acellular vaccines are associated with a lower frequency of reactions, and except for convulsions, there are less frequent adverse reactions among recipients of acellular vaccines. Both fever and convulsions were significantly lower among recipients of the acellular vaccine.

Summarizing the adverse reaction data, DTaP vaccines are associated with a significantly lower frequency of mild adverse reactions than whole cell vaccines. Fever of equal to or more than 40 degrees, hyper responsive, hypertonic episodes, and persistent crying are less frequently associated with DTaP than whole cell vaccines and when given at three, five and 12 months schedule, the convulsions are also significantly fewer among the recipients of acellular vaccines. But, we don't have enough experience with the acellular vaccines to evaluate the risk of

the more real but more severe adverse reactions such as anaphylactic shock and acute encephalopathy.

There are four vaccines licensed. The Connaught vaccine and the Wyeth Lederle vaccine are the most commonly used, but we don't have manufacture-specific estimates for efficacy of these vaccine estimates in the U.S. The estimate of 85 percent is based on a household contact study which used a separate case definition of 14 days of cough which is a CSTE case definition of pertussis.

All DTaP vaccines are equally or more efficacious than at least one whole cell vaccine used in the U.S., that's the Connaught vaccine. The efficacy for DTaP vaccines in other studies is within the range of estimates obtained for whole cell vaccines. The effectiveness of the _____ vaccination program, the whole cell vaccine is high, however, the efficacy data suggest that DTaP vaccines are likely to be equally or more efficacious.

There are some other conclusions that I want to mention. The number of antigens in an acellular vaccine does not appear to

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We heard discussion on adverse reactions and efficacy and also to some extent the lack of contribution of immunogenicity data in helping state a preference between an acellular and whole cell.

To incorporating acellular vaccines into the infant schedule, we would introduce acellular vaccine for the first three doses in the series, we clearly will have three shots at two months of age, two at four months, and three at six months, and still will be faced with three to four shots at a single visit in the second year of life.

On the schedules, the fourth dose of acellular is recommended from 15-18 months, whereas the fourth dose of a whole cell is from 12-18. It is unlikely that we'll have efficacy data on a fifth dose for any of the acellular vaccines, and at present, the fifth dose of a whole cell is recommended at 4-6 years of age.

Given that some studies show high efficacy with whole cell vaccine, with a four-dose series of Lederle vaccine, we would want to allow for continued use of whole cell vaccine. One of the analyses which I think would help make this decision, would be the analysis of protection against the so-called minor

_____. Because most of the hospitalizations and deaths occur in babies less than six months of age, we don=t want to loose focus on disease in babies in this age group. We need to know how we can best improve pertussis immunization.

If acellular pertussis was safe in pregnant women that would be the ideal way to protected babies during the time of maximum vulnerability. There may be three strategies to further attack the problem of infant disease. One is lowering the age to one, two and three months, if one had bridging studies that showed adequate immunogenicity and safety. A second is vaccination of adults to reduce circulation in adults and decrease spread from them to young infants, and third would be vaccination of pregnant women. All of those approaches are feasible, but first we need to get these vaccines used to see the impact and begin to think of those studies.

Experience with vaccinating close to 1,000 children with first, second, third, and booster doses in a field trial over several years shows that there have been no pain and swelling or tenderness at the site of the injection readily observed by the mothers. Mothers who have had children who received the whole

cell products in the past and then had young infants participating in the study, it was very obvious to them that there was a very significant difference.

Polio Vaccination Recommendation and Schedule

Dr. Davis: Since we met in October and the Committee unanimously endorsed adopting a sequential schedule of IPV followed by OPV as the future preferred U.S. immunization schedule, the issue of revising polio recommendations in the U.S. has continued to attract great attention and generate a lot of controversy. CDC staff and ACIP members have participated in briefing a number of groups in the interim including the Commission on Childhood Vaccines, the National Vaccine Advisory Committee, FDA's Vaccine and Related Biologic Products Advisory Committee, CDC immunization grantees, as well as the Assistant Secretary of Health, Phil Lee. A number of groups who are either strongly opposed or strongly in support of the change, and the Committee has been provided with written comments that were submitted with these concerns. Many of them have already been expressed in other meetings, and I believe some of them will be expressed today. We will continue to provide the ACIP members and liaisons

with information from those supporting and those opposed to policy as it becomes available.

Since the February ACIP meeting, the Polio Vaccine Policy Working Group has had two conference calls: one to review issues regarding the specific sequential schedule to be recommended, and one to review a first draft of an ACIP statement articulating the new policy. In addition, CDC staff has met to define a rough time table for completion of the draft ACIP statement and review by CDC.

Dr. Snider: With regard to ACIP and all advisory committee recommendations, just for the Committee's and other's information, it's a two-step process. It always has been a two-step process in that the Committee makes recommendations as those of you have read in the Charter know, to the Director of CDC, the Assistant Secretary for Health, and the Secretary. This has been a seamless process throughout the existence of the ACIP in that the program people sit in deliberation with you as a Committee and make contributions as do CDC officials. This two-step process doesn't show to the external world, but we want to maintain that seamlessness to the extent possible. Because of the extensive

public interest about this particular topic, we feel that a special plan is necessary to reach a set of recommendations on polio vaccine policy. That plan is to review, at this meeting, for the first time, a draft document, and hear comments from the Committee members and other persons represented here on this draft recommendation. In June, there will be approximately four hours on the agenda for the public to comment on the revised statement. At that meeting members of the public, the Committee, liaisons, and ex officios, will have an opportunity to speak to Committee members as well as CDC officials which will include the Deputy Director or the Director of CDC.

Dr. Ward: More than two years ago the ACIP took on one of the more complex and serious charges, to revise the polio recommendations. There have been enumerable discussions at ACIP meetings in addition to separate IOM-sponsored meetings, conference calls, exchanges of correspondence, and ad hoc working group sessions. We are far along in the process and as we go further into the process there's always folks who come back to issues that were addressed early on. The Committee itself has taken the stance to try and reach almost complete unanimity on every step of the way. Initially we evaluated and reviewed in

great detail the new data that became available on the sequential use of IPV and OPV and new data on the use of IPV vaccines alone. In reviewing this data, a number of issues became clear, and each of those issues has been addressed here and at the Institute of Medicine workshops. The decision was made to revise the original polio statement written back in the early '80s.

The Committee, decided that the mechanisms for preventing polio, are an all OPV and all IPV or a sequential IPV/OPV regimen, were relatively equivalent. There were advantages or disadvantages to one regimen or the other, but there was not sufficient data to say one was less good or inappropriate for general use. There was much discussion on the need to have a preferred schedule for public health use and it was decided unanimously that a sequential approach with the clear caveat to allow for three acceptable approaches to polio immunization. With that decision, the working group was faced with the task of making a recommendation for a preferred schedule which would be for a sequential approach. Two doses of IPV at two and four months of age are given before the first polio challenge, and to obtain an optimal gastrointestinal immunity, two doses of OPV preferably initiated before two years of age are sought. To minimize the

risk to those with congenitally acquired or undiagnosed immunodeficiency states, OPV would not be given before six months. Some were concerned that perhaps OPV should be given at even an older age and there was much discussion about how many such cases there are in the U.S. and at what ages they occur; there was discussion about a two-month interval between OPV dose. The current statement is a little bit ambiguous between 4-8 weeks. As has been our theme for the last three or four years we wanted to maintain harmony with the existing immunization schedule so that implementation was not complicated, and we also wanted to reduce the number of injections following that theme. It became clear in the discussions that many groups involved in the immunization of children have different considerations, and that maintaining maximal flexibility in the recommendations would provide some advantage to different groups. And there was some desire to try and complete immunizations of polio by the second year of life as opposed to stringing it out over a longer period.

To accommodate these principles, the Committee considered five options for this recommended schedule. The advantages and disadvantages of the five, basically started with an IPV at two and four months of age and the first OPV dose given either at six

months or in the second year of life, and then there's variability as to when the second dose of OPV was given.

After considerable discussion and debate, the working group voted for an IPV at two and four months of age; the first dose of OPV at six months of age. The Committee voted for maximal flexibility on the second dose of OPV between 12 and 18 months of age and such a regimen would not necessitate a fourth dose or a fifth dose at preschool entry. The advantage here was that it completed all polio immunizations, it provided presumably the benefits of OPV mucosal immunity and potentially secondary immunizations and it fit into the existing recommended schedule. This was voted upon and endorsed at our last meeting in October.

It became clear that the statement needed a total rewriting. In writing the first draft, it became clear that certain issues were ambiguous or difficult to explain or unclear. The one issue that came up relates to the schedules that are recommended for an all OPV. The current all IPV schedule, which would be offered as an equivalent option, was dictated by the drug, and of course the recommendation for a sequential schedule.

The Committee had a conference call to discuss this issue. It would be nice to harmonize all polio vaccine recommendations such that whether one was going the route of all IPV, all OPV or sequential IPV/OPV, that it was done at the same ages, at the same milestones of number of doses, and not at different ages. There may be situations where one child started on an all IPV or a sequential and before the OPV was given there might be the opportunity to switch track if they were on an identical schedule. There would be an advantage to standardizing pre-school evaluations, children either needed a dose or didn't need a dose at pre-school but that those who were making that evaluation wouldn't have to validate which schedule they had come from initially.

There are advantages to giving the first dose of OPV at six months and there were also advantages to giving two doses of OPV during the second year of life to achieve essentially all of the benefits of presumably of the OPV regimen in children following the sequential step.

There were two issues that had to be addressed. One is the compatibility with the current drug inserts. This is

particularly an issue with the IPV, I think the issues with the sequential have been addressed some, and the need to review existing data in the U.S., and I wasn't sure whether there was data available from Europe or elsewhere in the world on some of the schedules.

The existing recommendations are somewhat in congruent and the options that we considered or are considering, because there has been no decision made, about harmonizing it. One could harmonize it by taking the OPV as the model, the IPV as the model, or the IPV/OPV sequential approach as the model. There are two other options which with flexibility could be stretched out by giving the second dose of polio between 12 months and six years, a very broad range, the fourth dose of polio. The other approach would be to provide two windows between six months and 18 months for the first dose allowing a one-month interval here, and giving the second dose anytime between 12 months and six years. The advantage to this is that the polio recommendations could be presented as a P rather than an OP or an IPV, and whatever one chose, whether it was IPV or OPV, on would use appropriately or in the case of the sequential one would use IPV/IPV/OPV/OPV.

There are some advantages to each of these five options. There are the two major considerations that we need to discuss and that is available data and compatibility with drug inserts; and then the issue as to whether drug inserts can be modified so as to accommodate these. The working group has not taken a vote on this officially but there was a consensus that following the principles that we've followed to date, the more flexibility that's provided to the providers is optimal and I think these latter two options provide more flexibility for either OPV/IPV or the sequential approach.

Dr. Hardegree: At the last two ACIP meetings, FDA made public statements concerning the package inserts for IPV and OPV and the possible sequential administration of these vaccines. FDA considered the sequential administration of these vaccines in terms of the now proposed ACIP recommendations of a sequential schedule of two doses of IPV followed by two doses of OPV. FDA's public statement on this issue indicates that in light of the current labeling of IPV and OPV, the manufacture of either product may hold such product for sale or introduce the product into interstate commerce for administration pursuant to the sequential schedule previously described without violating the

Food, Drug and Cosmetic Act or the Public Health Service Act. The FDA has not considered any of the options regarding harmonized scheduling at this time and therefore I would not be in a position to make any comment about any other schedules.

In order to change labeling other than references to the ACIP recommendations as was alluded too earlier, the manufacturer must submit adequate data to support that change. Those are the only comments that I would like to make.

Dr. Modlin: Regarding the data that exists to support each of the possible options for a harmonized schedule, it is best to analyze each option and make specific comments about that, and in the interest of time I'm going to pass, although I will weigh in when it gets to the point of discussing each of the specific options. The one question that did come up in our discussions last week was what is the data to support a schedule in which IPV is given in three doses at two, four and six months of age, the enhanced potency IPVs, and for the most part, to my knowledge, almost all of the development for the enhanced potency IPVs have involved a schedule of two doses in the first year of life at two and four

months of age, with the third dose being given in the third year of life. I believe that Neal Halsey had one arm in his sequential study in which he gave IPV at two, four and six months of age, and he may want to comment specifically about the immunogenicity following three doses. Obviously, since the immunogenicity of enhanced potency IPV following two doses virtually achieves more than 98 or 99 percent seroconversion rate after two doses for all three types in most studies, I think there would be very little concern about immunogenicity after the third dose since I recall in Neal Halsey's study that there's 100 percent seroconversion for all three types in the group that he studied. So if seroconversion is the issue I don't think anybody is going to have any qualms about a schedule which includes three doses of IPV, and I think that was one of the issues. I think there will probably be others that will come up and I'd be happy to discuss them at that point in time. I think it is maybe helpful to point out that how we come to the two-dose IPV schedule and that's sort of a historical quirk. I think there are others in the room who are far more qualified to discuss the history of polio vaccine development, but you'll recall that with IPV, the old IPV vaccine, was given at two, four and six months of age originally, and even after three or even four doses, it

was only about 80 percent effective. Because of that, when OPV introduced, it was naturally given according to the same schedule and for the first 10-15 years that we gave OPV, we gave it at two, four and six months of age. Until the early to mid-70s when it was recognized, by studies actually supported by the old Immunization Division, that two doses of OPV were as immunogenic as three doses of OPV in the first year of life, and so schedules converted over to a two/four schedule with a third dose being given at 18 months of OPV. When the enhanced potency IPVs were being developed thereafter, they naturally followed that same schedule because they were being compared with OPV. So that's where the basis for the fact that almost all of the data we have are based on; the two-dose schedule in the first year of life; and there are very few data regarding the third dose. There may be some that the vaccine manufacturers are aware of that I'm not, but I believe at least the only domestic data I've seen are those that Neal Halsey produced in his study.

Dr. Ward: This is where we stand currently, this is what's being grouped within the current revision of the statement. The ACIP could decide to just leave it that way or it could try and take one more step which is to try and harmonize. These I think are

the five options, there may be others that others can suggest but the key sticking point is here and that is the current IPV recommendation is for an interval greater than six months between the second and third dose of IPV. There is historical data to suggest that need not be necessary. There is data from some more recent studies, particularly one conducted by Neal Halsey showing that giving IPV gives you equivalent immunogenicity to the other regimens, and I suspect the manufacturer will have to comment on other data that may or may not be available. I'd like to just get a charge from you Dr. Davis as to where the working group should go in trying to resolve this or back off or wait, or have more discussion here.

Dr. Peter: The crux of the issue is to what extent we need to establish gastrointestinal immunity at a young age and we know that we need two doses of OPV in order to do so, and if we accept that principle and we believe it's important from a pubic health perspective, then indeed the subject is more complicated. If the idea is to ensure a broad range of intestinal immunity beginning at five years of age, then indeed if we adopt option no. 2 for the harmonized schedule, then we are indeed consistent I believe with the package labeling of products, because up until a year

ago we recommended OPV-3 between basically 12-18, it was really 15-18 months of age, but I think it could be interpreted as 12-18, and if one takes that then I think the problem becomes relatively simple to harmonize.

Dr. Zimmerman: I think in terms of education and the pragmatics of implementing there's going to be a lot of confusion if there's two or three different schedules. Timing wise there will be confusion among providers, confusion among parents, and I can just imagine the confusion that schools are going to have with school-entry laws, do you count this dose or not, parents who switch because their insurance switches from one to another, leave one provider, go to another. If we don't have a harmonized schedule, I see a lot of implementation problems for those of us who are practicing and I think for those who will be tracking immunizations. I think you can make arguments for a number of these harmonized schedules. I'd like to speak very strongly in favor of coming up with one of them and I can see pros and cons to several of them, but I guess I would encourage the Committee to really consider this issue and come up with a harmonized schedule so that we don't have two or three different ones.

Dr. Halsey: I would strongly support the need to have a harmonized schedule and I think it's been very helpful that Joel Ward put this together and put it on an overhead so we can look at it and listening to all of the comments I think I would focus on the decision between option one and two, both of which would allow people to give the vaccine in accordance with the package insert for either vaccine. In other words if we went to option two, we now have a 6-18 months for the third dose of OPV, and so that is certainly consistent with the OPV package insert. That is the schedule currently recommended for the IPV package insert, and option one allows you to be consistent with both schedules. I tend to prefer option one; it gives a little bit more flexibility in terms of the decision-making that people are going to have and so some of the decision that we make may have to be of how much flexibility and how much a precise schedule that we will be recommending. But I think that would simplify things, instead of having the five options which we did discuss, but I think we could focus on one or two. I would also point out that even though we do have package labeling for precise schedules, the vast majority of children do not receive their immunizations at the precisely labeled times that are in the package inserts

for any of our vaccines, based upon studies that have been done on large numbers of children throughout the country.

Dr. Orenstein: I wanted to go back to what George Peter had said about gut immunity, because if there is transmission, then transmission is more likely I think in young children, certainly that's been the case in a number of countries and if I go back to some of John Modlin's data there's quite a difference in gut immunity between one and two doses. After a two-IPV/one-OPV of 54 percent of infants challenged secreted type III virus compared to 20 percent who had received two-OPV earlier. And so the disadvantage of going to option one is that the gut immunity I think would be substantially less than if you go with options such as option three or potentially option five that would have the OPV doses given earlier in life which is the real reason we're giving OPV to begin with.

Speaker Not Identified: A question that pertains to the situation that I think we see especially in some of the border sites relates to the very early immunization with OPV in populations of immigrant children coming from Mexico and Central America where it's given shortly after birth and whether or not

that would be a consideration for any of these schedules and if any particular modification has to be made for those populations.

