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Advisory Committee on Immunization Practices

Minutes of the Meeting

February 12-13, 1997

Atlanta, Georgia

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ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

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Opening Comments

The Advisory Committee on Immunization Practices (ACIP) was convened by the Centers for Disease Control and Prevention (CDC) on February 12-13, 1997. Chairman Dr. Jeffrey Davis began the meeting at 8:25 A.M., and Dr. Steven Hadler served as Acting Executive Secretary. Dr. Davis welcomed several new ACIP liaison members: Dr. Walter Faggett, the new liaison for the American Medical Association (AMA); Dr. Luis Matus, Mexico's Director of General Epidemiology; Dr. Jane Siegel for the Hospital Infection Control and Prevention Advisory Committee (HICPAC); and Dr. Gordon Douglas of Merck Vaccine and the Pharmaceutical Research and Manufacturers of America (PHARMA). Dr. Paul Verughese of the Canadian Advisory Committee on Immunization attended for Dr. Scheifele, and Dr. Bud Anthony attended for Dr. Carolyn Hardegree, the Ex-Officio member from the Food and Drug Administration (FDA). Throughout the meeting, an Envision link was open with the Human Resources and Services Administration (HRSA).

The meeting notebooks included several statements, published in the *Morbidity and Mortality Weekly Report* (*MMWR*) since the last meeting, on polio prevention, adolescent immunization, plague, and one on adverse reactions and hepatitis A vaccine. Publication of the meningococcal and pneumococcal recommendations were anticipated shortly.

Dr. Davis reported the imminent completion of the February and June 1996 minutes, and subsequent expected completion of the October 1996 minutes. The next ACIP meetings will be held on June 25-26 and October 22-23, 1997. The members were asked to indicate their preferred 1998 meeting dates on the calendars to be sent out. Staff changes announced over the course of this meeting included NIP Director Dr. Walter Orenstein's six-month sabbatical, to begin in June. Deputy Director Dr. José Cordero will serve as Acting Director. Dr. Steven Hadler also announced his plan to leave the National Immunization Program (NIP) to work on polio eradication in Pakistan. The committee members expressed their regret at his departure.

The members then disclosed their potential conflicts of interest. Dr. Davis reminded them that all members may participate in discussions after this disclosure, but may not vote with any conflict of interest. The Ex-Officio and liaison members were not required to state any conflicts of interest.

Dr. Glode, Dr. Davis and Dr. Thompson had no conflicts of interest. Dr. Schoenbaum had no personal conflicts; his wife holds stock in Amgen, Bristol Myers, and Squibb, but for no current

vaccine manufacturers. As Director of UCLA's Center for Vaccine Research, Dr. Ward reported their receipt of grants in the past year from SmithKline Beecham, and Merck, Sharp and Dome. Grants are being considered from others in the next year, but he himself had no direct financial interest in any vaccine manufacturer. The total research so funded is <15% of their total funding.

Dr. Guerra of the San Antonio health department reported their past demonstration project support from Merck Vaccine Company. They are now doing a hepatitis A vaccination project with some support from SmithKline Beecham, and they completed an acellular pertussis clinical field trial project for North American Vaccine. A current project is underway with Metamune Corporation. Dr. Modlin reported support for several small research projects from Viropharma and Metamune, and he and/or his wife hold stock in Merck, Amgen and Chiron. He also has served as a consultant or participated in education programs conducted by Merck and Pasteur-Merrieux Connaught. As chair of the Pediatric Section of the National Medical Association, Dr. Sherrod reported educational funding from North American Vaccine, Merck, Connaught and Lederle. The liaisons, CDC staff and other attenders then introduced themselves, with no reports of conflict of interest.

National Vaccine Program/Compensation Reports

Dr. Geoffrey Evans, of the Bureau of Health Professions, Division of Vaccine Injury Compensation, reported that 5,110 claims had been filed as of January 31. About 78% of all claims have been adjudicated. They are continuing to process the claims for cases stemming from vaccination before October 1988. Over $700 million has been paid to date.

Dr. Evans reported that the second final rule to change the vaccine table had been approved. These were based on the second Institute of Medicine (IOM) report of 1993, which covered the remaining program vaccines but rubella and pertussis, and included hepatitis B and Haemophilus vaccine. The changes add brachial neuritis for tetanus containing vaccines; for measles vaccines, thrombocytopenia will be added and residual seizure disorder removed. Hib and hepatitis B vaccines will be added for coverage, as will varicella, the latter with no related condition specified. The claimant would have to prove illness with causation effect. If conditions are found to be connected over time, a rule will add those and cover them eight years retroactively.

In another change, any routine CDC-recommended childhood vaccine will automatically be added to the Compensation Program, assuming Congress' approval of an excise tax. This flat tax, proposed since 1995, would allow 51 cents per each vaccine's covered antigen. Though it has support, it has been lost in the budget process. But once approved, the tax is expected to be quickly applied to any vaccine added to the program.

Dr. Robert Breiman, Director of CDC's National Vaccine Program Office (NVPO), reported on the current funding process for unmet needs. A broad focus by NVPO is vaccine safety issues. Among the more specific areas is post-licensure evaluation of the use of acellular pertussis vaccine in children, adolescents, and adults. Combination vaccines are also receiving attention, as are vaccines in development which will likely require recommendations. Other proposals are

coming in on novel approaches to new vaccines, optimal use and increased coverage. This process should be finished in mid-March. The unmet needs process itself will be evaluated by assessing how well the research funded in recent years improved the understanding of vaccines and development of new ones.

He reported further on an inter-agency work group convened by the Department of Health and Human Services (DHHS) to develop an action plan for adult immunizations, closely following the 1994 National Vaccine Advisory Committee (NVAC) report. It is hoped that this process will help improve adult immunization coverage as well as new vaccines for adults. A draft report should be distributed soon. NVPO is also involved in the pandemic flu report development, and is coordinating with the Canadian government on their own developing plan.