Dr. Modlin: I just want to point out that you can boil these issues down into two very important trade-offs. To really focus the Committee's discussions about two points which are important: one is the trade-off of early OPV administration vs. late OPV administration where there may be some physicians who adopt a sequential schedule, and prefer to give the first dose of OPV later on in order to absolutely reduce to a minimum the chances of vaccine-associated disease. This would be, for instance the group of physicians that represent the Immune Deficiency Foundation for kids who have congenital immune deficiencies. I've had communications from them and others have had as well and they would strongly prefer delayed administration of OPV. The trade-off there is that you need to wait to give the second dose of OPV later on and therefore you probably will reduce the chance of having optimal gastrointestinal immunity up until at least the last dose is given just prior to school. So that's one trade-off, and a few cases of vaccine-associated disease in immunodeficient kids vs. how important optimal gastrointestinal

immunity between the ages of 18 months and 4-5 years of life. The other trade-off is one of flexibility vs. the expressed desire to have some sort of a uniform schedule, just tell me what to give and when to give it, we'll be better off, so that we don't create confusion for public health programs and for providers, and so on. And I think arguments can be made either way, but I think there is an argument to be made for flexibility for those practitioners who do want to consider it important to delay the first dose of OPV, for instance, and there may be others who consider it important to get the gastrointestinal immunity in their particular population. And if you really wanted to fine-tune it to the nth degree it may very well be that some flexibility is important so that in different populations different schedules are going to be slightly more optimal than the other.

Dr. Peter: The other point John is of course if you don't give two doses of OPV before two years of age you therefore reduce the likelihood of transmission to unimmunized contacts, so you have further impact on the reduction of that, on the other hand to have earlier intestinal immunity. I'm just not sure how important intestinal immunity is now in the presence of lack of

circulation of wild type polio. And you'd still by administering the second dose at age five. It still has a substantial barrier within the population. The point I'm making is that a five-year-old who is toilet trained, is not likely to spread that vaccine strain, whereas a 18-month-old would.

Dr. Glode: Just thinking about those considerations that were just raised, I clearly am in favor of a harmonized schedule. We confused everyone in America with so many vaccines now with the conjugate H. flu vaccine in different schedules, etc., I just think that's a disservice and we should avoid confusion and try to have a harmonized schedule. I'm very in favor of that. I was wondering whether or not if there's another option and that option is that there would be two doses of OPV in the second year of life so that you wouldn't give the first dose until 12 months of life, anytime after, you know, and hope that children are seen twice in the second year of life, at 12, 15, 18, 24, so that you defer the first dose of OPV until 12 months, but you gave two doses of OPV ideally, not everybody obviously would get it and some people would get it at the pre-school visit, but you would get two doses of OPV in the second year of life.

Dr. Ward: That's basically options three and five accommodate that.

Dr. Glode: But it's not option three or 5 because it would be a separate option where the third dose of polio vaccine is given after 12 months of life and the fourth dose is given before 24 months of life, ideally.

Dr. Davis: I think there has to be clarity in terms of how we're going to proceed. We have to consider some very key issues and that has to do in large part with the comments that Carolyn mentioned. There's two basic options: one is a statement regarding a preferred sequential schedule and having all IPV and all OPV acceptable, but not harmonized. Second would be the preferred sequential and having all IPV and all OPV acceptable but we would attempt to harmonize and recognize that it would be ideal, that we would attempt to harmonize. The third would be basically that we would have the preferred sequential and all I and all O would be acceptable, and we would recognize that it would be ideal to harmonize but not attempt to harmonize. I see those as basically the different ways in which the Committee can go. And whether we choose to harmonize or whether we would

recommend that it would be ideal to harmonize and move in that direction, and hope that there would be good movement in that direction, then you start getting into the ideal options for harmonization.

Dr. Ward: Let me be clear. We're here and that statement is being written. What I'd like to get a vote from the Committee on is whether they would prefer, would like to try...**END OF SIDE B OF TAPE NO. 2**

SIDE A OF TAPE NO. 3:

Speaker Not Identified (not sure if same speaker continued from side b of tape 2 above):...additional step, I mean the implications of what Carolyn said are that if one wants to harmonize and it sounds like there's a lot of support for it, then the additional step would be to, once a decision is made about the option for harmonization, FDA would have to look at what data were available and make a decision about whether that recommendation is compatible with the labeling and then compatible with the interstate commerce in these vaccines. I just wanted to make sure people understand that. It's not to try to throw any cold water on the harmonization at all but to make

sure the Committee clearly understands that it does throw this other step into the process which then may impact on your timetable. But so be it if that's your desire.

Dr. Davis: I think that's a very important caveat call, it certainly would allow for very productive discussion regarding what our preferred recommendation would be for a harmonized schedule. It doesn't preclude us from discussing harmonization further and from attempting to gain consensus regarding harmonization. That's my understanding.

Dr. Ward: It would be helpful to me to get a vote, either a straw vote or official vote, realizing that the current drug insert as I read it and have spoken with the FDA about does not permit us to go to a whole cell harmonization, but a) does the Committee want us to at least discuss this further and explore additional data. In other words does the Committee want us to go forward on the harmonization or just drop it as an issue?

Dr. Davis: The question is does should the ACIP pursue further discussion of harmonization of the polio immunization schedule? All in favor? There is basically everyone around the table now,

Glode, Guerra, Griffin, Schoenbaum, DeBuono, Modlin, Sherrod, and Davis, favor that. There are none opposed. We will proceed with further discussion on harmonization.

Dr. Davis: As the chair, I just wanted to make sure that we had a reasonable amount of time to discuss these options before we move to adopt any one of them. I'm willing to move at a slower pace for reasonable comfort so we can all absorb this. I think issues regarding compatibility with product inserts is very real and very important and I just want to make sure everyone is clear on that.

Dr. Ward: This is the first discussion of this issue at the ACIP and I think we will proceed through the working group to get all the data and all the trade-offs, and you know that there is much sensitivity about each of these issues and I do think it should be done very prudently and carefully with review of the data and with conversations with the FDA and with the manufacturers on their data base.

Dr. Davis: There are minutes of meetings that we had as a working group where there's fairly detailed discussion of how things proceeded. I would point that out to people here in attendance. I think these have been very well documented.

Dr. Snider: We are totally dependent for the minutes of this meeting on the recordings that are being made, as opposed to at other times when we've had someone here also taking notes in addition to recording, and so that's why we are trying to get people to speak up into the microphone so that we can capture the full discussion that takes place at this meeting.

Dr. Hardegree: Can you just lay out what the next steps are in terms of what to expect at the next meeting?

Dr. Snider: What we were hoping is that the working group would take the current draft with comments from everyone. They would have these discussions about harmonizations and options for harmonizations, and other comments received, and develop another document which would be the subject of discussion at the June meeting. It would be mailed out in advance of the June meeting and made available to you so you'd have ample time to look at it

and be ready for discussion at the June meeting. In anticipation, there would be a high probability that we could finalize the statement at the June meeting if everything falls into place the way we hope it will. There has been some discussion about announcing the next meeting in the Federal Register so that all interested people would have an opportunity to make public comments at that time as well.

Dr. Hardegree: I just really wanted to know if we were going to move toward closure of the statement at the June meeting?

Dr. Ward?: Yes, that is certainly what has been planned. Actually at this point what we were planning to do is have Dr. Halsey and Dr. Zimmerman give very brief summaries of where the Academy of Pediatrics and Family Physicians are on policy-making. I will try to be very brief in talking about issues on timetable for implementation, and that's not something we need a decision on. I think this will have to be discussed by the working group but to begin to lay out some of the thoughts we had and then Roland will talk some about the statement and where we clearly will need the most input.

Dr. Halsey: The Academy of Pediatrics is continuing the process of reexamining the polio immunization policy. We have not had formal meetings of the Committee on Infectious Diseases since the ACIP last met, and George Peter read to you the AAP position at the end of that last meeting. We have had additional meetings with other Committees within the Academy and we have sought out input from other members of the Academy through a couple of mechanisms and we have received feedback from those individuals. We will be drafting and working on a revised statement and we will be working on that over the next few months. We anticipate having an in-depth discussion at the May meeting and anticipate finalizing such a document within a couple of months after that meeting. We're on track for revision of our policy made through July of next year. I would like to point out, we have received mixed comments from the public and pediatricians in response to our formal request for input, as well as in response to surveys that have been sent to physicians. The comments are mixed, some highly supportive and of interest. A few physicians have decided on their own to go ahead and offer options to families and a high percentage of them accepted the sequential schedule or IPV. We've also received some very strong negative comments, including negative comments because we were presumably undertaking a review

of the policy to recommend four injections at each visit for children. I would like to go on record to indicate that our Committee has never made such a statement, has never adopted such a policy and it is not the policy of the American Academy of Pediatrics to recommend four injections. So I think that information is not correct and I'd just like to make sure everybody understands that. Thank you.

In response to the changes at ACIP on this polio statement, we've looked at some of the potential legal ramifications, some of the issues relating to group practice when we have a pediatrician and family physician practicing side by side, and issues with state laws and implementation of universal purchase. In response, our Commission on Clinical Policies, Research and Scientific Affairs has made a number of recommendations to our Board of Directors. I should note that these are recommendations made to the Board and have not been acted upon by the Board and is therefore not yet the policy of AAFP. First of all I'll mention that we have given preliminary approval to the use of acellular pertussis vaccine upon licensure and we use that as a preferred statement. We also consider polio vaccination to be a standard of care, i.e., all children in the country should receive polio

vaccination. The type of polio vaccination, we recommend balanced, parent, provider, choice. That's choice between all OPV, all IPV or the sequential schedule with implementation to be in 1997. We are planning to develop balance sheets to help our constituents explain the pros and cons of these three options so that they understand them and they are able to explain them to their patients.

Issues that we have been concerned about are that the lack of a combination vaccine and with the pending licensure of acellular vaccines, there would be an increased number of injections. That does have cost implications if a parent is unwilling to accept multiple injections. We're also concerned about the overall cost of effectiveness and I think we are somewhat comfortable with giving our patients options. Working with them to choose what is best for their families instead of the issue of choice is perhaps not as scary or as feared among our practitioners. We are somewhat used to providing patients with choices. I would ask that ACIP consider, and I think there is precedence in the Department of Health and Human Services for this, including balance sheets and the ACIP recommendations, this is done by the Agency for Health Care Policy & Research, for instance, including

a section on recommendations of other groups, and including the issue of cost.

Within the National Immunization Program we have met several times to review the key issues and what might be rate limiting steps to implementation, and to begin to talk to how to develop appropriate educational materials to permit implementation. The four broad areas that we've talked about are logistics and program, information, education, enhancing surveillance and assessment, and other issues. The first is to develop the revised ACIP statement and as we've said we now have a solid working draft which we will get comments on from this meeting. It will be distributed, revisions will be distributed to Committee members and made available to the public before the next meeting and we'll get intense discussion at the next meeting. At least our plan at the moment is to try and finalize it following the next meeting to submit it to the Director of CDC.

A draft has been prepared within NIP and approved through the office of the general counsel of the vaccine information sheets which are required by law to be given to parents who are receiving polio vaccines. This information sheet assumes a

sequential schedule, but it includes information on all three options including IPV alone and OPV alone with some information on both the benefits and risks of each. The next step on this would be to submit it up to the Department for review and possible revision and ultimately to put this into the Federal Register as a public notice for a two-month comment period after which it would be revised based on those comments and could be prepared for publication and distribution

Vaccine availability, in discussions with Connaught we've been told that there would be an adequate supply by the middle of this year.

Some more minor issues, how to phase in the schedule, I shouldn't say minor issues, this is perhaps focusing on selecting a date, clearly states providers, manufacturers would like to know the dates ahead of time. We need to coordinate with the other advisory bodies. Our earliest working implementations date of January of 1997. It would make sense in that it's the beginning of a calendar year when we republish the harmonized schedule based on our current work with the ACIP statement and with the vaccine information sheets, we are on target for that date, if that were to remain the date for implementation, or if that were

to be accepted as the target date for implementation. We would need to revise the harmonized schedule.

Other issues to keep in mind, is the anticipated DTaP vaccines will be licensed during the coming year but not as combination vaccines. The timetables for DTaP combinations are uncertain. We know of one that has been submitted to FDA for possible licensure but they are clearly not coming rapidly and some companies have found difficulties in compatibility of Hib and DTaPs when combined in the same vaccine. This is just reminding you that the combination products which would make an implementation timetable easy to establish are unfortunately some time in the future.

Information education...it's clear that we will need a major effort. Clearly certain efforts need to be focused on parents and others on health care providers, the vaccine information statement is being modified now, brochures that we've used for educating parents, Parents Guide to Immunization, and a new brochure focused on the polio policy change will begin to be developed now that we have a draft ACIP working statement and could be available by the end of the year.

And finally we've discussed within NIP the need to have a meeting with the provider group, physicians, nurses, on public health to discuss the issues which have been discussed before the Committee to make them aware of them, to try to reach more of a consensus on how to implement this.

Items such as enhancing surveillance both of wild polio and vaccine-associated polio so that we can pick up any changes, that a change in policy might result in, surveillance for adverse events from much broader use of IPV is an item we will work on with FDA and monitoring effects in coverage to not only of polio but of all vaccines to determine whether this is resulting in any change in coverage or any reduction in coverage.

We've heard about the package labeling issue. The other issue which I think we cannot lose track of and which the Committee is fully endorsed is maintaining the focus on global polio eradication which we all strongly support and needs to be done with OPV and the strategy that the World Health Organization has defined and to make sure that is kept as much in the limelight as any change of polio policy in the U.S.

The likelihood that this change in policy would result in a change of vaccine coverage and an increase in vaccine-preventable

diseases, and basically, and I don't recall the exact votes, but most members felt there would either be no or a very small change in coverage and that there would be no increase in vaccine-preventable diseases.

Dr. Sherrod: Would it be too costly to do a pilot study to look at the outcomes and therefore prior to your implementation you would have some scientific basis for going on with your implementation. I think people would feel a little bit more comfortable if they could be assured that this change would not result in decreased vaccine coverage. And the other thing I think the Committee really needs to consider is what's going on in health care right now and that's the transformation to managed care and the fact that physicians will not have a lot of time to talk about options in the managed care setting, and I think we really need to seriously consider that because the push to managed care is actually to decrease flexibility, to decrease variation, and to standardize. I think that is a major point of discussion and should be considered.

Speaker Not Identified: There is one other point that has been raised to me that I think is important to bring up as well. The

Committee I'm sure fully understands that there is no way to go back to where we were with having an OPV recommendation. In terms of having had this discussion the public exposure of this and so forth, there has also been the question of what would happen if one went with OPV to the credibility of the entire vaccine program given what we know about the adverse effects of OPV. I only made this point to say we're in the new world so there's no way to go back to where we were. We have to go from here to whatever recommendation that we...recognizing that there's going to be implications with any decisions that are different from the implications of the decision that was made in 1982.

Dr. Sherrod: I understand the implication of change, there is a lot of fear, but I don't see any scientific data to make me feel comfortable that this decision is going to mean a better scenario than the 8-10 cases that we are talking about per year of vaccine-induced polio. Is there any data that would suggest that the scenario would be different, considering all of the risk factors. I think we're kind of skewed toward the data that there will be a reduction in the cases but we haven't looked at the

impact of compliance and the possibility we could end up worse off.

Dr. Peter: We've really considered a lot of information and there have been a lot of models that have been developed. It's been a very intensive process for those of us that have been going to the various meetings and have been participating in these discussions. There really have been a lot of different models that we have considered. We recognize that based on the scientific data that is available to us that there are certain theoretic precepts that we have to consider. There is no question in that we would certainly want any implementation of a change to be done in as smooth and in as a well-informed way as is possible. If anyone else wants to add to that, any good ideas that facilitate reasonable implementation certainly would be important.

Joel Ward: I feel the need to comment, Jessie, as Chairman of the working group. This has been a two and a half year process. The amount of data and information on my desk is probably 3 feet and it has been carefully delivered in sequential steps. There has been a series of votes that have been taken. There have been

discussions. There have been big public meetings, public hearings, and you're coming in at a stage farther along in the process. The Achilles heel of the whole evaluation process is to back to square one at every point and I think it may be appropriate to ask those questions, I know it's appropriate to build in evaluations as one implements, but I would like to make sure that you are fully aware of all of the issues and all of the past decisions before we potentially shoot ourselves in the foot.

Dr. Sherrod: Right, but the only thing I'm asking is, is it possible to look at a scenario, is it possible to do a pilot study, to actually see what the outcomes would be? I mean could you do that prior to implementation? Then you would have some basis for going on with your decision.

Speaker Not Identified: I think it is possible and in fact it is going on right now. Since the discussion was opened a year ago many people have adopted an all-IPV or I suspect some have been using the sequential approach, and it's just a question of monitoring it. The problem is that the people who choose these various approaches are not a random sample. They tend to have high compliance because they believe strongly in one approach or

the other. But I think that we can and need to consider it. This question comes up on every recommendation ever made from this Committee, whether it was H flu or a change in DTP or DTaP. We never can anticipate every question and every impact and I do know for this issue with polio there have been more discussion, more dialogue and more evaluation than any other issue during my tenure here. So perhaps we could review some of that.

There is somehow a debate between a prescribed regimen and the alternative being parent/provider choice. Because so many people come in and out of these discussions we almost need to articulate at every iteration of this that there is no question as to whether there is and will be parent/provider choice. That is not being debated. The ACIP in taking a recommendation or making a recommendation for a sequential schedule with OPV and IPV on long regimens being acceptable alternatives is acknowledging that there will be choice. We are not in any way considering eliminating or limiting that choice. We are exercising our responsibility to make a recommendation as to what we believe is best, but both parents and providers, by the content of this statement, would have the clear option of choosing one of the other approaches if they wanted to do so. We run the risk of

being cast as anti-choice in this and I don't think that approach has ever been considered by the Committee in this discussion.

Dr. Sutter: This draft statement reflects the 2nd draft and basically includes the comments that were made by the polio working group on the conference call last week so it's hopefully already an improved and better draft than the first one.

In the preface and page 2 we state how we deal with an all-IPV and an all-OPV and a sequential schedule and it would be very helpful to have your thoughts on the wording. We have a lengthy background section going into polio epidemiology, secular trends and vaccine associated polio. And we have also the first table up front, the Risk or Ratio of Number of Cases of Vaccine-Associated Polio by Number of Doses. The statement actually gets into the vaccines and those are more composition and scientific information about the different vaccines, and what we know about sequential use of IPV following by OPV, the rationale for a sequential schedule and safety issues. Also we have a table where we try to summarize all the immunogenicity data of the two IPVs that are currently licensed in the U.S. The statement gets

into recommendations for poliovirus vaccination including routine immunization, recommendations for infants, children, adolescents, recommendations for adults, and so on. It ends with precautions and contraindications, adverse reactions and investigations and reporting of suspected cases of polio. We would appreciate your thoughts on the structure as well and the content of the statement.

In terms of issues, there are a couple of major issues, some of which have been discussed this a.m. already, including the schedules for each vaccine series. Should there be specific indications for an all-OPV schedule, get a little bit into vaccination of adults and vaccination of infants residing in households with unvaccinated or inadequately vaccinated persons, and again these issues came basically out of the conference call last week. A minor issue which I will not get into at all is vaccination of infants with diarrhea, and please comment on that section when you send in your comments.

I think this is the first of the major issues that I want to get into and that is should the ACIP recommend indications for an all-OPV schedule where OPV would be the preferred vaccine, and

that could be as is presently in the statement, infants that start late, that start when they're older than six months of age or children who fall behind in the schedule, it means a dose would be delayed by more than three months. Those children could receive OPV or perhaps should receive OPV, particularly if the number of injections is a concern with the parents. The other example I have here, OPV may be preferred in the unimmunized migrant populations or populations with no vaccination coverage and I'm interested to hear comments from the Committee. I think in terms of pros for having an indication for an all-OPV schedule would be clear programmatically, it clearly would decrease injections that perhaps would have to be given at one visit if one had to give MMR, DTP, Hib, hepatitis B, varicella, etc. and perhaps would increase parent/provider acceptability.

In terms of adult vaccination recommendations, the question has come up, should one just give IPV to anybody who is older than 18 years of age regardless of previous vaccination status, if they are previously vaccinated or unvaccinated, should one just recommend IPV, and clearly this would programmatically be a clear message, it would be easy to do, there would be no vaccine-associated polio associated with this policy, there would be good

individual immunity. On the cons, perhaps one would be a little bit worried about the message that would go out and say OPV is okay for infants but not for adults. It perhaps would require that we designate IPV as the vaccine as choice during pregnancy if vaccination is indicated and perhaps it would also lead to less optimal population immunity although just slightly less than with an OPV and IPV schedule.

Vaccination of infants residing in households with unvaccinated or inadequately-vaccinated persons and what should be done, created quite a bit of discussion during the conference call. Should one try to get the unvaccinated parent in and try to vaccinate them; another way would be to perhaps designate IPV as the vaccine of choice in those situations. But the questions that have come up to ask I think is how often do health care providers ascertain vaccination status of parents; can any recommendation be based on requiring or ascertaining adult vaccination status? So in this situation if we know that an unvaccinated adult resides in a household of an infant, that infant could receive IPV only. Again, programmatically it would be a clear message whether it's feasible, practical, is another question. It may reduce contact VAPP. In terms of cons, clearly

we wouldn't know at this point what proportion of households would qualify for this and also in terms of legal implications we would put the burden of screening on health care providers.

In terms of sections that are not currently in the statement, there are three sections which were proposed including a pros and cons section of the three different schedules of an IPV/OPV and a sequential statement lay out the pros and the cons, and the recommendation of other groups, and that has been reinforced this a.m. again. It also was suggested to put in the details on the cost benefit study as well to provide more information on that aspect.

That's basically what I was prepared to say and I appreciate comments and particularly appreciate written comments and suggestions.

There are two individuals who register for public comment, the first is Garnett Slaten from St. Simons Island, a concerned citizen, and the second is John Salamone, a concerned parent with a child who has a vaccine-related polio injury. He is a member

of the HHS Advisory Committee on Childhood Vaccines. Mr. Slaton first and then Mr. Salamone.

Mr. Slaton: I appreciate the chance to talk with you this morning and I'm a little disappointed there were several other groups who were planning to be here I know, both with concerns about the domestic issues and concerns of international issues, but we were told that there wouldn't be time for public comment today. In light of that I'd like to encourage you, I know there's been discussion about publishing this statement in the Federal Register and asking for public comment, and I'd strongly urge you to do that before the June meeting. I'm not sure how much good it will do to have a 4-hour session after you've made all your decisions. I think it would be much more valuable information for you to get public comment and response to the published statement in the Federal Register, so let me strongly urge you to do that.

Last October I spoke with you representing MAP International which is a global organization which shipped over $300 million in medicines over the past three years under my direction. I've since left MAP but my interest in this issue continues because I

think it's one of very, very high importance to worldwide health. Since October I've continued to stay in touch with literally scores of organizations involved in international health and I'd like to update you today on what I'm finding. As I've talked to more and more of these organizations, a consistent pattern has emerged. Not a single organization that I've spoken to has supported a U.S. schedule which includes IPV, not a single one supports this schedule change. These organizations which together provide a significant percentage of the health care in the developing world have been unanimous in opposing the proposed changes to the U.S. polio immunization schedule. These organizations have been unanimous for two reasons: 1) they unanimously support the joint position of WHO, UNICEF, Rotary and CDC which states that OPV is the only vaccine recommended for polio eradication. They are unanimous on this point for reasons which you well understand, the economic advantages of OPV, the fact that OPV is much safer to administer, and the superior protection that OPV provides to children in polio-endemic countries. Secondly, and more to the point of this debate, I guess, these organizations are unanimous in their concern that the U.S. inclusion of IPV in the recommended schedule will encourage other countries to use IPV, thus undermining the global

eradication program. In letter after letter to Secretary Shalala and Dr. Satcher and others, these organizations have shared their experiences of how U.S. policy has influenced developing countries. I've provided Dr. Sutter with copies of a number of these letters. I hope that you all will take the time to get them from him and if you'd like me to provide you all with these copies I will as well.

I know that CDC has in the past and will continue to support OPV for developing countries. However, I've heard again and again from these international practitioners that actions speak louder than words. I've heard again and again that a position of do as I say and not as I do have very little credibility to people in other countries. Now I understand that this can be an emotional issue for many people and even in light of that I've been surprised to hear such inflammatory language as the U.S. being held hostage by the rest of the world. As a parent I try very hard to teach my children that their actions have consequences and that they have responsibilities to those consequences. Now all of these organizations from Africare to Church World Service to International Aid, to International Medical Corp, and many more, they are saying to you all, this change will have

consequences as well and we can't put blinders on that limit our view just to the boundaries of this country. What we do here has impact on the rest of the world.

I'm asking you again today that you consider the consequences that this change will have not only for a handful of children in the U.S., but for millions of children outside the U.S. It's possible that all of these organizations are wrong about the impact that this change will have. It's possible that all these organizations seriously misunderstand the countries they work in and the people that they serve. But what if they are right? What if they are right? Is it wise to risk millions of lives in an attempt to save a few? Is it wise to put the worldwide eradication program in jeopardy when the end is so near? Thank you.

Dr. Ward: As a routine, since all of the members of the Committee have been asked to give financial disclosure, I wonder if it's appropriate for any speakers to state as to whether their organizations or individuals have been funded by the pharmaceutical industry, as a point of information? Could I ask the question, because I'm not familiar with MAP International, whether there is any pharmaceutical funding?

Mr. Slaton: I no longer work for MAP International. I'm here just a private citizen. MAP International does however receive pharmaceutical donations, that's the business that they are in. They received donated pharmaceuticals from literally hundreds of companies in the pharmaceutical industry and they distribute them worldwide. That's correct.

The next public comment is from John Salamone.

Mr. Salamone: I might actually save you a little bit of trouble today. I have formal comments that I'm willing to present for the record, but I'm so glad that this question was brought up regarding the influence of pharmaceutical companies on this process, and I'm just going to go out of line here and take these comments and toss them. The bottom line is my son who is five years old, David, has polio, and he received polio from his vaccination. Now I realize that I'm talking as just one parent out of perhaps 8, 10, maybe more whose children contracted polio and contract it every year as a result of this vaccine. And I suspect by the way that number is even larger because it took three years for David to be diagnosed with polio. In any case,

it was very fratuitous that I was sitting next to the gentleman who preceded me at this microphone today because as I was sitting there as you were having comment, suddenly my remarks that are over there at the table come running up to him by this bearded gentleman and he said did you see this, did you see this, and I couldn't help but ask him, who was that man. Want to guess? Well, he's a scientist from New York. I said is he with a pharmaceutical company up there? Yeah, I believe so. I'm gonna leave it at that because I believe that issue can't be decided by the pharmaceutical companies. This issue can't be decided on what's happening overseas and whether or not a policy in the United States is going to affect the entire world, and I think it's quite presumptuous of people to say that if we make a change that's good for our children, good for the U.S., that we can't make that change because the rest of the world will just follow suit. So I'm gonna spare you these five minutes of remarks and I'll ask the secretary to please send them to you, but I'm going to end it with this and thank you.

Approval of Pneumococcal Vaccination Recommendation

Dr. Breiman: People are dying from a highly drug resistant strain of *S. pneumoniae* that is essentially resistant to everything except erythromycin, and it's actually the first time we've seen an outbreak. This is the first time we've investigated an outbreak of streptococcal pneumonia resistant to just about everything. We can strongly recommend pneumococcal vaccination for immuno-incompetent persons, but the evidence is less compelling, it starts coming down to our expert opinion and that's why we want to say that we recommend. Jane Sisk who was involved in the original cost effectiveness work on pneumococcal vaccine that was done in 1980, is fortunately with us today. As of last Friday night they had their first results from the model which they are currently creating. This model is only looking at persons age 65-74, only at bacteremic cases, and only with an assumption that the vaccine works for six years. Her first estimate is that the vaccine under those conditions has a cost effectiveness ratio of $20,000 per year of life saved.

Pierce Gardner raised the issue of whether or not giving pneumococcal vaccine, such as with influenza vaccine, might lead to a burst in HIV replication. We know that the data had been somewhat equivocal about what the significance of that is and he

has suggested we put in a statement with a reference which says, "preliminary evidence has shown that immunization with pneumococcal vaccine may result in tangent increases in HIV replication. The significance of this is unknown and the marked increase in invasive pneumococcal disease and HIV-infected patients outweighs the theoretical risk associated with immunization."

The next issue is re-vaccination, and it's been noted that we have made a weak recommendation about re-vaccination. In this statement we made a recommendation to re-vaccinate on a five-year basis. The language for the current re-vaccination recommendations is fairly passive and yet we have a big section on the need for tracking and a recall systems. Therefore the way the statement reads is, if you find a patient who has been vaccinated more than five years ago, and has not been re-vaccinated, you might consider re-vaccination. We don't know about long-term efficacy so we're not sure whether re-vaccination should be done, however, at the present, from what we do know, we think you should be re-vaccinated.

The re-vaccination issue first came up because of the recommendation to immunize everybody at age 65, and individuals who were immunized earlier would get a second dose. The current pediatric-focus is to immunize everybody every five years, and persons at highest risk, would be re-vaccinated, not just until they are 65, but continue every five years. We routinely re-vaccinate, so it would be easier to simply say that a child receives a vaccine at two years of age, should routinely be re-vaccinated at a later time. And that in part is based upon both the complexity of the current recommendations and secondly the fact that children between two and five years of age don't really respond as well as adults. That doesn't necessarily answer the question, but it indicates some of the realities of the situation.

Summarizing, if persons are at highest risk, on the basis of our expert opinion, we would recommend they be re-vaccinated every five years, and that most of those probably developed high-risk conditions and are known to be high risk as a child. Persons who are 65 and older who get vaccinated for the first time, or re-vaccinated once if they had not been vaccinated within the previous five years.

Preventing bacteremic disease in the 45-64 age group and probably even go beyond. But I think we're most concerned with the fact that 85% or more of the disease occurs in people above the age of 65, and only about 30% of those folks have ever been vaccinated. Our concern is that in a time of limited vaccine availability, focusing on where the population at risk really is, an today, it is not in the 50-64 year age group. This started with whether or not we should broaden from people who have these high-risk conditions to the entire population over age 50. Steve Schoenbaum says that in the 65 and older you have a cohort of 31 million people, and then the document says below age 65 there are actually 32 million people who are supposed to be candidates for the vaccine. If you broke down those 32 million by age what percentage of those would be in this 50-64 age group and what percentage of the total is that? People probably are over the age of 40, but where the cut is at 50, I don't know.

One point I wanted to make has to do with smoking as a risk factor. There's no discussion of it in the statement and I'm mindful based on what Steve mentioned that there aren't strong data, however, I do feel that it's prudent for us to at least

consider it and present the data that are there so that we don't ignore the fact that smoking may be a risk factor.

I want to thank the working group, they are continuing to do an excellent job on this statement. There's a lot of new concepts that are clearly being brought into it and I think we are moving definitely in the right direction. I want to encourage you to review the statement and provide your comments to Gloria three weeks from Friday.

HARMONIZATION

Jacqueline Gindler presented an update on the proposed publication of the Recommended Childhood Immunization Schedule for July-December 1996. Because of the necessity of publishing an Ainterim@ schedule in July 1995 following licensure of Varicella Zoster Virus Vaccine (Var), the committee decided last year to publish the schedule twice in 1996 (i.e. in January and in July) in anticipation of licensure of acellular pertussis vaccine for infants. However, as the time approached when final drafts were required for July publication in *MMWR, Pediatrics,* and the *American Family Physician,* DtaP had not been licensed for infant use. Therefore, it was necessary to discuss options for

publication of the July-December 1996 schedule. The committee agreed that since no vaccines routinely recommended for use in children had been licensed, and that no recommendations had changed, the only option was to reissue the January-June schedule for July-December. There were suggestions to indicate in a footnote that this schedule may change as new products are licensed, but that the official schedule would be reissued in January 1997, and each January thereafter.

Dr. Gindler indicated that there had been an error in the MMWR publication of the January-June schedule in that the shading in the bar for adolescent hepatitis B vaccination indicated that this was Aprimary@ rather than Acatch-up@ vaccination, and that MMWR had indicated that they were going to republish the corrected schedule in an upcoming issue.

In terms of DtaP, the issues to be considered were the following: 1) should a preference for DtaP for infants be stated, and if so, how strongly; 2) should a preference for DtaP vs DTP for age for administration of DtaP as the fourth dose; 4) are there data to support recommending the fourth dose at 12-18 months of age; and 5) will DTP be an acceptable alternative to DtaP?

A draft footnote for the schedule was presented, relating to recommendations for DtaP vaccination for infants, when the vaccine is licensed for infant use. The draft footnote states that DtaP is licensed for use in children beginning at two months of age and is the preferred vaccine for all doses in the series. Whole cell DTP vaccine administered alone or in combination with Hib vaccine, when Hib vaccine is indicated, is an acceptable alternative to DtaP. DTP may be administered as the fourth dose at 12 months of age, if at least six months have elapsed since the third dose. DtaP may be used for the fourth dose only in children at least 16 months of age. The figure has been changed to list DtaP before DTP to indicate the preference for DtaP (i.E. ADtaP or DTP@ instead of ADTP or DtaP@ [as in the previous schedule]).

Dr. Dixie Snider commented that the Committee needs to address whether licensure of a vaccine is sufficient to that vaccine=s being included in the published schedule, or whether it is necessary for the Committee to have completed its recommendation. He indicated that without an official ACIP statement, there is no agency policy.

Dr. Geoffrey Evans: We have over 5,000 claims now filed and have been receiving about 100-150 per year. In the postprogram we had a little bit of an increase this year because we changed the table and that has slowed down, we've had a decreased number of filings within the past 4-5 months because there has been a challenge to the vaccine injury table revisions Under adjudications we are more getting through the pre-claims; 69% of them have now been adjudicated and we've paid currently over $600 million in awards.

Another brief update, I've spoken a couple of times about the excise tax provision, the flat excise tax, that was sent to Congress by Secretary Shalala. There is no opposition that we are aware of but it has been lost aside with all the other things that are going on.

The first section of the Vaccine Injury Act that pertains to studies had to do with section 312,was published in 1991 and under that Sectary was mandated to propose changes to the Vaccine Injury Table for pertussis and rubella vaccines in particular. That was released in '91; revisions to the table and we finally had a final rule published on February 8 which went into effect

March 10, 1995. That made significant changes to the conditions under DTP vaccine. And it is that set of revisions that is now into challenge by the Court.

PHS agencies meet with the FDA, CDC, who have their own guidelines in terms of use and recommendations and try and come up with some agreement so we can then propose a rule that will have some of this information in it.