As part of its work on developing a partnership between vaccine manufacturers, public health and academia, NVAC convened a November 1996 meeting to explore a more expedited approach in developing safe and effective vaccines. A related paper has been submitted for journal publication. Another paper has identified areas of shared responsibility (parents, industry, etc.). In response to interest in involving non-traditional health care providers in immunization, NVAC also conducted a survey of state epidemiologists. The Spring (May 1-2) meeting agenda will evaluate such use further. NVAC also recently recommended a presidential apology for the Tuskegee syphilis experiment, as it affected public trust.

Discussion
Dr. Halsey asked Dr. Evans if adverse events would be covered from new vaccines used prior to ACIP recommendations and later determined compensable. He confirmed that; once the vaccine is added to the program, it is covered for eight years; or any condition added with rulemaking is covered for eight years retroactively. Dr. Gardner urged quick involvement of nongovernmental organizations (NGOs) and agencies in NVAC's process. Dr. Sherrod asked who would be liable for adverse outcomes if alternative providers deliver adult immunizations. Dr. Breiman reported that this has normally been done with standing physician orders, with the responsibility resting in the provider, but he was unsure if this is true across the board.

Combination Vaccines Work Group Report
Dr. Mimi Glode reported work group discussions in October and December 1996 and January 1997. They addressed major issues on combination vaccines in general and the recently licensed ComvaxJ vaccine in particular. About 30 people were involved; ACIP members, staff from NIP, FDA and state health departments; the American Academy of Pediatrics (AAP), public health communities, vaccine companies and two private practitioners. They developed an overview and common definitions, reviewed the draft statement on combination vaccines; discussed such vaccination issues as polypharmacy, extravaccination and interchangeability; discussed ComvaxJ, and potential recommendations to offer ACIP.

Dr. Glode noted the ACIP's double dilemma of assuring that all children are up to date on their immunizations, and that providers are up to date on the latest vaccine licensures and

recommendations. Multiple groups' recommendations and updates on licensure can lead to justifiable health care provider confusion. The vaccine updates also are published intermittently throughout the year in various venues; she suggested a regularly scheduled time for coordinated vaccine updates.

Dr. Bruce Weniger then the work group's 17-page draft working document. Increasing numbers of new vaccines which must be incorporated into routine immunization schedules. Fourteen diseases have been become vaccine-preventable since the 1980s, and several more with significant infant morbidity are expected in the next few years. Although parents are reluctant to give their children more than 2-3 injections per visit, the current schedule now requires an average of 2.75 injections in the 2, 4, 6, and 12-15 month visits. Increasing the number of visits would increase both direct and indirect related cost.

Combination vaccines both address and complicate this situation. They involve both polypharmacy and oligopharmacy, and the latter's corollary, extravaccination. The issue of interchangeability involves mixing and/or matching sequential vaccines. Duplicate vaccinations are almost ensured by inadequate vaccination tracking systems, and duplicate or extravaccination may not be reimbursed by health insurance companies.

The combination DtaP/Hib and Hib-hep B licensures ushered in an age of Acombination chaos@, and with their successors demand choices in the public and private sectors. Hib-hep B and DTaP-Hib vaccines presented the first overlapping, non-complementary antigens in different vaccines. Previous vaccine pairs were either duplicate combinations from different manufacturers or inclusive/complementary products.

One current challenge is the interchangeability of different vaccine formulations/brands in children's primary or booster series. Mixing vaccines has been validated for vaccines with serologic correlates of immunity (e.g., Hib or hep B), but for those without such serologic correlates (e.g., DTaP or DTaP-Hib), insufficient data on mixing has led to a preference for matching throughout the series. Nonetheless, the current ACIP recommendation is that any acellular pertussis vaccine can be used when the previously used brand is unknown.

This clearly leads to stocking considerations. Dr. Weniger defined "polypharmacy" as stocking multiple- or all possible vaccine products, with redundant antigens in multiple products, even though not all such products are needed to fully immunize any one patient. With "alternative permutation polypharmacy", duplicative backbone vaccines are stocked. "Component polypharmacy" would stock combined vaccines (DTaP-Hib) as well as one or more of the component vaccines (DTaP and Hib).

"Brand polypharmacy" would stock multiple brands of the same vaccine type from different manufacturers. This allows any child to receive the exact antigen needed, avoiding the unnecessary cost of extra antigens and the hypothetical risk of increased adverse effects from multiple antigens. But the disadvantages are the administrative burden and complexity in

buying/handling multiple products; the extra overhead costs, possible staff confusion and potential error in administration; cold storage requirements and space, and wastage of products that expire before they can be administered.

On the other hand, "Oligopharmacy" stocks only a limited but sufficient number of vaccine products to immunize children. But this may well involves "extravaccination", defined as using combination vaccine even when one or more of its antigens are not needed. Polypharmacy and extravaccination are trade-off concepts like sensitivity and specificity. Although extravaccination is a new term, giving unneeded extra antigens to children is common practice. Even if the child seroconverts on the first one or two doses, multiple doses are given to ensure a high protective immunity in the population (e.g., fourth and fifth doses of tetanus antigen).

Dr. Weniger outlined the extra vaccinations that might occur with new combination vaccines. A dose of hepatitis B vaccine at 12-18 months is unnecessary if a birth dose is given; and 40% of U.S. children receive a birth dose. Or, if a clinic used a backbone product of DTaP-IPV in an all-IPV schedule and did not stock separate IPV vaccine, five doses would be given at 2, 4, 6, 12-18 months and 4-6 years. The IPV dose at 6 months would be extraneous to the schedule.

This is complicated by the fact that in our mobile society, about 25% of 0-2 year-old patients change vaccine providers. Medicaid and managed care enrollments average 9-10 months. This leads to a frequently absent vaccine history, and strongly suggests tracking registries. Some methods to facilitate this are standardized vaccine record forms and peel-off stickers for accurate transfer of vaccine information.

In the absence of such information, duplicate vaccination may inadvertantly occur. Dr. Weniger defined duplicate vaccination as Aadministration of vaccine by a provider unaware of previous vaccine history, despite reasonable efforts to obtain it, in order to avoid missing an opportunity to immunize child. This is done on public health grounds to maintain high coverage, but it is later determined that the child is already up to date on all the vaccine's antigens.@) This may be discouraged if physicians are worried about denied reimbursement for duplicate and extra vaccinations, thus lowering herd immunity and increasing the disease burden.