When the program went into effect, it turns out that there really wasn't any mechanism to add new vaccines, so the Omnibus Budget Reconciliation Act of 1993 not only permanently reauthorized the program which is a very good step forward for us, but it came up with some things for the secretary to do such as publishing within two years the final rule adding vaccines that at that time had been recommended by CDC for routine administration of children. At that point it was Hib and Hib B vaccine. Obviously we have not made the two-year deadline. We also have within two years with any new vaccine that's licensed and recommended for routine administration, and when we make those kinds of additions we are supposed to also include injuries, disabilities, illnesses, and the time periods that are associated with it. Adding a vaccine to a table through the regulatory process,is

only half the step. The other step is that Congress must assign an excise tax to any vaccine that's added to the program, and only then it receives coverage.

The ACCV met and asked for the Secretary to assemble an expert panel to review the report. The FDA, CDC and the Vaccine Injury Compensation Program put together a set of proposals based on or at least reactive to the Section 313 report and put together some proposals that the NVAC Committee met and did a review on. And so FDA staff would do it for information that would go back to the Vaccines and Related Biological Products Advisory Committee, and the CDC staff would do it for information that would be germane to the ACIP, and of course we did it for the Advisory Commission. And in March of '94 the NVAC Subcommittee met and then ACCV we have now published a notice of proposed rule-making that detail changes to the Vaccine Injury Table in terms of conditions, and adds two vaccines to the Vaccine Injury Table.

There is a public comment period by statute lasting six months; and there's going to be a public hearing scheduled on the second day of the commission next week on the 29th. And hopefully we will have a final rule with these proposed changes or some variation therein within the next year or two.

areas of change that were part of this. The IOM found GBS to be a category four conclusion meaning it favors causation Bronchial neuritis is added, that was also a causal category condition, and the NVAC agreed but left an age qualifier open and we decided that since case reports listed at least two cases in infants less than six months of age that it would be appropriate to add that for coverage for both infants and adults

One area of disagreement also was Thrombocytopenia. The category 5 conclusion was definitive and therefore we decided that it should be added to the program but recognizing that most, nearly all cases of Thrombocytopenia following MMR are transient Residual Seizure Disorder was removed under MMR is questionable biologic plausibility in the absence of Encephalitis. Under Vaccine-Strain Measles and Polio Viral Infections, these were both category 5 conclusions and the way the Vaccine Injury Table exists today, polio is covered, and any polio virus condition that is tissue-specific, The same would be true for measles,

And finally, going back to legislation 101, the last category is any new vaccine recommended for routine administration by CDC. What we're trying to do by incorporating that in the rule is

stating that once the rule passes any vaccine that you recommend and is endorsed by CDC for routine administration would automatically be added and that once it=s automatically added by virtue of the rule-making that there's a flat excise tax automatically implied. So a process that is now taking several years will take only a couple of months and that would mean some practitioners and manufacturers would have liability protection.

Lastly, I'd like to mention Hib. We went back and forth and at the NVAC Subcommittee we decided not to propose adding it to the table because of concern over a time lapse,

Dr. Rob Breiman: To remind you, the National Vaccine Program Office which was part of the office of the Assistant Secretary of Health, was moved to CDC in June of 1995 as part of a reorganization of the office of the Assistant Secretary of Health. After reevaluating again what the NVPO does and its role as the coordinating organization for Federal vaccine activities to try to create a coherent, and try to ensure a coherent Federal vaccine program. There was agreement that the program should continue and CDC found the resources largely due to the help of so now NVPO is basically going to continue and in

the process we were reviewing, as I say, the function of the National Vaccine Advisory Committee, There was a feeling that this kind of composition of that group could provide advice and recommendations that would be very useful to the NVP and to the U.S. Public Health Service. NVAC because of its composition and also because of its charter, is designed to make recommendations on vaccine policy, how to get people immunized and how to get over hurdles regarding vaccine safety, and looking at new vaccines, developing new vaccines and so forth. I'd like to propose and I think we should find a way in the next few months for Geoff and probably Ed Marcuse who is Chairman of the NVAC and perhaps a couple of other members of both the ACIP and the NVAC to get together and consider ways that there could be a sort of symbiotic relationship between the two and provide the kind of public health recommendations that we need,there is still the unmet needs of funding which is a relatively small pot of money that the National Vaccine Program Office distributes to fill in weak areas or voids regarding priority vaccine issues. And we are actually in the process now of collecting proposals and over the next month or two we will be meeting to make decisions about some of those.

Dr. Strikas: I'm going to give you an overview of what is the current state of knowledge on vaccinating HIV-infected people, with the exception of influenza vaccine which Dr. Belay is going to talk about in some detail. So the real question is: Are the current recommendations that the ACIP has and Public Health Service has adequate? Should the recommendations, and we believe they should, discuss more completely the potential risks and benefits of vaccination of HIV-infected people? Does the ACIP with to alter their recommendation for vaccinating HIV-infected persons.

It's fairly clear that pneumococcal infection poses a great burden, with on increased incidence and severity of perhaps 100-fold increased risk of pneumococcal infection in HIV-infected persons as compared to the general population. There's some controversy that Hib is an increased risk for HIV-infected people, but there are people who do recommend vaccinating them. Measles has been documented to cause severe disease and death in HIV-infected folks, and Hepatitis B causes an increased risk for the carrier state.

To round out the list with the exception of influenza, Zoster is a frequent manifestation of compromise in this population, Pertussis hasn't been clearly documented to be a problem as yet, and we haven't seen any reports of mumps, rubella, or polio, in HIV-infected people.

Some of the concerns that have us bring these issues to you include the safety of vaccines in HIV-infected populations, the effect of HIV-infection on vaccine effectiveness, and is there exacerbation or progression of HIV-infection following vaccination. The data we're aware of say that in children rates of common adverse events are similar between HIV-infected and HIV-negative persons. The effects of HIV-infection on immunogenicity and vaccine effectiveness in general is fairly clear: responses are impaired as HIV-induced immunosuppression progresses, or the more disease you have the less you respond to the vaccine, And antibody levels may be lower in people who do respond to vaccine than those who are healthy. Responses to vaccination after the onset of HIV infection appear to be lower than responses that occurred before the people were infected. Vaccine-induced antibody probably declines fairly quickly over time, as well.

As far as exacerbation/progression of HIV infection following vaccination, we've seen no differences reported from HIV-infected unvaccinated controls in their rates of progression to AIDS compared to vaccinated HIV-infected persons. There is no reduction in T4 cells in vaccinated people compared to unvaccinated persons, and no decline in CD4 cells or increase post-vaccination in p24 antigen.

No one has found any increased progression in clinical disease in anyone receiving pneumococcal vaccine who is an HIV-infected person. Rhoads found no changes after TD vaccination and some other vaccines in military recruits, but a recent abstract by Ostrowski at an AIDS meeting suggests that there is increased isolation of HIV following tetanus-toxoid vaccination. Some studies following measles vaccination say there is no increase in p24 antigen, no change in clinical setting, and no one's found vaccine viruses in this population. There are no data on effects of Hib vaccination on HIV-disease or virus progression. And lastly on Hepatitis B, Steve Hadler and colleagues documented there was apparently an increased risk of a carrier state in HIV-

infected persons shortly after hepatitis B vaccination if they're exposed to that virus.

So there's a smattering and a mix of information about worsening of HIV viral replication, nothing about clinical progression of the disease. We have mixed data about the risks and benefits of vaccination in terms of the burden of the disease.

Last year the CDC, with other Federal agencies and the Infectious Diseases Society of America put together comprehensive recommendations for preventing opportunistic infections in HIV-infected persons and those have been published now in several places, most recently in the February 1st issue of the Annals of Internal Medicine. These recommendations focused on the most important things that affect HIV-infected persons, such as Pneumocystis carinii pneumonia and on down the list, and in fact vaccination was really very much a secondary aspect to that effort. The vaccine recommendations were for influenza and for pneumococcal vaccination, that vaccination should generally be offered but the pros and cons should be discussed and they need not be considered a standard of care. Vaccination in HIV-infected persons has become a more visible issue, particularly

this last fall with influenza vaccine. There was at least one key publication which indicated the possible complication of an increased viral load and therefore potentially acceleration of HIV disease, and that lead to a lot of concern about this issue.

Dr. John Ward from the Surveillance Branch of the Division of HIV/AIDS Prevention: There have been some suggestive reports that the load of HIV increases in response to vaccination and perhaps other immune stimulating events. Those would just be interesting laboratory findings except for the concern that those may actually be telling us that this may hasten HIV disease progression and shorten the survival of people infected with HIV. We looked at this question to see if we can look at the data in the context of survival of people with HIV by various interventions to see if we could detect an adverse consequence of being vaccinated with a pneumococcal vaccine or with the influenza vaccine.

The study has been going on since 1990 and we now have over 32,000 patient records reviewed and in the data base. We collect a variety of information as to the type of therapies and interventions including vaccines that are given to persons and a

variety of illnesses are surveyed for and a variety of laboratory markers are as well including the CD4 count. As you can see over the course of the study the rates of the use of influenza and pneumococcal vaccine have increased over time, and some people may have actually gotten this vaccine earlier before the study started or at some other care facility. That's true for both influenza and pneumococcal vaccine.

The other thing, we do not yet collect a viral load in the data base, it's still a relatively new test and it's not really done that routinely yet in clinical care. So we looked at the CD4 decline over time for people who received the vaccine compared to those who did not. You can see that the rate of CD4 decline is almost exactly the same regardless of whether you got influenza vaccine or not.

Basically this shows you the same graph for pneumococcal vaccine and actually we do have a difference whereby the rate of CD4 decline is actually less for persons who receive the pneumococcal vaccine compared to those that did not receive it.
And then last we're looking at the survival analysis which is a proportional hazards model using an Anderson Gill formulation

which is essentially an accounting procedure to take into effect how long people are on certain therapies and then taking into controlling for a factor such as age, the presence of an AIDS opportunistic illness, whether they're on AZT or not or some other antiretroviral, and those types of things. The risk ratio for pneumococcal vaccine is .93 and the risk ratio for influenza is .93, and with the confidence limits approaching one and actually touching one in the case of influenza, so in essence, essentially no benefit or at best a slight benefit in survival if you receive these vaccines. So based on this survival analysis there is certainly not a detrimental affect of influenza vaccine or pneumococcal vaccine among HIV-infected persons.

Influenza Vaccine Recommendations for the 1996-1997 Season

Ermias Belay, VR, NCID, presented a review of the scientific literature to summarize current knowledge of the following issues as they relate to persons infected with HIV: 1) the impact of influenza; 2) the immunogenicity of influenza vaccine; and 3) the effect of influenza vaccination on replication of HIV-1. Although it was acknowledged that further research was need to clarify all of these issues, there was general agreement that: 1) HIV-infected persons may be at increased risk for severe

influenza illness and complications; 2) although persons with low CD4+ counts may have a poor immunologic response to the vaccine it had been shown to produce protective antibody titers in HIV-infected persons with higher CD4+ counts; and 3) administration of influenza vaccine, vaccination has not been associated with deterioration of CD4+ counts or progression of clinical HIV disease. It was agreed that the recommendations should include a brief discussion of these issues and that influenza vaccination of HIV-infected persons should be encouraged, although there is no firm recommendation as there is for other high-risk groups.

Nancy Arden, VR, NCID, discussed proposed changes in the statement concerning vaccination of pregnant women. The 1995-1996 recommendations introduced a new recommendation for vaccination of women who would be in the third trimester of pregnancy or early puerperium during the influenza season, including those without other underlying risk factors. For the 1996-97 recommendations, it was proposed that language be included to clarify the rationale for this recommendation, and such changes were approved by the committee.

Another proposed change in the recommendation for vaccination of pregnant women concerned the statement regarding the safety of influenza vaccination during pregnancy. After considerable discussion, it was agreed that the statement Aalthough definitive studies have not been conducted@ would be added to the previous wording, Ainfluenza vaccination is considered safe at any stage of pregnancy.@ This change was not prompted by any data suggesting that influenza vaccine is not safe during pregnancy, but because there are no large scale studies to provide data meeting criteria established by the Food and Drug Administration that provide definitive evidence of the safety of the vaccine in this population.

Dr. Davis: Recognizing that there is an opportunity to work on a statement, at least for the next statement, not for the influenza season 1996-97, but for the influenza season 1997-98, we need to develop a working group to look at it in a more generic way. I see a lot of changes in the populations that are infected with HIV, we really need to revisit it on an antigen and vaccine-specific basis because I think there is a lot of misinformation and confusion and I think it's our obligation to do that.

Dr. Davis: The statement as reads on page 7 is regarding persons infected with human immunodeficiency virus. Limited information exists regarding the frequency and severity of influenza illness among HIV-infected persons, but reports suggest that symptoms might be prolonged and the risk of complications increased for some HIV-infected persons. Because influenza can result in serious illness and complications, vaccination is a prudent precaution and will result in protective antibody levels in many recipients. However, the antibody response to vaccine can be low in persons with advanced HIV-related immunodeficiency; a booster dose of vaccine does not improve the immune response for these persons.

Dr. Snider: A motion is being made to leave the recommendation as it stands but to include a statement to acknowledge the existence of some information that suggests that there may be increased viral replication after administration of the vaccine, although that significance is not know.

Dr. Davis: Takes the vote by asking all in favor and noting that there are 10 members present, nine are in favor and one is opposed and no abstentions. So it carries.

Now we need a group of people to work with the influenza folks and the opportunistic infections folks or anyone else who needs to be involved with the statement to get final word. The recommendation would stay as it is, but that what's needed is additional information to acknowledge that there are data that the Committee is aware of, although we have to try to make it something relatively brief. We want to say we are aware that this is a problem and the results are varying with different studies and the significance is not known. It's not really informative but I agree that it does tell people that we are aware of this and this is about all we know right now.

The issue regarding vaccination of HIV-infected persons, the broader issue, not only HIV-infected persons but people who also have other reasons for being immune deficient, that's something that I think we need to have an ongoing working group.

Dr. Arden: What we normally do this time of year is to give a brief summary of influenza surveillance findings in the U.S. and

a summary of global virologic surveillance and to explain the rationale for changes in the vaccine strains.

Most of you are familiar with the components of surveillance. We have reports from state and territorial health departments on a weekly basis and those are the maps that I'll be showing you, the report influenza activity based on their own surveillance, on a scale from no activity, sporadic, regional meaning outbreaks occurring in parts of the state with less than 50% of the population, and wide-spread. We have our own sentinel positions who report the proportion of people with flu-like illness every week.

Summary of Influenza Surveillance, 1995-1996 Season and 1996-1997 Influenza Vaccine Strain Selection

Nancy Arden, VR, NCID. The 1995-96 influenza season began somewhat earlier than average. Regional activity was first reported in the United States in October. Indicators of influenza activity increased from late October through mid- to late December. Activity declined during January, but during the first week of February, 19 states reported regional or widespread activity. Influenza type A(N1N1) predominated in all regions

except the Mountain, Pacific and New England regions, where type A(H3N2) viruses predominated. Influenza type B has accounted for only about 1% of isolates so far this season.

The proportion of deaths attributed to pneumonia and influenza exceeded the epidemic threshold by only a small margin during three of the eight weeks from October 29 through December 23; the proportion of influenza-associated deaths increased from the end of December through the third week in January and began to decline thereafter.

Most outbreaks have occurred among school-aged children, which is consistent with other seasons during which type A(H1N1) viruses have predominated. Some outbreaks were also reported from nursing homes, but culture-confirmed outbreaks in these settings were associated with type A(H3N2) viruses.

Helen Regnery, VR, NCID. The yearly recommendation for the composition of the influenza vaccine is based on three criteria: (1) the identification of a variant antigenically distinct from the current vaccine strain, (2) increased isolation in different geographical locations and (3) a reduced immune response of

vaccinated individuals. When the data are analyzed recommendations are made either to update the vaccine or to retain the current vaccine strains. The data addressing the three criteria are primarily collected from a network of WHO National Influenza Centers located throughout the world and from U.S. WHO Collaborating Laboratories. As the WHO Collaborating Center the Influenza Branch is responsible for monitoring influenza activity, performing antigenic and genetic analysis of virus isolates and evaluating the immune response of vaccinated individuals.

WHO and the Food and Drug Administration Vaccines and Related Biological Products Advisory Committee recommended that the trivalent vaccine for 1996-97 contain A/Wuhan/359/95-like (H3N2), A/Texas/36/91-like(H1N1), and B/Beijing/184/93-like viruses. Of the three influenza vaccine components only data for influenza A(H3N2) met the three criteria and was updated. During July, China reported outbreak level activity and the isolation of A/Wuhan/359/95(H3N2) which was determined to be antigenically distinct from the 1995-96 vaccine strain, A/Johannesburg/33/94. Thereafter the identification of A/Wuhan/359/95-like viruses occurred in Guam, Singapore, and the U.S. Finally, analysis of

sera collected from individuals vaccinated with an A/Johannesburg/33/94-like strain demonstrated a reduced immune response to A/Wuhan/359/95.

During 1995-96 influenza A(H1N1) virus activity increased significantly in Asia, Europe and North America as compared to recent years. Of the viruses antigenically characterized the majority were closely related to A/Texas/36/91. The immune response of vaccinated individuals was not reduced by strains selected as representative of currently circulating strains. Therefore, an A/Texas/36/91-like strain remained as the recommended strain for the H1N1 component of the vaccine.

Similarly the influenza B component of the vaccine was not updated. Influenza B viruses circulated at low levels and sporadically isolated viruses were found to be antigenically related to the vaccine strain, B/Beijing/184/93. In addition, serological results of vaccine sera did not demonstrate a decreased immune response.

Dr. J. Watson. Because of the elimination goal for measles, rubella, and congenital rubella syndrome that=s been adopted, we

are revising the recommendations for prevention of measles, mumps, and rubella. A goal is to strengthen these recommendations and thus hasten the achievement of these disease elimination goals. In addition, by combining these recommendations into a single publication for MMR, all the changes would be available in a single document. Some of the changes that have Acrept in@ since the previous ACIP recommendations for measles, mumps and rubella were published in the 1989 and 1990, include: A0 the routine first-dose changed to 12-15 months [1994], B) the routine 2nd dose recommended at either 4-6 years or 11-12 years [1995], C) changes in the recommended interval between immune globulins and measles vaccine [1994], and D) the addition of thrombocytopenia as an Adverse Event and Precautions/Contraindications, in the soon-to-be-published AUpdate on Vaccine Adverse Events and Contraindications.@

The current MMR recommendations include the following basic points: A) routine childhood vaccination with two doses of MMR, B) the statement that adults should have evidence of immunity to measles, rubella, and mumps, and C) certain Ahigh risk@ adult groups include international travelers, health care workers,

students at college and vocational schools, and women of childbearing age.

Evidence of immunity is based on a number of criteria which differ somewhat for each of the three diseases. Measles and mumps immunity is based on documented vaccination, a prior history of disease, serologic testing, or the year of birth of the person in question. All of these criteria are being reviewed and evaluated. Major issues being proposed for the revised MMR SAT include strengthening A) the two-dose recommendation including recommending the routine use of MMR versus monovalent vaccines B) the recommendations for health care workers. Although the current two-dose policy has been in effect since the early 90s, it must be fully implemented in order to achieve and sustain disease elimination.

One change would be to recommend stat laws requiring a second dose for school entry or for middle school entry. A second change would be to recommend a timetable for complete implementation of the second-dose policy. A third change would be to recommend that the second dose be given at primary school entry rather than either at primary school of middle school entry. The high number of primary vaccine failures in 12-18 year

olds led to the recommendation in 1989 by both the ACIP and the American Academy of Pediatrics (AAP) for a second dose of measles vaccine. The AAP recommended that the second dose be given at the entry to middle school or junior high school. The ACIP recommended the second dose at entry to elementary school.

In June 1994, the ACIP voted to provide the Vaccines for Children (VFC) Program funding for second dose of MMR. In January 1995, the ACIP ARecommended Childhood Immunization Schedule@ was published with reconciled differences between the AAP and the ACIP such that the second dose was recommended at either 4-6 years or 11-12 years. In February 1995, the ACIP voted to provide funding for an additional age or grade cohort so that two new cohorts could be immunized each year using VFC Program funds for eligible children. For example, now a state could immunize all school enterers and all middle school enterers.

The first study was published in 1989, took place near Vancouver and took advantage of a series of vaccine trials which took place between 1974-76 comparing the Merck vaccine to a Connaught vaccine. In these vaccine trials there was 98% seroconversion by hemagglutination inhibition or neutralization assay. There was a

measles outbreak between 84-86 and then in 1986 the investigators followed up children who had been enrolled in the earlier trials.

About half the children were included in this follow-up and of these 188 children, 185 seroconverted by some measurement. There were some differences between hemagglutination inhibition and the neutralization assay that they used and this 175 number is the one they considered in their subsequent analysis as indicating seroconversion.

One of the tantalizing issues that were discussed was that children of these nine children who developed measles after seroconversion, they had a lower antibody level after seroconversion than children who didn't develop measles but were seroconverters.

In terms of vaccine failures with measles among school-age children, you can see before the 2nd-dose recommendation had been made most of the vaccine failures occurred in high-school-age students. During and after the time that the recommendation was made the proportion of vaccine failures in high-school-age

students has declined and some of that has shifted to elementary-school-age children.

In terms of the final recommendation, the advantage of moving to full-school coverage would basically be that elementary-school-age students would be protected by 2nd dose which in many of the states there is not a requirement for that. It would give us a uniform policy across states and it would shorten the period that children who experience primary vaccine failure remain susceptible to measles. The disadvantages are that there is a one-time cost that some states would have to change their laws, that it would require some renegotiation with the other groups that have agreed to the recommended policy, principally the American Academy of Pediatrics and the American Academy of Family Physicians. And if waning immunity is a significant problem it is conceivable that the time between school entry and that period of increased risk for high-school students, that would be enough period that we would see more waning immunity.

What we are talking about with the school law issue is to institutionalize a recommendation this Committee has made and to assure that it is implemented and it is perfectly consistent with past recommendations of the group. You want the serologic data

to support whether or not it looks like waning immunity, basically secondary vaccine failure as opposed to primary.

This recommendation is aimed at the schools and in improving the recommendations we would hope to be clearer about the post-secondary school, and that would not change the recommendation.

Dr. Chen: This is preliminary but it may have a major impact on this decision. In two of our HMOs the large data base, in one the 2nd dose is given at primary school entry and the other is given at teenage and we looked at where there was a difference in safety profile and it turns out there was a major difference between the two age groups. In the teenage years the safety was worse, the side effect rate for MMR was higher compared to if the 2nd dose was given at primary school entry.

Davis. Does the Committee agree that there is a goal by the year 2001, that all children between such and such age, under a certain age, should have two doses of measles-containing vaccine or MMR? And second, does the Committee support aggressive

policies on those two? One is do we support an aggressive policy on dose two and is there a _____

Barbara Debuono: My motion is that we move toward a 2nd dose for all children, move as aggressively as possible in that direction, and that we set our sights on the year 2001 as the date for implementation of that recommendation.

Dr. Davis: We have a motion that has been seconded. All in favor? It's unanimous. We have nine voting members at the moment, and all in attendance are in favor.

Dr. Dykewicz: Since licensure of the rubella vaccine in 1969, the number of reported rubella cases in the U.S. has declined from over 57,000 cases in 1969 to 225 cases in 1988. The number of reported rubella cases increased to more than 1,000 cases a year in 1990 and 1991, but has since decreased.

The goal of any rubella control program is elimination of congenital rubella syndrome. The surveillance definition of a compatible congenital rubella syndrome case is a case that is not laboratory-confirmed but has two of the following: cataracts,

congenital glaucoma, congenital heart defects, hearing loss, or pigmentary retinopathy.

From 1985 to 1995 124 confirmed and compatible CRS cases were reported. The number of CRS cases was only two in 1989 but

From 1985 to 1995 83% of CRS cases of known race were white, 13% were black, and 4% were Asian Pacific Islanders. This racial distribution is similar to the racial distribution for all births in 1990.

There have been two recent rubella outbreaks. The first occurred from late 1993 to 1994 in Massachusetts. A total of 128 cases were reported; 60% were adults with an age greater than or equal to 20 years old.

The most recent rubella outbreak occurred in 1995 in Hartford, Connecticut where 36 cases were reported. Thirty-two or 89% were greater than or equal to 20 years of age. On February 13, a rubella elimination working group meeting was held in Atlanta.

Key conclusions of the rubella elimination working group were that elimination of indigenous rubella and CRS should be the goal

of rubella control programs in the U.S. Rubella immunity should be defined as documented rubella vaccination (one dose) or serologic evidence of rubella immunity (a positive serum rubella IgG). No changes are necessary in the rubella immunization schedule for children, in that two doses of MMR are recommended, but states should not be required to administer 2 doses of rubella vaccine.

Priority should be given to ensure rubella immunity in the following groups: child-bearing-age women; students; and health care workers. Given the high percentage of Hispanic CRS cases from 1985 to 1995 and the high percentage of Hispanic cases in rubella outbreaks in 1994 and 1995, it may be appropriate to target Hispanics for rubella immunization.

The group concluded that the U.S. will never achieve rubella and CRS elimination as long as rubella circulates freely in neighboring countries. Therefore, the U.S. should promote rubella control activities throughout the Americas.

Dr. Maes: We're talking about a statement that deals with programmatic strategies to increase immunization coverage and this statement is focused on measurement of coverage levels in a

clinic or provider-practice setting, and using that data to feed back information to the provider about how their practices could be improved. Missed opportunity rates start up in the high teens, maybe 20% median rate, and basically crashed over a period of four years, down to a median of zero.

WIC has been known to have an impact on coverage. If you divide the population into kids who were in WIC and who were not in WIC, you see that both rise.

A law was passed which basically makes measurement a mandatory feature of individuals who get Federal immunization funds Georgia measured and used the information. States are only required to measure now.

In conclusion, it's our belief that the Georgia Public Clinics coverage rose significantly as a result of the measurement and feedback process. We would like this Committee to endorse these activities as being something that would be useful for raising coverage, and a statement has been prepared to be looked over by the Committee.

How could you reduce a late-start problem...in Georgia the folks who were successful in reducing late-start basically in many of the counties, all the births took place in one location, and immunizations take place distributed over many places, births take place in fewer locations. The folks who were successful in reducing late-start intervened at the birth and said your kid needs to come in, here's where they should come and intervened at that level.

This is the best scientific analysis of what has been going on over time, but this issue has been broached repeatedly at immunization conferences to the point that people have been embarrassed to name Georgia because it keeps coming up over and over again. On the other hand, there are a number of states who have adopted it, more and more states are using this and in fact, it is a grant requirement. The big issue now is the private sector and how do we get private sector physicians and managed care organizations to take on similar efforts. Some States have started doing clinical assessments back in 1993 and some in 1992. All those states have seen dramatic increases in all their public health clinics.It's a law now, all the public health

clinics who are getting immunization funds needs to present data on their causal evaluation or clinic assessment plus the feedback.
The goal is of course 90%, at least.

In large urban communities that have a large population of immigration families, that's another group that has to be looked at and try to figure out how one can bring them in when you don't have access to a birth certificate to put them up in either a registry in the public health system. The other has to do with the tremendous changes that many of the populations that we've previously served within the public sector clinics are moving into managed care organizations and there has to be a way that we can built into the statement a recommendation that part of the transfer of a patient from one system of care to another implies taking an immunization record with you
I hope that you will include in any statement from this group comments to the effect that these principles of successful strategies also should apply to other age groups as well.

Dr. Davis: The ACIP recommends the regular assessment of individual clinic or provider immunization rates including

feedback on vaccine delivery practices in order to motivate the provider and staff to provide immunization practices. Implementation of these recommendations will contribute markedly to improving vaccination rates among all providers of childhood vaccinations. We could add something to the effect that the Committee recommends that there be careful attention to understand the efficacy of these practices in managed-care settings and that there should be clear distinction between persons who are continuously enrolled in a program and persons who are not.

One of the reasons for looking at those people for whom a health care delivery system has had responsibility over a significant period of time like most of the two years are that they really have no excuse for having less than 100% performance. And until we reach that goal something is wrong with the way we deliver care. I think here we are concerned about the total population and not just those that are continuously enrolled in an HMO because we are concerned about outbreaks and hurt immunity and protecting our kids.

Speaker Not Identified: I think the recommendation said all individual clinics and providers, so that's the whole population.

Dr. Davis: Is there a motion to move on the recommendation?

The motion was moved and second.

Dr. Davis: All in favor of the recommendation...we have eight voting members in attendance right now. Dr. Thompson and Dr. DeBuono are not here. The eight here are in favor.

Dr. Susan Reef: Geoff Morges from Merck and I will be updating you on the issues concerning usage of the varicella vaccine since the last ACIP meeting. As you might remember there were concerns among members of the Committee about the distribution of the varicella vaccine in relationship to the public health sector, in particular to Outreach Clinics. Dr. Morges will start this update with discussing the usage of the vaccine in the private sector, then he will briefly discuss all the proposed wording changes in the package insert.

Dr. Geoff Morges: As you all know VARIVAX was approved on March 17, St. Patrick's Day, 1995. We started shipping product on May 1; and by August we had actually distributed a million doses and by December we had distributed 2 million doses. This wasn't evenly distributed across the country. There's a really wide variation between the low adoption states and the high adoption states.

A lot of factors can explain various coverage but a large part of it is the level of VFC penetration in the different states. States that are not using a lot of vaccine are states that have a very high VFC population and therefore you wouldn't expect them to be using the vaccine because it's not available in the VFC program.

In terms of specifically the private segment, we've conducted serial surveys of several hundred pediatricians; we have a panel that's a random sample across the country to look at the acceptance of the vaccine and what they're doing in terms of recommending the vaccine. In March nobody was using this vaccine, but in August, October and December there was a strong trend toward more and more pediatricians recommending the

vaccine. We think approximately 60-70% of pediatricians are now actively recommending the vaccine according to the AAP guidelines.

This is important information because we have done a survey of consumer awareness of the vaccine and we have high levels of awareness based on the media coverage. Around 70% of parents indicate they are aware of the vaccine, and roughly half have discussed the vaccine with their physician.

Of the parents who discussed the vaccine with the pediatrician, if the physician recommends vaccination, 75% of parents will have their child vaccinated. If you go the other direction and the physician doesn't recommend the vaccine which at that time was around 15% of consumers, then 0% are willing to overrule their pediatrician and get their child vaccinated.

When the pediatrician is mutual, which at that time was around 40-50% of the pediatricians, the child is only vaccinated in around 1/3 of the cases. Two-thirds of the parents interpret a

neutral stance by the pediatrician as a recommendation against the vaccine.

This was a real revelation for us and we need to get pediatricians to start recommending the vaccine rather than leaving it up to the parents. We don't leave it up to the children's parents whether they get an antibiotic or not, so I feel that they are advocating some responsibility there.

Another thing that we've done is to look at how VARIVAX is being accepted compared to other immunizations We went back and looked at the first measles vaccine and looked at milestones to see what immunization rate was achieved in the recommended cohort at the appropriate time shortly after the vaccine was introduced. The measles vaccine was rapidly accepted, the only data we have is four years after introduction, 60% of two-year-olds were being vaccinated. For mumps,it was around 35%; rubella around 40%. Here, one year after the vaccine was introduced, the full coverage was only around 30%.

The acceptance of varicella vaccine has been consistent and in some cases more rapid than other vaccines that have been

introduced. This is only private sector. We estimate an average across the country of about a 40% immunization rate in two-year-olds in the private sector.

When we talk to parents,and pediatricians there were concerns. The first was storage, and that was an issue very early on The other big issue was investment. We have heard from a number of managed care organizations who are saying we won=t reimburse for this vaccine until it's recommended by the ACIP. So the recommendation that comes from this Committee impacts not just the public sector but has a big impact on the private sector as well. Physicians don=t have dual standards of care in their practice, so they're saying I'm not going to give the vaccine to my private-sector kids until it's available in the public sector.

There's still a perception that varicella is a very mild disease that we don't need to worry about. There's a concern about transmission.

There are three main areas that we are making changes. The first is transmission; the second is in the adverse reaction reports; and the third is in storage and handling.

We put a language here which says that post-marketing experience of just the transmission of a vaccine virus may occur infrequently between healthy vaccines and healthy susceptible contacts. There the only real documentation that we have right now is that transmission occurs in the presence of a varicella-like rash.

We have distributed 2 million doses of vaccine and there have been 20 reports of transmission total. We keep the language about weighing the risk of natural varicella vs. the vaccine virus, and then we specifically state, and...the susceptible high-risk individuals include immunocompromised individuals, pregnant women without a documented history of chicken pox or the serologic evidence of prior infection, and newborns without a documented history or the _____ evidence of prior infection. We basically get reports from all over the country about anything that a physician has any concern about and we report that to the FDA. These are low-frequency occurrences and there's no proof of any association with the vaccine, but nevertheless, we do disclose them in the circular.

Finally, I'll address the storage issue This is the existing circular language, basically it says you have to keep it in a freezer, a frost-free freezer is okay, it retains potency for 30 minutes after reconstitution and for information regarding stability at other temperatures call Merck. The proposed change is that we are inserting this language here. Specifically we are saying that prior to reconstitution VARIVAX retains potency when stored for up to 72 continuous hours at the refrigerated temperature. Any freezer that reliably maintains an average temperature of -15 degrees C and has a separate sealed freezer door is acceptable for storing VARIVAX.

VARIVAX may be stored at refrigerator temperature for up to 72 continuous hours prior to reconstitution, and then we're going to include language that says vaccine stored under such conditions should be used or discarded. Now we will continue to offer the 800 services if people do something that's outside these guidelines, they'll still be able to call Merck and we'll be able to assess the vaccine, the shelf life, the temperature it's been And just an addition to that you might be able to update it by the statement that you made a few moments ago that two million doses have been distributed and 20 cases of possible transmission

have been reported I'm sure you don't know whether it was wild type, a vaccine virus, etc.

There was a concern among the members of the ACIP in the October meeting about the distribution of the vaccine in the public health sector. Drafting an addendum, Merck proposed changes in the storage and stability sections of the package insert, and is currently under review by the FDA. The substances of these proposed changes are included in the ACIP language in the vaccine handling.

The distribution storage is divided into 3 sections and the first section is the handling of vaccine within a clinic or for clinics which do not have adequate facilities to store vaccine.the recommended handling of the vaccine is to remove it from the freezer of -15 degrees C immediately prior to use.

The second paragraph talks about that when the immunization session is being held at a cite distant from the freezer where the vaccine is normally stored, the vaccine can be placed and stored in a suitable container with an adequate quantity of dry ice, probably around 6 lbs. per box so that the dry ice remains

until the unreconstituted vaccine can be returned to the freezer.

The presence of dry ice in a suitable container will maintain a temperature of -15 so there will be no exposure of the vaccine to anything higher than -15. So you don't need to worry about the 72 hours. The expiration date does not change.