Dr. Steve Hadler defined the key issues of extravaccination as the safety of extra doses, the vaccine cost, and programmatic issues of simplicity (emphasized by providers at the work group meeting), polypharmacy (stocking many rather than fewer vaccines), potentially fewer missed opportunities, and increased vaccine coverage. He outlined similar situations to Dr. Weniger's in which overimmunization might occur, adding the issue of children with a late start on immunizations. The percentage (4.4%) of children beginning vaccination at >6 months of age may be reduced, but an accelerated schedule may present different timing considerations for antigen components of combination vaccines.

For example, giving the Hib-hep B combination to a child with no hep B birth dose is ideal, but there are tradeoffs in children who received a birth dose of hep B. While the combination offers

simplicity in the schedule, it delivers an extra dose of hep B vaccine. To avoid that, a second Hib dose could be given in monovalent vaccine at 4 months, but that involves extra stock and different schedules for children with- and without birth doses. Another option would administers all monovalent vaccines (Hib at 4 and 12 months and hep B at 6 months); but again, three vaccines must be stocked.

Dr. Hadler summarized the advantages of extra vaccination: simplicity, oligopharmacy, reduced likelihood of using a wrong vaccine, fewer missed immunization opportunities, and possible increased vaccine coverage. But the clear disadvantage is cost. So, while extravaccination may be necessitated by combination vaccines and programmatic issues, ACIP must also consider safety, cost, and programmatic issues. The best approach may be through flexible ACIP recommendations to provide room for the provider's judgement.

The work group reached nine conclusions, to which the members were asked to respond in this meeting and/or in writing. First, in general, combination vaccines can and should be used to minimize the number of injections and reduce the consequences of a greater number of injections; and (2) it is reasonable to reduce polypharmacy by purchasing and stocking a limited number of vaccine products (oligopharmacy).

The work group also concluded that (3) reduced polypharmacy may lead to extra vaccination. Potential harms (adverse events/cost) of administering unneeded antigens must be balanced by the benefits (avoiding polypharmacy and improving timely immunizations). They considered extravaccination acceptable within a proper standard of medical care, e.g., when the provider does not possess other vaccine products (routinely or has depleted stock due to use) containing only the antigen on a child's schedule, and no data indicate increased risk of adverse events from extra antigen(s).

The work group offered two conclusions on interchangeability. Vaccines with serologic correlates of immunity can be used interchangeably. E.g., since multiple studies indicate that different manufacturers' Hib and hep B vaccines are interchangeable, ComvaxJ may be mixed in a schedule with other Hib and hep B antigens. But for vaccines without serologic correlates of immunity such as DTaP, (5) since the efficacy of mixing/matching cannot be proven, when feasible, the same acellular pertussis vaccine should be used throughout the entire series. However, the provider need not stock more than one brand of acellular pertussis vaccine; it is acceptable to use any acellular vaccine stocked.

They supported an ACIP statement on combination vaccines, not just for ACIP but others as well to see how ACIP is evolving. This could simply be circulated, rather that published in *MMWR*. And, while they supported preparing a combination hep B/Hib statement, this should not be viewed as a precedent for a stand-alone statement for each new combination issued. They supported regular updates every six months or per year on new vaccines.

Next, regarding vaccination history and tracking, the work group identified two issues. They suggested involving various groups to improve the timely availability and accuracy of immunization records to the provider while the patient is still in the clinic. E.g., the ACIP, AAP, American Academy of Family Practice (AAFP) and others could develop a nationally standardized vaccination record form. Immunization registries will be key. Tracking can be aided by peel-off stickers/bar coding to facilitate clinic record keeping, as well as other ways to help parents keep accurate records. Finally, the work group urged making health insurers aware of the pending issues. The companies should be urged to reimburse for all monovalent vaccines and combinations, and not refuse to reimburse for combinations.

Discussion

Dr. Chin Le suggested that the draft's page one "recommended standard" for extravaccination be changed to an Aacceptable standard@, since limited data may not adequately convey the possible adverse reaction. He also advocated a more proactive ACIP response to the market forces driving the combination vaccines, particularly in light of the likely public health conditions to rise. Dr. Davis cited the manufacturers' encouraging initiative in asking for ACIP input and thought the solution to be a consistent dialogue with them and other advisory groups.

Dr. Halsey appreciated the document's attention to key issues and amny of its principles. But he voiced concern, echoed by several members, that inventing new words and changing common definitions would only complicate matters. He also was the first of several members to advise an abbreviated document for practicing pediatricians, and anticipated strong Redbook Committee support and cooperation in developing a standard immunization form.

Dr. Zimmerman suggested a combined statement on combination vaccines by ACIP, AAP and AAFP, similar to that on adolescent immunizations. Dr. Halsey was willing to consider that, but warned that this could be a lengthy process, and preferred to release this current timely document. But Dr. Guerra hoped for as much input as possible from local health departments, e.g., through the National Association of County and City Health Officials (NACCHO) or other state organizations, to inform the process in a practical way.

Dr. Hinman recalled a successful past development of a standard immunization form, before the current proliferation. He stated that registry access to providers is supported by CDC data showing that patient-held records are often incomplete. Finally, he noted that the focus of vaccination is to improve a child's protection; to improve coverage is a secondary community function. Dr. Ward suggested developing an abbreviated standardized format to address the emerging new vaccines, outlining what is known and unknown about them, listing their advantages, disadvantages and potential uses, and appending the appropriate tables from the unified schedule.

Dr. Robert Chen of the NIP raised the need for additional data on the safety of additional doses. He suggested that ACIP with the PHARMA representative to institute a standard lot number

sequence to identify the combination vaccine used. This could accurately track what each child receives in individual or registry records. Dr. Breiman reported NVAC interest in this as well.

Dr. Harrison, a private practitioner who participated in the work group, noted practitioners' pressure to lower costs and personnel while increasing the number of patients seen. With the increasing complexity of vaccine requirements, a physician must spend 3-5 minutes deciding on vaccines with non-nursing personnel. He urged a simple statement, and that guidelines be provided for the future, especially since the market forces driving this process are well ahead of the government's response. He urged ACIP, AAP and others to develop 5-10 year strategies based on the current medical indications of children's needs, in concnert with the manufacturers, health maintenance organizations (HMOs), FDA and others. He also supported the introduction of vaccines at regular intervals, so that practitioners could review the recommendations periodically (preferably yearly) and adjust their practices accordingly.

Dr. Plotkin noted that data are available for some vaccine antigens used in greater-than-recommended doses (e.g., IPV and hepatitis B). He also suggested that ACIP discuss whether pharmaceutical companies should maintain monovalent vaccines on the market, as this could involve safety issues as well as extra doses. Since the companies are unlikely to do mixed-vaccine studies with other manufacturers' products, academia or public investigators will need to address these. He took exception to the acellular pertussis vaccine example cited, as every vaccine on the market has been shown efficacious in controlled studies, and are all based on the same antigens.

Dr. Rabinovich noted that there are opportunities for ACIP and NVAC to discuss what combinations should be developed. However, much development is driven by the technology, and some of the desired simplicity could be achieved now by adopting or adapting the European two-dose schedule. This is now being compared to the U.S. three-dose schedule adopted in the 1950s for whole-cell DTP administration. The Vaccine and Treatment Evaluation Units of the National Institute for Allergies and Infectious Diseases (NIAID) are closely monitoring current studies to determine the needed data areas in immunization scheduling.

After a short break, Dr. Hadler requested the members' comments on the draft combination vaccine document, particularly regarding CDC's leadership in the free enterprise of vaccine. Dr. Davis requested the members' comments on the combination vaccines document by February 15.

Issues Regarding Recommended Uses of ComvaxJ

Dr. Frank Mahoney, National Center for Infectious Disease (NCID) Hepatitis Branch, called the members' attention to the draft document on combination vaccines. This was developed in response to the committee's interest in addressing ComvaxJ in a stand-alone statement. The document reviews the diseases addressed by ComvaxJ and describes the vaccine. It also addresses specific hepatitis B issues related to infant vaccination, particularly the prevention of perinatal transmission and the birth dose of hep B vaccine. It provides recommendations.

Merck's immunogenicity data showed ComvaxJ' PRP response to be equivalent to that of the monovalent Pedvax7 and Recombivax7 vaccines. For hepatitis B, it offers a slightly lower geometric mean titer (GMT) response, but is expected to be highly efficacious with excellent long-term protection.

The issues involved in the routine use of ComvaxJ Hib-hepatitis B vaccine in infants of HBsAg-negative women are overimmunization (4 doses rather than 3) and polypharmacy (provider's stocked products may decrease, but perhaps not include monovalent vaccines). The programmatic issues include improved hepatitis B coverage without any likely effect on that for Hib, and a decrease in required injections. However, costs are likely to increase. This was demonstrated on a chart which showed the December 1996 vaccine costs and extrapolated the cost of overvaccination with an extra dose of hepatitis B.

Data from the 1995 National Immunization Survey show that 75% of children received three doses of hepatitis B and Hib, with the use of hep B rising steadily over time. It follows that the advantage of increased coverage will probably gradually be less apparent over time. Dr. Mahoney also presented data from several studies of hep B vaccination at birth; reported rates of children receiving a birth dose vary from 26% to 89%.

The current cost of monovalent vaccine in the public sector is less than that expected for a ComvaxJ dose (about $20). The projected cost of a complete monovalent series is $111; DTaP and ComvaxJ is $130; DTaP, Hib-hep B and a birth dose if hep B is $137; and DTP-Hib, hep B monovalent and a fifth dose of DTaP is $96. In the program's model (of only vaccine costs), adding the fourth dose for about half of U.S. infants did not appreciably affect the public sector's cost benefit. It was still quite favorable in terms of cost per year of life saved.

Dr. Davis asked on what basis the incremental cost was defined as not appreciable. Dr. Mahoney responded that this is relative; while it might be appreciable to a state health department at an extra $7 per child, it was not significant in the cost analysis compared to what is normally done in medical interventions.

In summary, the ComvaxJ Hip-hep B use in HBsAg-negative mothers would decrease the number of injections and products stocked, and may improve overall hep B coverage and simplify the schedule. However, it will increase costs and deliver an extra dose of vaccine to some infants.

Overimmunization is another issues for infants born to HBsAg-positive mothers, as the current schedule would adminster four doses of vaccine. However, this is such a low-frequency event, and a harmonized schedule for antigen-positive and -negative mothers would simplify the provider's schedule. It could decrease the number of products a provider uses and avoids concern that physicians may not stock monovalent vaccines.

Dr. Mahoney briefly reviewed several efficacy studies which showed ComvaxJ used in a 0, 2, 4, and 12 month schedule. These support the expectation that ComvaxJ will have a high efficacy (>90% of infants showed seroprotection after two doses) and potentially improve three-dose coverage earlier in life. Surveillance also is in place to monitor coverage through post-vaccination serologic testing.

He outlined the current status of infants of surface antigen-positive mothers. Over 7000 of such infants annually receive HBIG at birth, and data from state immunization programs show 60-70% to be fully vaccinated by 6-8 months of age. Those incompletely vaccinated have a high likelihood of infection, and CDC is working with the states to improve the delivery of six doses by six months of age. The serologic testing also done by thos state projects show an infection rate of about 3% in about 1500 tested children born to HBsAg-positive mothers. Post-marketing surveillance should indicate ComvaxJ' effectiveness for providers in state-based programs.

Finally, Dr. Mahoney addressed the use of hep B vaccine among infants of mothers who are not screened for HBsAg status. The document recommends vaccinating the infant within 12 hours of birth, and screening the mother at delivery. If she is HBsAg-positive, HBIG should be administered within one week, and the second and third dose of ComvaxJ delivered at 1-2 and 6 months. In communities without screening (e.g., Alaska and the Pacific), all infants should be vaccinated at birth, 1-2 and 6 months. This is important particularly in the Pacific, where about 12% of pregnant women are HBsAg positive and there is a high e-antigen prevalence.