When optimal handling conditions are not possible or feasible, and that's like due to the location of the freezer storage area or concern for security of the room where the vaccines are administered within a clinic, The varicella virus vaccine can be stored up to 72 hours continuously at temperatures of 2-8 degrees C which is refrigerator temperature. And then once you remove it from the freezer area it should be used or discarded within the 72 hours.

To minimize vaccine waste there was a couple of suggestions given. One is to order frequent and smaller shipments, like maybe every 3 months, and the second one is to use vaccine with longer expiration dates like 12 months to expiration.

The next section is the transfer of vaccine between the clinic sites, and this is for only when it's necessary to transfer the vaccine like to adjust supplies. The vaccine should be packed up into the original manufacturer shipper container or something comparable of the same quality with dry ice and then once it's received at the receiving site dry ice should be present. If not, the vaccine should either be discarded or if there's a temperature recorder that has been included in the transport box and we know that the temperature is equal to or less than 2-8 degrees for up to 72 hours, the vaccine can be used within the 72 hour period after it's been taken from the freezer area.

Why don't we just settle on the language? How does the Committee feel about the current wording may be directed to Merck vs. should be directed to Merck?

A motion is made and is seconded. There are 8 in attendance of the 10 members and it is unanimous that the word should be "should.@

Dr. Davis: Let's vote on this language up to the statement on requirements because we haven't discussed that yet. Any motion to accept this language? There is a motion to accept the language and there is a second. We have seven voting members, Drs. Glode, Guerra, Griffin, Schoenbaum, Ward, Modlin, & Davis. All vote to accept that language.

The first sentence which I didn't include is the ACIP recognizes the challenges to public health departments and the private health care providers in assuring proper distribution, storage and handling of the varicella virus vaccine. It continues to say state health departments should assure reasonable access and distribution to all vaccination sites and ease of administration of varicella virus vaccine to children before including varicella virus vaccine as a required immunization for entry into school, head start, day care, or as a part of the routine vaccination series required for WIC or receipt of public assistance. Concerned by putting all of the attention on state health departments And they're not willing to give the same kind of assurance in terms of protection of the vaccine supply and the inventory and the cold storage, because they're just not set up to do that.

Steve Schoenbaum: Is the intent though to encourage state requirements or simply to encourage reasonable access before any state chooses to do so, in other words, how directive is this in terms of to state health departments for...you're asking them to, encouraging them each to go to their legislatures or to their regulatory bodies and have such recommendations for requirements of school entry?

Dr. Davis: There's basically an assurance function that's indicated then, any requirements would be predicated on that assurance, so the assurance would take place before it became a requirement.

Dr. Davis: I open the Committee for discussion. High immunity levels in school-age populations are extremely important in order to derive the maximum public health benefit and avoid public health risks, and states should require the use of varicella vaccine.

Alan Hinman: One could consider making two sentences, this is a very awkward sentence as it now exists, but one could consider two sentences, one of which would say, "to foster rapid control of varicella and improve immunization levels, states should consider instituting requirements for varicella vaccination"... Before doing so however it is essential to assure reasonable access and distribution to all vaccination sites, etc. of the vaccine. That would get both points across.

Dave Fleming: I was going to comment that I think the statement is yet unclear to the extent for which varicella vaccine is going to be like other vaccines in ease of distribution. The natural tendency of folks is to move quickly to make it a school requirement. This was intended to serve as a caution saying that please consider these issues in your deliberations at the state level before being too precipitous in moving in that direction. People at the state level when they're making these decisions, need to be aware that there may be some special concerns about varicella vaccine and its distribution that need to be taken into account before moving automatically to making it a school-entry requirement.

Carolyn: Some of my colleagues at FDA who have received this have been very concerned about that it sends a message if you can't store it, don't use it, as opposed to sending the message that everyone should be trying to figure out a way to store it properly and get it used. And so whether the emphasis should be placed on assuring proper storage so that it can be used in the most rapid manner is where people like Phil Krause have come from.

Speaker Not Identified: Not in the main body of the statement, but in the last section we have future issues in varicella surveillance and in that right now there is a sentence..."however, school requirements for varicella vaccination are possible mechanisms to prevent the development in of an increase in the population of susceptible adults." It deals with this issue of low coverage, and I guess what one could propose is to take that sentence and turn it into what Alan suggested which is to foster more rapid control of varicella, states should consider establishing requirements, and then add a version of this sentence and make that a paragraph in the future issues, and that I think would get both pieces of what we want.

Dr. Davis: There are issues here because of the transmission in classroom settings, because of the issue of immunity and you have large birth cohorts, you have very high rates of infection, you have two dynamic things occurring. I think in the early phase of vaccination with the use of this vaccine, you will have reinforcement of vaccine-induced immunity with wild virus for a period of time. So that even with a single dose of vaccine you're going to have probably decent immunity being induced with vaccine because of continual challenges with wild virus. It clearly is a different type of vaccine and we clearly do have issues of major risk of transmission in those settings. But it's unprecedented for us to make recommendations for the use of a vaccine to be required so soon after the licensure of the vaccine. I don't know how much experience one needs to have with a vaccine in order to make a strong recommendation about requiring the vaccine for school entry. It would be a very rapid recommendation that we would be making for making school-entry laws for this vaccine and I just want to make sure as we entertain this that we just have the right language.

Dave Fleming: If we include language about school-entry requirements I think we would need to include a caveat to the extent that given the way VFC funding is working and the way the vaccine is likely to be administered that you really need to be thinking now about school-entry requirements for the entering class 3-4 years from now, that we would not want to imply in the statement that states should proceed today with the school-entry requirement for kids that are entering in the fall because that would require a catch-up with varicella vaccine that we don't have the funding to do, and so maybe some language that talks about the need to be planning ahead for a varicella entry requirement and giving providers enough notification of that requirement so that they can be immunizing their kids now for an entry requirement a couple of years from now. That might be a way to sort of compromise on this issue.

Fernando: To make a similar point I think that we need to have the assurance of one, adequate funding that could be sustained to assure that we can meet that requirement, and two that there's also an adequate supply from the manufacturing standpoint of the vaccine to make that requirement.

Steve Schoenbaum: The two points were the points that Alan Hinman made and I don't see that there's anything that I've heard in the discussion that negates those points, is why don't we position ourselves for saying that when it's feasible then one would build this into the requirements. You need to start building for the future because otherwise it takes years to get this stuff to happen. These are the things you want to be sure are happening before you write an act of law. Why don't we charge the group to come up language to that effect?

We need to re-identify the key working group members so we can put together language and FAX it out to the Committee. That's the only way I see to do it but we have to all recognize there's a short time fuse on this.

Speaker Not Identified: Well now Alan's sentence was to foster rapid control of varicella, states should consider establishing requirements for entry into school, etc. and then follow with something like that. That's I think the sense of what Alan said. I think it's stronger than what some people might want.

We have one additional item is where to place the requirements sentence. The consideration was to put it at the end of the childhood recommendations section in the body of the ACIP statement.

I would like to talk about the draft wording on a statement about post-licensure adverse events. We would write, "during the first nine months following vaccine licensure, a small number of certain serious medical adverse events have been reported after the receipt of varicella virus vaccine including encephalitis, ataxia and anaphylaxis. In addition, 13 cases of erythema multiform have been reported. At the present, data are insufficient to determine a causal relationship between these illnesses and the vaccine. A small number is 5 or less of each of the encephalitis, ataxia and anaphylaxis.@ When we looked at the viruses up to this point in time there were 5 cases of ataxia, encephalitis, and only 2 cases of anaphylaxis.

John Modlin: Just I think if you do insert that as written, that inevitably is going to invite questions as to what the rate, even of these very uncommon adverse events are, and I would suggest

putting in a rate there less than such and such per 100,000 or per million doses of vaccine distributed or to state during this same period approximately 2 million doses have been distributed...

That would require permission from Merck to do so, as that data is given to us from them.

Speaker Not Identified: I think a point is important, if there is anything we have on background rates and expected, because I think this is a very alarming statement as written and it will serve to discourage. We have not put in a numerator kind of thing like this without any evaluation that I'm aware of in other ACIP statements, and I think that anything we can put in to evaluate it with data on background rates or expected would be helpful. For example, some of these...I don't know what the time interval on encephalitis is, if some of these are very shortly after vaccination, that would suggest that we know that's probably not vaccine related...it is concerning to me to just put it in like that.

Speaker Not Identified: Certainly it's unusual for us to put something like this in. We put it out at the suggestion that the package insert is being considered to add these in. It doesn't mean we have to add them. It does give some perspective on what's being reported but since these are not validated cases...

Dr. Davis: I need to get a sense of the Committee, if this should be included with caveats.

Dr. Davis: All in favor of including this statement with the appropriate caveats regarding appropriated background occurrence of these conditions? All eight are in favor. The absentees are DeBuono and Ed Thompson. The 8 voting members present voted in favor of including the statement with the appropriate caveats.

Speaker Not Identified: The caveats, is the Committee voting on the caveats? You see, what happens is when the data come in preparing the incidents here with expectations in the population, when the data come in as to the temporal occurrence of these

events with the vaccination, the caveats then become things that you might say, that doesn't belong in your statement, and yet you're voting to include caveats without knowing what those data show, and I just want to point that out. When you really look at the so-called caveats, it's going to be a set of data.

Dr. Davis: Well what's happened is we're concerned that data without the appropriate background context would be misinterpreted and it would seem alarming when in actuality it may not be alarming at all. So when we are talking about the caveats, we're basically saying that we want to make sure the data is adequately stated. Am I correct in that? Is that what the Committee feels? That's our reason for doing it. We obviously don't have the data so our choices not to put this in at all; to put it in without providing appropriate background; or to put it in with the appropriate background to be less alarming.

Speaker Not Identified: I guess what I'd propose is that we really look with FDA at these adverse events to see if they fall within a reasonable interval following vaccination and if indeed they are the diagnosis that is what they've been reported as, then we come back to the working group to apply the language on

it. But it's possible some of these cases would drop out as one looks at them really closely.

Dr. Davis: So the language will be brought to the working group for finalization and once the working group concurs it will go out to all the Committee members for rapid concurrence and it will be published in the MMWR at the time that the full statement is published.

Melinda Wharton: Our efforts to control vaccine-preventable disease have been phenomenally successful in the last few years and the surveillance data document that very clearly. As probably most of all you know, disease elimination goals were established for indigenous transmission of six diseases in the U.S.: measles, diphtheria, rubella, tetanus among persons less than 15 years of age, polio due to wild type disease, and amophilus influenza type B among children less than 5 years of age.

In 1995 there were less than 300 cases of measles reported in the U.S. which for a provisional total is about the same that we had in 1993 when we reached an all-time low of 40 cases of measles.

There were no cases of diphtheria reported in 1995 and we'd had only one case reported in 1994.

There have been no cases of paralytic polio due to wild type disease in this country since 1979.

As stated earlier, rubella is now at an all-time low with only 146 cases reported last year and there were only seven cases of congenital rubella syndrome reported with birth dates in 1995. That figure may be adjusted upward as delayed reports come in which they tend to do for this particular disease.

Tetanus cases have been about 50 cases a year for the last many years with almost all these cases being among adults. A provisional total for 1995 is 34 cases, 2 medical failures did occur among tetanus cases in 1995. There were 2 cases among children less than 5; one was a case of neonatal tetanus reported from Tennessee who was a child born to a mother who was a migrant farm worker, correct me if I'm wrong on that. And the other case was of a preschool-aged-child who had not received any

immunizations at all because his family belonged to some religious groups which do not accept immunizations.

Finally, hemophilus influenza type b is a major success of the last few years and the number on this slide really obscures what is probably a much more dramatic reduction. These data are primarily from the National Notifiable Surveillance System and what is reportable nationally in this country is hemophilus influenza invasive disease, not specifically type b and we do not have serotype information on all these cases. Based on the active surveillance sites that look at type b disease in particular, we estimate that there are only at this time around 200 cases of hemophilus influenza type b disease, invasive disease each year in the U.S. So it really is a very remarkable success story down from about 20,000 cases prior to the introduction of vaccine.

Dr. Wharton: The disease elimination goal obviously is based on wild-type polio disease. We often, as you know, the only cases of paralytic polio that have been reported in the U.S. for many years are either imported wild cases from other countries or vaccine-associated cases and the 0 will be adjusted; the 0 cases

that have been...we do end up getting delayed reports in the surveillance system because of the nature of case confirmation and at this point I think there have been suspected cases of vaccine-associated polio reported with onset in 1995 but those are not included in that figure. Those are wild-type disease.

Speaker Not Identified: On this revised statement, my issue comes up with the last sentence that says because influenza can result in serious illness and complications the influenza vaccination can result in protective antibody titers, vaccination may benefit many HIV-infected patients. My only question is do we want the recommendation to be that soft or should this sentence say vaccination is recommended for HIV-infected patients.

Speaker Not Identified: I might be tempted to soften it just a bit and say vaccination will benefit many HIV-infected patients. That's not an explicit recommendation. We don't yet have the data to prove that vaccination improves the outcome of HIV-infected patients, other than the data that we saw yesterday

which was intriguing, but I would just say will benefit HIV-infected patients.

Speaker Not Identified: I would agree with may or will and not make it any stronger because I think in the absence of data with a lot of people out there who now don't want to do it, I think us pushing it without data puts us in a difficult situation. If we had more data or if we knew the disease was more severe in HIV-infected people, but I think we have a community some of whom are very uncomfortable now with giving vaccine and I think in the absence of more data this is not the time to push it.

Fernando: I think it's easier for us to say we may benefit as a transitional statement and I think as we get more data then go to will benefit, perhaps making it stronger would certainly be appropriate, but I can already anticipate a lot of questions and people asking for proof of this.

Dr. Davis: I want to give Steve a chance to read the statement. We're talking about the persons with human immunodeficiency virus infection and the influenza statement.

Fernando: One other comment while Steve is reading, the first sentence, and I realize this may represent fine tuning here that may or may not be appropriate, but one of the issues regarding influenza in HIV-infected patients has been that it frequently causes them to come in with an illness that mimics more serious disease such as pneumocistis pneumonia and they almost immediately go straight to bronchoscopy to rule this out. And this is just the clinical picture that we've seen a number of HIV-infected patients present with influenza. You might want to add to the end of the first sentence, but reports suggest that symptoms might be prolonged and the risk of complications increase with some HIV-infected patients, and/or influenza may mimic more serious disease such as PCP. That may need fine tuning but it gets at the broader issue of morbidity of influenza and HIV-infected patients.

Walt: It seems to me this statement backtracks from what you already voted on before. The statement that you voted on yesterday, at least the jest of it was, vaccination as a prudent precaution, which to me suggests an encouragement. Here is you leave it as may it's really iffy and it seems to...it gives the message that the Committee isn't sure and I think we'll

discourage vaccination. If that's what you want then that's what to me that says, and I think that if you think vaccination is the prudent thing to do, i.e., the good thing to do, it ought to be a stronger statement.

Speaker Not Identified: I think we ought to be supporting those or providing support for those who wish to vaccinate HIV-infected patients and that was my sense of the discussion yesterday. The information that we saw that indicated that influenza immunization was associated with a slight increase in survival, I think was compelling albeit not all the data we'd like to see.

Speaker Not Identified: Jeff, I would certainly go along with changing it to will, but I think then we certainly should take those steps that are necessary to inform the broader community of the other AIDS service providers and certainly the infectious disease people that there is at least that early benefit or potential benefit that is being observed. Because there's a lot of confusion out there right now.

Dr. Davis: Well I think that would be important to get into a variety of other publications. It would benefit many HIV-infected patients and also adding what Walt said, and as a prudent precaution. It's not a quote/unquote recommendation in those words, although these are ACIP recommendations. But given the state of information right now it would reflect our thinking.

John Modlin: I move that we accept the draft statement as written with the change in the last sentence to read vaccination will benefit many HIV-infected patients.

Marie: I second. Fernando said he would support that.

Dr. Davis: John Modlin made a motion, seconded by Marie.

Dr. Glode: Let me just clarify for myself...if we didn't have the negative information, the negative scientific information which is controversial in terms of reproducibility in different labs, but if we didn't have that information and there was no evidence that there was harmed caused by it in HIV-infected individuals, would we still have the same hesitancy because we aren't sure whether the disease is worth in the population, or

would we recommend it in anybody with a chronic illness and for the reasons you mentioned in terms of would we be comfortable doing that...

Speaker Not Identified: It seems to me at this stage that HIV-infected patients are like patients with diabetes and renal disease and some of the others where we don't have hard data that influenza immunization is a good thing for them although we encourage it and I'm not sure that our language should be any different for HIV-infected patients.

Dr. Glode: And our language for those other groups "is recommended" is encouraged, what? I think it says "is recommended" so I think it still should be stronger to say "vaccination may benefit HIV-infected patients and is recommended" because I'm going to consider the information above to be accurate, that it's not reproducible from lab to lab and that to date one can change the recommendation next year based on new scientific information.

Marie: Again, I think there's a lot of people out there who are uncomfortable and I think in this situation we have to be very

careful about making a recommendation. We don't have evidence that the disease is worse; we don't have evidence that the vaccine is effective in people at the highest risk, like people who would get PCP. We don't know if the vaccine is effective for those people. I think there are a lot of unknowns and we should try to get that information, but I personally feel uncomfortable recommending this without any of those data.

Dr. Davis: We have to vote. It was seconded so we really do have to vote on it.

All in favor of the language which would be taking the statement and changing the word "may" benefit to "will" benefit. All in favor? There are six...okay, Glode, Griffin, Schoenbaum, Ward, Modlin, and Davis are in favor. The other four are absent, Dr. Guerra has stated that he is supportive.