Regarding ComvaxJ use among infants of women with unknown HBsAg status, the programmatic issues differ. In areas where HBsAg screening is the standard of practice, infants should be vaccinated according to the mother's HBsAg status. Where HBsAg screening is not done, ComvaxJ with hep B is the recommended dose. Vaccine along (without HBIG) is highly effective in communities where HBsAg screening is not done. And, transmission occurs among infants not vaccinated at birth.

Dr. Mahoney addressed the use vaccine alone without HBIG. The data show good efficacy with the 5 Φg dose, comparable to Engerix7 at a 0, 1, 6- or a 0, 1, 2, 12-month schedule; the schedule with ComvaxJ would be 0, 2, 4, 12 months schedule. Data showed that routine infant immunization at the 0, 1-2 and 6-month schedule in endemic Pacific areas drastically reduced prevalence.

He summarized the committee's recommendation for ComvaxJ use in infants of women with unknown HBsAg status. Where HBsAg screening is the standard of practice, ComvaxJ use would depend on perinatal screening; where it is not, perinatal transmission is related to infants not receiving vaccine at birth. ComvaxJ is expected to have high efficacy.

Discussion

Dr. Anthony asked if HBIG were used in the Pacific and Alaskan populations. Dr. Mahoney responded negatively, due to the absence of screening. Dr. Halsey and other members advised CDC to be clear that this is only one of several ways to immunize children, to avoid any perceived endorsement of ComvaxJ.

Dr. Gall was concerned that this draft's message could counter ACIP's drive to immunize all children at birth. Dr. Mahoney responded that the document does not discourage a birth dose. Dr. Davis agreed, but also observed that the wording opens the door to evaluate the birth dose. Perhaps it should be continued, but its greater costs should be assessed. Until those evaluative data are in, the document should be neutral. Dr. Gall, however, noted that the data shown support a birth dose. Dr. Ward suggested changing the document's order of presentation so that surface antigen-positive mothers are addressed first.

Dr. Peter stated that the work group was not seeking to change the birth dose, but to address the range of the recommendation (birth to two months). He questioned if the birth dose should be retained indefinitely with the advent of combination vaccines. He also felt that the document did not sufficiently emphasize that ComvaxJ is not to be given before the ages of 6 weeks. Dr. Chin Le recommended that this be listed with the disadvantages on the draft's page 13. He also disagreed that the combination vaccine's availability could decrease the number of vaccines that providers need to stock, thinking that any practitioner should stock monovalent for adolescents and Asian children. Third, he thought it may not be true that ComvaxJ would improve vaccine coverage, as that results from state mandates (e.g., for school admission) rather than from market supply. Finally, he stated that because of the lower GMT and greater cost of this vaccine, Kaiser Permanente does not stock it.

The draft document refers to the controversy over the birth dose on its page 12, but Dr. Thompson though that ComvaxJ obviates the need for that dose. Dr. Mahoney stated the perinatal programs' caution to retain the birth dose because all children born to HBsAg mothers are not identified. Dr. Thompson persisted that screening would identify them.

Recommendations on ComvaxJ Use

Dr. Mahoney read the draft recommendations for infants born to HBsAg-negative mothers:

1. ComvaxJ is licensed for use in infants born to HBsAg-negative women. A three dose series of ComvaxJ should be administered at 2, 4, and 12-15 months of age. ComvaxJ must not be given to infants younger than 6 weeks of age because of the potential for suppression of the immune response to PRP-OMPC with subsequent doses of ComvaxJ. Ideally, infants should receive their first dose of Hib conjugate vaccine at age 2 months and complete the full series as specified above for protection against invasive Hib disease.
2. If the series is started late, the number of doses of a PRP-OMPC containing product (i.e., ComvaxJ, PedvaxHIB7) that should be administered depends on the age vaccination is

begun -- three doses if initiated no later than age 11 months, two doses if started at age 12-14 months, or one dose if started at age 15-59 months. A minimum interval of two months between doses of Hib is recommended, although an interval of 1 month is acceptable if necessary. Three doses of hepatitis B vaccine are required irrespective of age at which this vaccine series is initiated.

3. Children who received one dose of hepatitis B vaccine at or shortly after birth may be administered ComvaxJ on the schedule of 2, 4, and 12-15 months of age.

4. In infants born to HBsAg-positive mothers, ComvaxJ may be administered at 2 months, 4 months and 12-15 months of age to complete postexposure vaccination. These infants should receive monovalent hepatitis B vaccine and HBIG at birth.

There was no discussion on these recommendations.

5. In infants of mothers with an unknown HBsAg status, where HBsAg screening is the standard of practice, the ACIP recommends prenatal HBsAg screening of all pregnant women to identify those mothers whose infants require postexposure prophylaxis to prevent perinatal HBV infection. Women admitted for delivery who have not had prenatal HBsAg testing should have blood drawn for testing. While these results are pending, the infant should received hepatitis B vaccine within 12 hours of birth at a dose appropriate for infants born to HBsAg-positive women. It the mother is later found to be HBsAg-positive, her infant should receive the additional protection of HBIG as soon as possible and within 7 days of birth. For infants of women subsequently found to be HBsAg-negative, ComvaxJ may be administered at 2, 4, and 12-15 months of age.

6. In settings with no routine prenatal HBsAg testing, infants should receive monovalent hepatitis B vaccine at birth. ComvaxJ may be given at 2, 4 and 12-15 months of age to complete the vaccination schedule for both hepatitis B and Hib. These infants would receive an extra dose of hepatitis B vaccine. Since these infants may be at high risk of perinatal HBV infection, especially in those communities where the prevalence of HBsAg is high among pregnant women, providers should ensure that infants receive three doses of a hepatitis B-containing product by 6 months of age.

Finally, the recommendation states that ComvaxJ may be administered simultaneously with DTaP (or DTP), IPV, OPV, MMR and/or varicella vaccines as necessary. Precautions and contraindications include anaphylactic reaction to a previous dose of ComvaxJ or to its Hib or hepatitis B components. ComvaxJ should not be given to children with moderate or severe acute illnesses. Children with mild illness with or without fever (upper respiratory infection, diarrhea, treated otitis media) may receive ComvaxJ.

Discussion

Dr. Davis recommended including in #3 and #5 that monovalent Hib vaccine could be administered at 4 months of age. This would also avoid giving extra doses. He also suggested a statement that testing of non-screened women should be expedited. Dr. Peter thought probaly justified but impractical in the real world, and wondered if there were sufficient data to advise discontinuing HBIG. With the efficacy of the vaccine, the additional benefit of HBIG is questionable. Dr. Mahoney agreed this was worth pursuing; the program would have to assemble the data for the committee's review.

Dr. Halsey thought that the statement was going beyond its intended focus, which is the use of ComvaxJ and not the birth dose, screening or other such related issues. He recommended deleting those policy issues from this document and examining them separately. He advised keeping the advisory simple, to say that ComvaxJ is acceptable in this schedule (2, 4, 12-15 months) for children born to surface antigen-positive or -negative mothers.

Dr. Glode was disturbed by the statement's ambivalence about the birth dose, fearing that practitioners may consider discontinuing it although ACIP things that inadvisable. Though this should be addressed separately, she recommended that the statement be clear that ACIP has not yet proposed any changes. It was generally agreed that this issue requires evaluation, including whether its salutary impact outweighs the costs.

Dr. Thompson noted that the current recommendation advises hepatitis B vaccination at either birth or two months, as equal options. The statement could indicate that the practitioner could evaluate which option they desire for ComvaxJ. Dr. Douglas anticipated increased combination vaccines containing common monovalents. The question of which parts of the relevant issues demand attention (screening, costs, etc.) must be decided. Dr. Davis added consideration of other factors such as benefits to others than the infant. Dr. Peter advocated as brief a statement as possible, emphasizing those aspects which differ from the package insert. He also noted the need for the full committee to agree or disagree with the work group's advocacy of a specific statement on ComvaxJ.

Dr. Katz emphasized the importance of disassociating the issues of perinatal screening from essential prenatal screening. He supported a brief statement, there being no need to re-educate health care professionals on the diseases. Only the permissive and emphatic recommendations on the vaccine's use need be addressed. Dr. Modlin asked if this should be independent or added on to the hepatitis B statement, which will discuss all these issues at length. Dr. Hadler reported that the hepatitis B statement was nearing finalization, and this could be incorporated. And, while he agreed to the advantages of simplicity, he also raised the field's need for thorough guidance.

Regarding the potential impact of the birth dose, Dr. Mahoney shared data on women who did not have prenatal screening, showing a high prevalence (6.7% versus 0.8% in the general population). This is why routine birth doses are recommended for unscreened women. A 1993 survey showed that only 22% of children were being vaccinated, and several state studies

showed barely 50% vaccinated; in some states, children of surface antigen-positive mothers were less likely to be vaccinated than those born to HBsAg-negative women.

Dr. Halsey was concerned that this ComvaxJ statement could complicate matters rather than simplifying them, and foresaw other combination vaccine issues that could change the hepatitis B schedule. He felt that the harmonized schedule published in January addressed the combination vaccines simply by allowing them if the vaccine's antigens are appropriate for that age. Dr. Ward agreed that a specific ComvaxJ statement could set a bad precedent, as ACIP's charge is to provide disease-specific, not vaccine-specific, recommendations. He reiterated his suggestion to add this to the hepatitis B or Haemophilus statements with a half- to one-page summary for new vaccines.

Dr. Mahoney pointed out that a number of the recommendations are not in the package insert, such as giving ComvaxJ to communities receiving a routine birth dose. Dr. Glode advocated a very abbreviated statement along with a complete ACIP response to practitioners' questions, particularly birth dose. Dr. Glezen suggested that the statement detail the essential priorities first, such as screening pregnant women and vaccinating the infants of HBsAg-positive women, then addresse how ComvaxJ is permitted.

VOTE. Dr. Davis called for a vote on a separate statement for ComvaxJ. Voting in favor were Guerra, Glode and Davis. Voting no were Schoenbaum, Ward, Thompson, and Sherrod. Modlin abstained, and two were absent. The result was that the committee tabled a separate statement.

Alternative suggestions were Dr. Ward's proposed 2-page standard format with the new vaccine's advantages and disadvantages, data, etc. Dr. Sherrod supported this, in addition to adding this to the hepatitis B statement. Dr. Schoenbaum thought this a transient issue, and that CDC could handle most off the significant areas of discussion in journal articles. He found most of this document most useful for internal CDC responses to the field's questions.

For inclusion in the hepatitis B statement (which is hoped to be completed this summer), Dr. Hadler asked for ACIP guidance on whether the recommendations' substance and intent are accurate, particularly the acceptability of 3 doses after a birth dose. He also noted that VFC will vote on using this vaccine, and that it generally follows ACIP recommendations. In the absence of an ACIP recommendation, that process is less clear.

Dr. Halsey observed that ACIP can vote on but still not publish a recommendation. He thought there was consensus to use ComvaxJ in a 2, 4, 12-15 month schedule for surface antigen-positive or -negative women, regardless of their birth dose status. This goes beyond the package insert, and such advice can be used as desired in the field. Dr. Hadler thought that this would be a clear interim statement.

Dr. Thompson supported published articles in the medical literature as opposed to an ACIP recommendation published through the *MMWR*, which also implied the slowness of *MMWR* publication. Dr. Hadler explained that *MMWR*'s new personnel have removed the previous backlog, and the process will be speedier. Dr. Mahoney also noted that a statement would soon be mailed on meningococcal disease.

Dr. Thompson moved that AACIP recommend the use of ComvaxJ as an acceptable option at 2, 4, and 12-15 months in infants regardless of the mother=s hepatitis B surface-antigen status, including those infants who may have received a dose of hepatitis B vaccine within the first month of life.@ Dr. Chin Le clarified to general agreement that this is simply one option among others. Dr. Guerra seconded the motion.

VOTE. Upon a vote, those in favor were Davis, Schoenbaum, Glode, Thompson and Guerra. Ward, Modlin and Sherrod abstained. None voted against the motion, and three were absent.