Nancy Arden: The issues that came up to do with the statement on pregnancy haven't been so easy to resolve. A statement to the effect that excess mortality among pregnant women has only been seen during the pandemics of 1918 and 1957 and '58, and many people have suspected that there is excess morbidity/mortality

during other seasons. We haven't been able to demonstrate it so this recommendation was to say however because death certificate data often did not indicate whether a woman was pregnant at the time of death, special studies are needed to suggest influenza-associated risks during pregnancy. And the intent of that once again was to strengthen the rationale for making the recommendation.

It's been extremely hard to find studies that definitely quantify the risk and we're continuing to try to fund those studies. Once again we tried to strengthen the statement by adding information about why there was a theoretical risk or theoretically why there would be an increased risk in late pregnancy, and someone may have specific ideas about what language they would like to include about the case reports on limited studies that exist. It's very hard to come up with any definitive statements that we can defend as being data that we would want to present that couldn't be challenged.

The other question that came up was protection to the fetus and in looking over the studies that have been done we could draft something. Once again, it's also going to be sort of an equivocal statement. The studies that have been done have very

mixed results. It would take up more time than this Committee has right now to go over the findings of the different studies that have been done. Some studies have shown some short-lived benefit of transferred maternal antibody. Some have shown none. And so we could make a general statement and say that some studies have shown transfer of maternal antibody to, and then give a range of the proportion of newborns for a period of, it's generally been 1-3 months, in some cases a few infants have shown some antibody up to six months. But it would be hard to summarize because the findings have been so variable.

Speaker Not Identified: Is there any evidence Nancy that the transfer of antibody is protective?

Nancy: Yes, there are some studies that show...and once again we could make a general statement but I think to be fair we would have to say that some studies have shown transfer of antibody...some studies have had results that wouldn't be very compelling in terms of conferring protection, and the studies that I've been able to review have shown very mixed results of transfer of antibody. Some have shown none at all. I would rather have a little more time to review the literature to have a

fair statement on transfer of antibody, but I think we could say something positive.

Speaker Not Identified: Do you mean that there are some studies that show there is very little antibody available to the baby, which is certainly true, but I don't agree with your statement that you imply that antibody when present doesn't protect the baby because I think all the evidence says that it does. In general, mothers usually do not have antibody to the current variant to spend to their baby and we've done numerous surveys, cord bloods, over the years that demonstrate this that unfortunately mothers haven't been infected with a recent variant so they don't give antibodies of the current variant, but that doesn't mean...that's why we think it's important to immunize them so they do have antibodies to the current variant and there will be some potential for protection to it.

Nancy: I think the question was does immunization of a pregnant woman...is antibody transferred to the infant?

Speaker Not Identified: Yes, and in the studies...two of the studies were done in 1976 and unfortunately the mothers didn't

make very much antibody to one dose of the swine vaccine so that there wasn't much antibody transmitted in those, but in current vaccines I think it's a little better.

Speaker Not Identified: Paul isn't the problem that it's not an all or none phenomenon with passive acquired antibody, that particularly with influenza there is a certain level of antibody that we deem as being protective, that is 1-40 or whatever level one chooses and that the passive acquired antibody in the newborn is not only the strain for which it's directed against but it's also the titer and therefore the duration and the degree of immunity and duration of protection is relatively short. It's only a couple of path lives, and so I think your figure of 1-3 months is right on, but also the degree of protection is highly variable depending on the amount of antibody.

Nancy: It wasn't really clear exactly what the Committee wanted to say about transfer of the maternal antibody through vaccination. It is my impression that there was a desire to say that in addition to benefit to the mother that vaccination of pregnant women may benefit infants. Is that correct? I think we can make some very general statement. Once again, I think it's

important not to overstate the potential benefits of vaccination of the infant.

The third issue with regard to the statement on pregnancy was the request through FDA of the sort of caveat that hasn't been included in previous statements. Previously, statements have been made that influenza vaccine is considered safe in any stage of pregnancy. That statement was changed a number of years ago. There was a request to add a caveat, although control studies have not been conducted and we were able to find two studies. I think Paul Glezen referred to two studies that were done, one was with 56 women and the other was 189 pregnant women and 517 non-pregnant women. And Carolyn Hardegree had tried to get in touch with someone at FDA to discuss how/if there could be some softened language about...I think it would be nice to be able to try to negotiate what we might say in this statement. The only thing we could come up with at this time was something to the effect that no large scale studies have been done based on the two studies that we could find.

So this would be what you have in the last part of the paragraph...we would add "as influenza in pregnant women would

have medical conditions and increased the risk regardless of stage of pregnancy influenza vaccine is considered safe in any stage of pregnancy, moving that from where it was at the bottom. And then something although it gets a little bit...although large-scale control studies of the safety of influenza vaccine during pregnancy have not been conducted, studies involving approximately 250 pregnant women showed no association between vaccination and maternal perinatal or infant complications, and furthermore during...and I will need some help with this...how many decades pregnant women have been routinely receiving vaccine..."X" number of decades of use of influenza vaccine in pregnant women, no increase in adverse events associated with vaccination have been detected. In my mind it would be nice to go back to...in a way it calls a lot of attention to something that hasn't really been considered something that we need to dwell on, the safety of vaccine in pregnant women. So I think the options would be of taking out the caveat if we can talk to FDA and have that changed or just go back to the kind of statement we have had for quite a few years now. The other alternative is something this which in my opinion it draws a lot of attention to something that hasn't really been an issue.

Dr. Davis: Discussion, Paul?

Paul: Yeah, I agree because I think you could probably add that phrase to a lot of categories of patients for whom we recommend the flu vaccine, so it's not consistent. Carolyn and I were talking about the large perinatal study that was done in the late 50's and 60's where there were 50,000 women followed and at that time influenza immunization was recommended for pregnant women and these woman and their babies were followed up to four years for all sorts of congenital anomalies and everything that can happen and there was no bad effects found so I think there is good evidence that flu vaccine is safe n pregnant women, and of course the vaccines which we used in the last 50's and 60's were not perfect vaccines. I think we have a lot better vaccines now than we had then so I really don't think there's concern that warrants this clause.

Dr. Davis: Is it the cause of the Committee to eliminate that?

Speaker Not Identified: Yeah, I know, I'm just asking specifically what phrase are you talking about deleting?

Speaker Not Identified: Nancy, was the flag raised about the issue of any state of pregnancy or during pregnancy? Was that what the control study issue was raised about?

Nancy: The rationale was that what the statement is saying is that influenza vaccine is safe at any stage of pregnancy and that in fact it is still a category C technically, meaning that there is no reason to think that there is a risk but there have been no definitive studies to prove that there isn't. That was the concern, that a very strong recommendation was being made for vaccination of pregnant women at any stage of pregnancy, and statement was being made that it was considered safe when according to FDA standards it was still a category C.

Speaker Not Identified: I don't have any problem with removing the last sentence as is, personally, but Stan Gall's not here and we're making these changes largely because of the concerns of the obstetrical community in the first place, that was my understanding why we're jumping through these hoops in the first place. I don't know if anyone else has any comments about that that could represent them.

Speaker Not Identified: The statement was simply that flu vaccine is safe for pregnant women. That's been in the statement for 5-10 years. I don't think anybody in the obstetrical community has ever objected to that before. So I don't know why you are concerned now. They were concerned about administering the vaccine in the third trimester of pregnancy, and certainly that's...if anything is safe, that's safe, so the recommendation we're making limits it. The original recommendation from 1957-1965 was that pregnancy was a high-risk condition and all women should be vaccinated, and it didn't specify what state of pregnancy. But I think we've turned back the clock for no reason.

Dr. Davis: So Paul, what are you recommending? Are you just saying...?

Paul: I'm just saying that the administration of influenza vaccine is safe during pregnancy which is what the statement was previously.

Dr. Davis: So in other words, no changes in the last paragraph, is that correct?

Paul: Drop the phrase...drop the phrase, although control studies have not been conducted.

Speaker Not Identified: I would like to question though Paul's statement was in pregnancy as opposed to making the statement about any stage of pregnancy, and I think those are different statements.

Paul: But if you look at last year's statement that's what it said. It said influenza vaccine is safe at any time during pregnancy and should be given to high-risk at any time during pregnancy.

Speaker Not Identified: I think that from what I've heard from Nancy that there was a question about that last year and there was not a chance to have this discussed, and so that's why this is on the table again this year, is my understanding.

Nancy: Right, it was actually brought up a year ago but not strongly and then it was brought up right after publication of the recommendations last year. And it's become hard to ignore.

Dr. Davis: Well it seems like we're in a quandary and the only way to resolve that is to then expand it like you've done over here. It's sort of like we do it like last year, but now we're getting a change to discuss it so we can't do it like last year's. So if we go and do it the way it was given to us, written to us, that raises problems also, so our next option is to go to what you've already written. What do people feel about what's been written?

Speaker Not Identified: I actually like the statement there except for the last sentence. I think it contradicts. You're saying you haven't detected but you also haven't looked because you say that in the first statement. So I would just delete that furthermore doing decades they haven't detected, because maybe you haven't detected because you haven't looked and you state that in the previous sentence, although large-scale control studies have not been conducted. And so I would just delete that last one.

Speaker Not Identified: I second that, if that was a motion, to delete the last sentence and pass it.

Nancy: The idea was to say that there have been decades of observation of use of vaccine. If you want to get down to trimester the 250 some odd...one of the studies had 56 women who were in the second and third trimester and the other study, the women were at different stages of pregnancy but most of them seemed during early pregnancy, so once again, if we want to get down to stage of pregnancy.

Jeff: I like the wording that's in the statement here and we don't have to add so many sentences and words, you just want to say that maybe the ultimate, 10 ultimate definitive studies haven't been done but it ends with a statement that it's considered safe at any stage of pregnancy. It's a clear firm sentence the way it's written. I would stay with it.

Dr. Davis: Do we have a motion?

Jeff: I move that we stay with the statement as written in the current draft?

Dr. Davis: Do we have a motion.

Speaker Not Identified: Yes.

Dr. Davis: All in favor? Six in favor; 1 opposed.

Okay, let's do varicella. To foster more rapid control of varicella and achieve high immunity levels, states may consider including varicella vaccination in their requirements for entry into school, head start, day care, or as part of the routine vaccination series required for WIC or receipt of public assistance. Before instituting such requirements it should be assured that there is adequate distribution of and access to varicella virus vaccine to accomplish universal vaccination of those subjected the requirements.

Ed: A wise person before lunch said it was always good to look at the language, I think that was you Jeff, but in reading it I think we may have gone a little astray. I'm not sure that the Committee has previously taken a stand on recommending routine vaccination series required for WIC or receipt of public assistance. That was originally put in this as a caveat that before you do that you want to make sure that varicella virus vaccine is available. I would propose deleting that part as something that the ACIP is servicing or something that states

should be consider doing. To me that's a bigger issue that would involve more of a discussion and would say instead that that sentence should end after day care.

Dr. Davis: Read it then the way you would have it.
Ed: Okay, so...to foster more rapid control of varicella and achieve high immunity levels, states may consider including varicella vaccination in their requirements for entry into school, head start or day care. Before instituting these or other such requirements it should be ensured that...and then to go on from there.

Dr. Davis: So moved.

Speaker Not Identified: Second.

Speaker Not Identified: I would add...we proposed to add this in the section at the end of the statement on future considerations as opposed to the body of the recommendations per say.

Speaker Not Identified: May I ask a question...what is this supposed to do now, what is the purpose of this statement?

Dr. Davis: Well the genesis of it was there was a lot of concern because of the difficulty in distributing the vaccine to end-users if they didn't have, in other words, clinics that didn't have the appropriate storage. So we got off into a situation where we needed to provide language through a working group and cooperation of the manufacturers, FDA, and a variety of folks, to try to make the vaccine more readily available to a broader population. And there was concern because of this difficulty that not everybody who would be receiving the vaccine would be under the aegis of any requirement would necessarily be able to get it. So it was a precaution that the distribution of and access to the vaccines should be broadened. We wanted to make sure that that would occur before there would be any required use of the vaccine. That's how this evolved. Then this morning we got into further discussion invoking the whole issue of what these requirements may be and there was some discussion that they seemed to amplify or at least potentially would create earlier use of the vaccination for required use in schools and some of us objected to that. So then where this particular language would be placed became important. We already have language that raises the issue of potential use of this language as a required vaccine

in schools, in the future use of the vaccine section of this very large statement on varicella. So that's how it evolved. And a lot of us are uncomfortable as this statement as currently worded with Dave's change would be in the future use portion of the statement. That seems to be the most reasonable place to put it.

Any further discussion?

Speaker Not Identified: The move is seconded. Do we vote?

Dr. Davis: It looks like Joel is moving to second it. The ACIP is voting on current language to foster more rapid control of varicella and achieve high immunity levels, states may consider including varicella vaccination in their requirements for entry into school, head start or day care. Before instituting these or other such requirements it should be assured that there is adequate distribution of and access to varicella virus vaccine to accomplish universal vaccination of those subjected to the requirements.

All in favor. Seven voting members present, all in favor. Those absent are Dr's. Thompson, DeBuono and Guerra.

Dr. Chen: For better or worse many of you have heard a lot of presentations on vaccine safety from me. About two years ago during NIP=s reorganization we were created as the Vaccine Safety and Development Activity. We have not done much in the arena and of vaccine development until recently when Bruce Weniger joined our group. Bruce comes to us from a substantial background working with AIDS. He started the CDC AIDS Research Center in Thailand and he is a member of the Presidential AIDS Commission, and so we look forward to his contributions. I think many of you know that basically in the last decade or so there's been a lot of new vaccines and there are many more in the pipeline. The ACIP obviously has looked at a number of newly licensed vaccines as well as potential new vaccines, some of which presumably in the near future like rotavirus and Lyme disease we'll be considering. We have also looked at improvements in previously licensed vaccines like Hepatitis B, acellular pertussis vaccine and hopefully in the near future pneumococcal and meningococcal conjugate vaccines. There is a wide variety of new biotechnology applied to vaccine development that is being discussed as well. We've had fairly simple combination vaccine products out there for some decades. We expect in the near future a number of

intermediate combinations vaccines to be licensed, on our way hopefully to a magic bullet of one-shot with all the antigens. But we wanted to raise to your attention is that there may be new difficulties with these intermediate combinations. First, given the mobility of associated with health care services in the U.S., physicians are likely to see children who may have received different vaccine combinations. Each immunization clinic, would need to stock all those permutations of vaccine, so polypharmacy would potentially be a difficult problem.

Alternatively certain children may get over-immunized. They may start their immunization series with one at one doctor. Combinations for his subsequent doses, he may go to another doctor who may only have a different combination of vaccines available in his clinic so the child who may get more doses of a vaccine than needed. There's also problems of mixing and matching. This may occur when one child gets started with the vaccine from one manufacturer and then goes to another clinic which stocks only the same vaccine from another manufacturer. Permutations of mixing and matching will be an exponential problem with more vaccines down the road. Obviously there is a need for us to harmonize all our schedules. There's concerns

that in order to create some of these combination vaccines, would we still have enough competition and innovation in the vaccine industry if many of the manufacturers are merging which may in some ways mimic an oligopoly. Finally, in terms of Federal procurement what are the appropriate ways in which we should think about how we move towards the future. Should we contract for every single combination out there; should we contract for certain ones that we think are optimal, etc., so these are difficult issues that we have to think about.

In summary, what we think is important is that we should at least on a priority basis try to define certain key principles as we look to the future. One is that we should definitely try to gather as much information as possible from all the players in a way that will maximize our ability to make good decisions. This will require the participation of as many of the key players as possible, from basic science, to the manufacturers, to the different institutes, constituents including the parents, will be important. Thirdly, is that it would be nice if we made this process as transparent as possible so that all the players know who is doing what. Fourthly, continuity, I think it would be nice for us define a process which requires only a minimal amount

of tinkering over time as we add new combinations and new processes. Finally, opportunity, I think historically the National Immunization Program has been the largest purchaser of vaccines in the country and I think if we used those resources in a thoughtful manner we hopefully can promote the development of new vaccines in a more constructive manner.

I'm going to just conclude and say we have started this process internally at NIP to create a working group. We have just expanded the group within CDC to include the other players that are important. We expect in the near future to involve a broadening circle, after we first define what the key issues are for NIP and CDC

Stan: I certainly applaud the idea of the ACIP taking up issues about new vaccines before they are actually licensed. I think manufacturers will welcome the input of the ACIP, but I would also caution you that there will be a problem with confidentiality which you will have to deal with in some way. That is, manufacturers will be reluctant to share data at an early stage unless they're protected and specifically if things are said in public session where competitors are present, they're

not going to like that very much. So, you want good information and you should be able to get it but you'll have to think about the conditions under which you'll have access to that information.

Speaker Not Identified: Stan raises a really excellent point. I'm new to this Committee but both Dr. Glode and I are veterans of committees at the FDA where there are opportunities for the committees to meet and deliberate in close session for just the purposes that Stan raised to be brought up to speed on new developments for new drug products and to serve as a sounding board for drug manufacturers, some of whom may actually request pre-licensure or pre-development meetings with the FDA committees. I don't know if Dr. Glode or Dr. Hardegree will want to comment any further or whether someone from CDC would like to comment regarding the precedent for closed meetings here. We're all within the HHS system and I just don't know what the prior thinking happens to be, but I do agree that there may be some advantage. This is obviously not the right time and right place to raise this issue given our time constraints so I would just raise it and maybe it's something that we could address at some future time.