Information on Combination Vaccines/Connaught

Mr. Philip Hosbach presented information on a non-complementary combination acellular DTP and Hib vaccine, currently licensed for use as a booster. Two sets of toddler studies supported the licensure, and over 4500 children have been immunized to date. About 500 received vaccine and were immunologically analyzed; over 4000 were analyzed for safety evaluation.

Mr. Hosbach first presented the safety data for the combination vaccine and separate vaccine groups. The responses to pertussis antigens were similar or equivalent, though some suppression (not clinically important) was seen in the Hib response. There was a 100% seroconversion rate (versus the normal range of 70-90%) at >1 µg for the PRPT vaccine. However, the combination group also achieved a high seroconversion rate (85% at >1 µg) after the third dose.

The blood of a subset of study children was tested after one month post-dose. The pertussis response was higher in the combination vaccine group; the anti-PRP values were a little low but still acceptable (>0.15 µg, and $>70\%$ above 1 µg). There were no statistical differences between the groups. However, pre-immunization values were not available on these children, as the study was amended for these analyses after they were already vaccinated.

Reactogenicity was tested for the combination versus separate vaccines. Local reactions were very similar to the DTaP group; in fact, if the separate groups' reactions were added, the combination's performance was superior. Systemic reactions were also equivalent between the two groups.

Mr. Hosbach concluded that the filed license application was under active review, and is hoped to be licensed in the first half of 1997. Although there are tendencies for the PRP response to be lower, they are in the protective range; and the acellular pertussis antigen responses are similar to the separate vaccines.

Discussion
Dr. Ward stated that the issue is the immune response to Hib, as other vaccine studies showed a more dramatic impairment than those cited here. He cautioned the committee to focus on non-responders rather than at GMT or the percent >1µg. Other studies showed as much as 20-40% of children did respond to the Hib conjugate at acceptable levels (>.05 µg) after two doses. A 95% response rate is still poorer than the separate vaccines' 100% rate. He wished to look at the data carefully on the full response and pre-immunization titers, suspecting that a higher proportion are not responding -- particularly since two other manufacturers have failed to resolve this issue. Dr. Davis agreed, as children with incomplete immunization after the first year are at some risk for invasive Hib disease.

Dr. Hosbach reported that the children were also boosted with the same combination vaccine, and achieved a "phenomenal" antimestric response in magnitudes of 50-400. The antibody is there, the mechanism is in place for priming, and the product is ready for licensure, with values and percentages >1 µg, which he also noted is higer than those seen for ComvaxJ.

Dr. Davis reported Dr. Patterson's requested to convene a lunchtime discussion group on the military's use of anthrax vaccine, and the committee adjourned for lunch.

VFC Discussion
After lunch, Dr. Hadler noted that several resolutions were pending on the Vaccines for Children (VFC) program, to address new vaccines with previously-approved VFC vaccine components, and to provide additional information on the use of acellular pertussis vaccines in infants.

VFC resolution #1 read as follows:

"The ACIP recommends inclusion in the Vaccines for Children Program of new vaccines that combine vaccines which have been previously designated for inclusion in the VFC Program upon licensure of a new combination vaccine by the Food and Drug Administration and the establishment by the CDC of a contract for the purchase of the new combination vaccine. Such approval does not constitute a preference by the ACIP for use of such combination in lieu of the non-combined forms of the vaccines until/unless a separate VFC resolution stating such a preference is adopted.

"Pending approval of a VFC resolution to specifically incorporate such new combination vaccine into the VFC Program:
"those groups of children approved for receipt of the non-combined forms of the vaccines shall be eligible to receive the new combined vaccine through the VFC Program; and
"the dosage, schedule and contraindications for such new combination vaccine shall follow the FDA-approved package insert."

Discussion
Dr. Glode clarified that any recommendation to go beyond the package insert's text would require an ACIP vote. Dr. Fleming asked if any language could be included about the cost disadvantage of combinations to the local level provider, perhaps discussing the cost-benefit to include it in the VFC program. Dr. Hadler was confident that the private sector would consider the many related unquantifiable costs, and was unsure that the text could specifically deal with them in any legally binding way. CDC is obligated to get a reasonable price for a vaccine (although a formula for such is unlikely), but an unreasonable price could defeat a contract. Dr. Modlin preferred not to address cost, in part because a combination vaccine would compete with the individual components, which is a user issue.

But Dr. Fleming observed that simple arithmetic indicates a costly decision about ComvaxJ, and intense public scrutiny supports addressing the cost implications along the way. Dr. Thompson cited the manufacturers' emerging attempts to coordinate their product development with the ACIP. A decision to include a vaccine in the VFC program could be one way to encourage that and discourage less useful combinations.

Dr. Halsey noted that ComvaxJ had just been recommended for an instance not covered by the package insert, which this resolution would not allow. Dr. Hadler clarified that this resolution was only for the licensed vaccine's interim use until it was addressed for VFC by a specific statement. In response to Dr. Thompson, Mr. Malone clarified that the contract consideration would theoretically be parallel to aCIP approval, but the vaccine would not be put into use until the ACIP recommendation was published.

Dr. Snider said that addressing cost-effectiveness issues would involve a more formal and very resource-intensive approach, which could be done for later combinations. For the moment, he cautioned against using one component (vaccine cost) as the sole basis for a decision for one approach over another.

Dr. Chen Le was astonished that the government would even consider purchasing this vaccine in light of lingering scientific issues such as the question of lower titers for hepatitis B, which leave children unprotected from 2-6 months. He also raised the 92% conversion rate as compared to 99% of others, and the $30 per dose economic impact. Dr. Hadler was not concerned about the titer differences as they were sufficient for long-term protection and well above the recommended 200 MIUs/ml level for infants #2 months of age. Both CDC and FDA were confident that the vaccine offered as- or better efficacy on this schedule.