Dr. Snider: I'm not sure ACIP has any tradition of closed meetings. I know in the last few years NIP staff have tried to work with manufacturers to get information directly. I think in the past we thought we would work through FDA but realized their confidentiality limits us from getting information. So we've had increasing contact with the vaccine companies but making very clear that they need to tell us what's confidential and what's not. I think we'd have to look at the ACIP by-laws as to whether a closed meeting can even be held. I don't know that, but it is an important issue, there's no question.

Dr. Davis: I would certainly concur. I don't know that we have a lot of time to get into this general issue any further now but I certainly appreciate Bob introducing it.

Dr. Glode: I think any mechanisms that would allow better flow of information from the sort of public health community in terms of vaccine development direction...I just think...you can tell me that we're going have to have all those interim combination vaccines and I just feel really bad about that. And I think that indicates some sort of lack of communication or something that we're going to have to potentially have all those on the market,

over-immunize all those children because we perhaps were, maybe not, but maybe weren't clear enough about what should be the ideal target combination vaccines, or whatever.

Dr. Davis: It certainly would make very good sense for general planning and it would help the vaccine companies tremendously to have this type of interaction and this communication to facilitate development of combination vaccines for example that have an opportunity to be on the market for an extended period of time that people are very comfortable in using and they could be readily incorporated into a very efficient delivery system and a good vaccine schedule. I think that should be an objective that all of us would want to dedicate ourselves to.

Jerry _____ from Merck: I'd just like to make two comments about combinations. Our short-term strategies for combinations are based on a meeting of two things basically: technical limitations on the one side vs. what you think you can make in the short term. Long-term combination strategies are based on what you want to make because you have the time to solve the technical problems. You don't really have time to solve all the technical problems. You're more limited by technical problems in

a short-term situation so guidance on both short-term and long-term is really useful from a manufacturing point of view so that you know what are reasonable technical problems to try and solve. In other words, to put a huge effort into something that people may not want for a long-term strategy is not useful either. So that is kind of a general comment but I think it would be very helpful for us to get that kind of guidance also.

Dr. Davis: Good point. All right, I think we ought to move on to the next topic. I want to thank you Bob and Bruce.

Okay, an update on the National Immunization Survey. Ms. Zell is going to be doing this. I see Alan Kendall is here too.

Ms. Zell: Just briefly I want to remind everyone of the reasons for measuring coverage is to look at protection in the population against vaccines, but also to help us monitor our goals and progress towards our objectives. And in 1996 we have antigen-specific objectives where we hope to achieve 90% coverage for DTP, polio, MMR and Hib, and 70% coverage for Hepatitis B. And then we'll move forward to the year 2000 objective of series

complete vaccination coverage of 90% for children under two years of age.

The National Immunization Survey was initiated in April of 1994 and the purpose was to provide state and 28 metropolitan areas with coverage on vaccination levels and for monitoring these trends over time. We are surveyed children 19-35 months of age at the time of the survey.

The NIS is a random digit dialing survey and at all 78 sites interviews were conducted throughout the year, and the data collected in quarterly increments to aggregate different quarters of the year and have moving averages.

The results we're presenting today are from April 1994 thorough March 1995, from children born bwtween May 1991 through August, 1993.

As we got into the project we learned that a telephone sample alone would not do it, so we added a second phase and contacted providers to determine or to help reduce the measurement area in reporting vaccination coverage.

This is summarizing the information from April through March and we can see our 1996 goal which we made for DTP and Hib. Now we need to maintain it. We=re only one percentage away in polio and MMR, and for Hepatitis B we still have a little bit of work.

Also with this release of the MMWR we are moving from just reporting these series complete of four DTP, three polio and one MMR to also include hemophilus influenza type b, and a major reason for this is that all children surveyed were born after the October 1990 recommendation for Hib vaccine.

Remembering that our national level for polio vaccine is 84%, we can see there are still six states with coverage less than 80% for polio, but there are five states with coverage over 90% for three or more doses of polio vaccine in children.

Our national coverage for MMR was 89% and we have only four areas with coverage less than 85%. We actually have one state with coverage higher than or at least 95%.

Hemophilus influenza type b our national total was 90% and we only have five states with less than 85% coverage and the range is 82-84%, with nine states having over 95% coverage for Hib vaccine.

When we look at our complete series level, we have one state with coverage of less than 60% and 11 states with 80% or higher. Vermont is the highest state with 86% coverage; and Michigan is the lowest with 59% coverage for four DTP, three polio, one MMR, and three Hib.

Hepatitis B vaccination nationally is about 42%. Here's where we see we have a lot of work to do. We have a number of states that have 20% or less coverage for Hepatitis B but there are four states with coverage greater than 60%. Only one state is at 70%, and that is our objective for 1996 with Hepatitis B vaccination. The vast majority are in the 21-40% range.

When you look at the age of the children, and it's difficult I know to think of children 19-35 months of age, we have young children and we have old children. But the older children are the least-well vaccinated, and the youngest age cohort of

children, the 19-24 months of age cohort is the best vaccinated with a coverage of 58%. We're seeing a positive trend with the younger children. I think it's a nice trend to see the implementation of a new vaccine.

Dr. Kendall: I think it would be appropriate to begin by just talking about the past, and pointing out that the survey represents an incredibly large amount of effort by the NIP team lead by Ms. Zell, as well as the NCHS team lead by Jim Massey. Everybody involved in this work deserves tremendous credit for what they have achieved, and I think that you can see the potential impact of this survey in terms of providing data which is needed to manage an immunization program and to track success and identify areas where further interventions are needed.

Many of you may have heard and there are questions as to whether NIP would be allowed to fund the survey in its continuing form. We are optimistic that the study will be able to continue in its present form. Data has been continuously collected so there will be updates based on exactly the same type of analysis of data collection as you have just seen. We do have a fallback position if it becomes necessary with the support of a substantial number

of the states to maintain the NIS in at least a portion of the country until such time might be found as to how it could be reinstituted as a truly total nationwide survey. I hope we don't have to actually utilize that fullback plan, but a lot of work has been done through ASTO to give us the support to enable that to be possible. So I think that we look forward to having further presentations expanding the data and hopeful we'll have good news in terms of the continuation of the NIS in its present form. I regret that it's not possible today to tell you with 100% certainty what will be happening, but to reassure you that every effort which can be made is being made to make this possible, including very active efforts to take advantage of the fact that a very large number of telephone calls are made to collect data from children in the age eligible group and that rather than simply abandon the calls which connect with the household where such children are present, we hope that there will be a possibility to integrate additional surveys for other program purposes that will provide an added benefit to the overall random digit dialing survey, and thereby reduce the actual cost of the immunization component and again increase the likelihood of it's maintenance for a long period of time in the future. We are all very proud of the survey and very committed

to trying to keep it going in the best possible fashion, and getting the maximum use from it.

I think the sort of current minimum turnaround time is in the region of 9 months allowing for the provider verification and combining two data sets to come up with the final analysis. I think we would all agree that if there are ways to speed it up further we would do so.

Ms. Zell: I think we've had the time delays so far because we instituted the provider study late and we hope to eventually, if this survey continues, to let the contractor take over the activity and then they may actually be able to do it on a more on-flow basis. And if that happens then it should turnaround our turnaround on it having the data in a much more timely fashion. Those were sort of our long-term goals but with the funding problems we haven't been able to move forward in that direction yet.

Dr. Kendall: I guess I would say that ultimately we hope that we would have a complete set of state-wide immunization registries

and all of the data will be available on line, but that isn't going to happen next year.

Dr. Rupprecht:

We appreciate the opportunity however being last to address the Committee about rabies. The last time you may recall that rabies was seriously considered was back in 1990 which resulted in the current recommendations in 1991. The previous recommendations were in 1984 so that time lapse in and of itself suggests one of the things that we'd like to put forward that the current ACIP recommendations in 91 actually contain a number of factual errors and one of the things that we'd like to bring to light is that we would begin to work on sections in order to update the ACIP from those 1991 recommendations in order to come up with recommendations relevant for 1997.

One of the things that you may be hearing about in one of the latest applications to FDA demonstrating the obvious need for an update in the recommendations is a new human rabies vaccine. Very recently there were discussions held with FDA towards phase four clinical trials. This is a PCEC or Purified Chick Embryo

Cell Rabies Vaccine. It's grown on primary chick-embryo fiberglass and it contains the flurry LEP strain, its's inactivated for propagation. It reportedly has very short production times and relatively high yield which at least in theory should make this vaccine a little bit less expensive than current products on the market. This PCEC vaccine is currently licensed in more than 20 countries. It's used both in pre- and post-exposure protocols; more than 12 million doses have been sold since 1985. From all of the safety data, NFC data, that we've been able to review and also in our WHO capacity as a collaborating center, it appears to have more than an adequate safety record along with all the currently-utilized global and some cultural inactivated vaccines and they have applied for this permit.

In essence on or about the time that an update application for this vaccine is made it would be in line with recommendations for ACIP for their next go-around, hopefully by 1997. So at the end of my presentation with the Committee's approval we would like to submitting for the next ACIP meeting updates of the '91 ACIP recommendations for human rabies prevention in the U.S.

Having said that and for more as a point of information rather than for a decision, there has been a change, if you will, in the epidemiology of human rabies over the last few years, certainly since the end of World War II. That is, if you look at the proportion of human rabies cases with an unknown source of exposure, it's risen from about 20 odd some to 80 some odd percent, although the overall incidence of human rabies has certainly decreased in the U.S. down to about 1 or 2 cases per year. In '93 we had 3 cases; in '94 6 cases; in '95 we had 4 cases. All of our cases in 1995 had no known definitive source of exposure. This is not because of vaccination failure, that is, the failure of the vaccine was potentially the case prior to the advent of current or culture vaccines in the 60's or 70's, but rather we feel the current cases are due to failure of recognition by the public. That is a failure of recognition that they are actually exposed.

Having said that and being able to analyze current human cases, the majority of the endogenously acquired human rabies cases appear to be associated with viruses from bats, this was firstly on the basis of monoclonal antibody and later genetic sequencing, to the point that not only are the majority of our indigenous

cases bat-associated, but the majority of our current human rabies cases of bat origin are associated with a single relatively rare variant of rabies virus.

One of the most recent cases for which you have handouts was in the last MMWR on human rabies, was this unfortunate case in Washington in the spring of last year. In essence it was a young child in which a bat was found in her room and although no bite per say was found and the animal was discarded, unfortunately this child did succumb to rabies. They were able to recover the carcass and unfortunately the sequence obtained from that carcass and the patient were identical. The point that we are trying to make in essence is that there are some 40 odd species of bats north of Mexico. They are all relatively small and they all have relatively sharp dentition. I can personally ascribe having handled thousands of bats in my career and having been bitten by bats hundreds of times, I can count on one hand the number of times that one of you could differentiate that in fact I was actually bitten. Having said that due to their small size and sharp dentition, we've come about with the current recommendation which is not really a change in the current '91 ACIP for transdermal, mucosal or aerosol transmission of rabies, but

rather a rather broad interpretation that where a bat is present and a bite cannot otherwise be excluded that post-exposure be considered, not necessarily recommended.

What we expect or what impact we expect this to probably have since bat/human contacts are relatively common occurrences, especially in the southern U.S., is that probably when bats are present more animals will be submitted, when there is a suspect case for instance, no good history could be obtained from a young child or if you were to awake in sleeping in a room and find the bat in the room, that more animals will be submitted and consequently when animals test positive more people will probably be treated for human post-exposure treatment when that animal proves positive.

That's a very brief update of two points one, a new vaccine coming down the roads, and two, current updates or interpretations of ACIP in cases involving bat contact in humans. I'd be happy to answer any questions that you may have. Thank you.

This particular species, one of the variants that we're identifying most readily is a solitary and migratory bat and

although it's range is somewhat restricted, that is it can migrate from Canada down into the southern U.S., it would not be found readily in all states, it's geographic range and the fact that it is a solitary migrant suggests that with the exception of Hawaii, it has the potential to reach all the 50 states, although it's distribution records would suggest that it's distribution is probably less than that.

Dave: I have a question about the new bat prophylaxis recommendations. I agree with you that in a setting where the bat is present that that's a situation you can deal with fairly easy. Unfortunately, as you know that may not be what happens most commonly but rather a bat is found in the bedroom of a child or otherwise found in a house and escapes before it can be tested. We know the numerator at least recently for how frequently that event results in rabies and it looks like it's one. Do you have any estimate for the denominator and the extent to which this more liberal recommendation will result in increased rabies prophylaxis?

Dr. Rupprecht: That's a very excellent question and it's one that we've been trying to come to grips with as of late. As you

know with decreasing resources and support about the only thing we can state at this time is that we probably will not meet the HP 2000 recommendations for cutting the number of human rabies post-exposure treatments in half by the year 2000. Why...because we don't know what end is and we don't have the resources to determine what end is. Hence we feel that that's probably not a very realistic expectation. Moreover, we have asked numerous times on occasion to try and better determine the epizootiology and epidemiology of human post-exposure treatment, or even for the reasons why bats are submitted or even the specie _____. We hope that we will be making some progress in getting some of the health departments to consider these opportunities, but until that time we don't know how many people receive post-exposure or why or why bats are submitted or even what species of bats are submitted at the present time.

One of the things that drove us to this rather difficult consideration was talking to the parents of some of these children who have succumbed. In essence they said that if this recommendation had been more widely circulated, in essence, they would have had their family treated and the child would still be alive. And in essence if you consider the relatively infrequent number of adverse effects, if you lead to more people being

treated, is that worth the increase in post-exposure treatments to even the decrease of fatality of one.

Certainly having a little bit more information to help support this recommendation even at first whip, you know it seems as though it's very prudent. I think David raised some very important questions and I would certainly like to see more information. But certainly I feel that it's something that we need to continue with in this Committee and try to bring more information to the Committee before the next meeting. That might be something we can even talk about in the working group format.

One of the biggest problems that we have is with animal exposures other than bats where the nature of exposures and recommendations are far clearer and where the data are more helpful is that we live right on a state line between New Hampshire and Vermont and deal with both state health departments on a regular basis regarding rabies prophylaxis. Human rabies prophylaxis is one of the very few areas and perhaps the only area where state health departments actually get actively involved in treatment decisions involving individual patients. Our experience has been that state health officials frequently

tend to be far more liberal and are much more likely to recommend prophylaxis above and beyond the recommendations from the ACIP and from others beyond what would be indicated based on the recommendations and resulting in my opinion a marked over-use of human rabies prophylaxis. It's a general statement and again it's late and I don't think this is the time or place to get involved in an active discussion, but I think it would be worthwhile putting it on the agenda for a future meeting to discuss this in greater detail.

Dr. Davis: I think it would be very useful to probably programmatically, if that's a big objectives, we might even be able to survey the states and trying to figure out some way of getting objective information.

One big help that data that are being collected now are the number of people who are being treated or types of surveys or why they're being treated or why they're being exposed to bats or various bat species, even the speciation of animals being submitted for diagnosis would be a help to get some sort of data base started. But again, it's not for wantive asking that these sorts of studies be implemented.

Stan: I just want to point out the dilemma. On the one hand one doesn't want to over-immunize and there will not be a problem with vaccine supply but there will be a problem with HRIG supply because of the requirement to test for Hepatitis C is reducing the amount of HRIG available, so that if one gets into a lot of primary immunization, that is going to be a problem. On the other hand, rabies has always been a disease where the ideal has been to reduce the incidence to 0. That goes back to _____. Now if you were going to convert into a disease in which you are trying to reduce the incidence rather than eliminate every single case.

In essence the recommendation is only an extension of what goes on in a daily basis any way. In essence, when you can't determine if a bite has occurred, we have a fairly good guess at what most physicians would decide to do in that situation, when the bat is in hand and the animal proves positive.

Speaker Not Identified: That's not quite correct. I know we don't want to labor this, maybe we could talk afterwards, but we

were talking about the incidence where the animal is not available...

Dr. Rupprecht: Exactly, but first I stated the one where the animal is positive, that was number one that the animal was there. The recommendations for which you're interested in, the recommendations did not address that issue. That's a subsection of this entire issue when the animal is not available. And actually it comes into a situation in the current ACIP talking about wild life and when wild life are available or not. It's the same situation if the animal is not available and when it's a young child for instance.

Speaker Not Identified: Well we should talk afterwards because I don't think people out in the field are reading it the same way that you just explained it.

Speaker Not Identified: I would just add that prior to today I didn't appreciate that you could be bitten by a bat and not realize it, so maybe that should also be incorporated into the statement either parenthetically or as a direct part of it.

Dr. Rupprecht: I assure you that you can. In essence we always liken it to a stick by a 26 gauge needle and then defy the individual to find where that transdermal occurred. I guess I should shed one little piece of information and that is we know that this kind of variant has the ability to replicate at lower temperatures and has the ability to do some things in terms of spread cell to cell that other rabies viruses that we've looked at so far do not appear to do. What that suggests to us is that there may be variants out there that are highly adaptive for peripheral invasiveness, hence why we think this is a rather conservative recommendation.

Dr. Davis: I think what we need is some specific language. Why don't you and Dave work at it...would there be a group that would like to just...among the people who have listened to this that would like to consider this further. I for one would be happy to participate...Dave...okay, the three of us...anyone else...you don't have to feel obligated...I think we can work with three. The key thing was having some virologic input and having some state input, I think, on this one would be useful, working with Chuck, I think the four of us can take a look at that and try to come up with some language that we can get to the full Committee

and then the full Committee can consider it. And if we feel that if it's something that needs to be done before the next meeting that could be done in a variety of ways. If it's something that can be handled at the next meeting, of course we'll bring it to the table. Fair enough?

We are at the end of our agenda of formal presentations. I like to offer the opportunity for public comment.

With no public comment, I=ll adjourn the meeting.