Dr. Katz did not approve of the language allowing contract negotiation before ACIP discussed a new vaccine. He knew of no pending or developing combination vaccine so pressing that it could not wait for ACIP consideration, even by a telephone discussion. Dr. Hadler recalled some comment that ACIP would be better advised to recommend changes once or twice a year rather than continuously. The advantages of this resolution were related to time (e.g., to

address a vaccine licensed right after an ACIP meeting or to proceed with an obviously desirable one). Dr. Hadler clarified for Dr. Glode that this would apply to licensed vaccines, for label uses consistent with current recommendations. It would not include combinations with all new components, because those components are not currently in the VFC program.

VOTE: Those members voting in favor of this resolution were Schoenbaum and Guerra. Those opposed were Davis, Glode, Thompson, Modlin, and Sherrod. Three were absent, and the resolution was defeated. Dr. Davis observed that its defeat did not mean the resolution was not a good idea, but was perhaps ahead of its time. Dr. Modlin said he voted no because he did not see a compelling reason to rush with the current products. But he hoped that if accelerating the contracting process becomes advisable in future, that could be done.

VFC resolution #2 addressed the use of the Pasteur-Merieux Haemophilus influenza type b conjugate vaccine (PRP-T), reconstituted with DTaP for the fourth dose of a DtaP-Hib vaccine. The resolution read:

"The ACIP recommends inclusion of Haemophilus influenza type b conjugate vaccine (PRP-T) reconstituted with DTaP produced by Pasteur-Merieux for the fourth dose of the diphtheria-tetanus-pertussis and H. Influenza vaccination series using the schedule and contraindications defined above and in the new ACIP recommendations on use of acellular pertussis vaccines for the Vaccines for Children program. Use of this vaccine for other doses of the DTaP-Hib vaccination series is recommended upon licensure of such use by the FDA."

Dr. Thompson approved of this language since this is a known vaccine, with the addition of the vaccine's approval on licensure. To avoid any indication of a preference for this versus other combination vaccines, Dr. Thompson advised replacing "use" in the last sentence with "inclusion".

VOTE: Those voting in favor were Guerra, Thompson, Glode, Schoenbaum and Davis. None were opposed. Sherrod and Modlin abstained; three were absent.

VFC resolution #3 addressed the use of Haemophilus influenza type b (Hib) - hepatitis B vaccine (ComvaxJ). The resolution was prefaced by the components of the developing ACIP statement on ComvaxJ (three doses at 1, 4 and 12-15 months; allowing use as a complete vaccine series in infants of antigen-negative mothers who did not receive prior doses of hepatitis B vaccine). It then addressed those infants of antigen- negative, antigen-positive and untested mothers who received the vaccine in their first month. It also referenced previous VFC resolutions on the consistency of Hib vaccines, interchangeability, and contraindications to the combined Hib-hepatitis B vaccines. The resolution read:

"The ACIP recommends combined Hib-hepatitis B vaccine with the number of doses, schedule, qualification and contraindications as noted in the text above for the Vaccines for Children program. This recommendation will become effective when

recommendations for vaccine use have been published in the *Morbidity and Mortality Weekly Report*."

Dr. Hadler noted that the text could be combined to mirror Resolution #2. Wording also could be added about using the vaccine with hepatitis B for a birth dose or in the first month regardless of the mother's birth status. The same contraindications apply as for the individual components, but this resolution could add the strong caution that this vaccine should not be used at <6 weeks of age. The effective date also would reflect the ACIP's resolution rather than publication in *MMWR*.

Dr. Peter questioned including the caveat that the provider may not stock the monovalent Hib and hepatitis B vaccine. That may provide a barrier to its use. Dr. Hadler explained that this was inserted to address extravaccination. It could be changed to delete the phrase Aif the provider does not stock monovalent vaccine…@ and mirror the ComvaxJ recommendation. He agreed to rewrite the resolution for a committee vote.

VFC Resolution #4 addressed the now-licensed acellular pertussis vaccines recommended for inclusion by the ACIP before their licensure in June 1996. The resolution read:
"The ACIP recommends the above qualifications to the use of DTaP vaccines, for the Vaccines for Children Program, effective February 12, 1997. Other qualifications as described in the new ACIP recommendations "Pertussis Vaccination: Use of Acellular Pertussis Vaccines Among Infants and Young Children" (in press) are approved for the Vaccines for Children program effective when these ACIP recommendations are published."

Specific clarifications on the June resolution included that the fourth dose of DTaP (or DTP) was recommended at 15-18 months, but allowed at 12 months if ∃6 months had passed since the third dose and the child was unlikely to return. A second clarification recommended the use of the same brand of DTaP for all doses, but allowed any brand if the previous vaccine is not available or unknown. The resolution was to be effective on ACIP approval.

VOTE: Those voting in favor were Thompson, Glode, Schoenbaum and Davis. None were opposed, and Sherrod, Modlin, and Guerra abstained. Three were absent. The resolution passed.

MMR Recommendation Discussion
Dr. John Modlin reported that the Measles, Mumps and Rubella (MMR) statement was almost complete, combining the separate statements for each. He requested the members' response to this draft in two weeks, and outlined the few remaining issues: (1) should birth before 1957 be considered acceptable evidence of rubella immunity; (2) should health care workers be immune to rubella; and (3) should physician diagnosed measles and mumps be considered acceptable evidence of immunity.

Two other topics with new information were about (4) the neurologic events following measles vaccination and (5) vaccination of persons receiving corticosteriods. He reported that the language on the latter almost mirrored the Redbook's and should not be controversial. He solicited comments.

Dr. Modlin raised for discussion of whether birth before 1957 was acceptable evidence of rubella immunity. Currently, this is not considered so for rubella, though it is of measles and mumps. A change would bring this recommendation in line with measles and mumps. Other advantages are that 92% of the overall U.S. female population were born before 1957 and are rubella seropositive (10 IU) per NHANES III, and fewer women born before 1957 are bearing children. Arguing against a change are that congenital rubella syndrome (CRS) occurs in the offspring of women born before 1957 (6 cases; 6% of births in 1985-1995). And, rubella still occurs among persons born before 1957 (222 cases, 11% of the total 1991-1996 cases with known ages). Finalley, there are ill-defined pockets of rubella seronegativity (NHANES III).

Dr. Modlin showed NHANES III data of the percent of rubella seropositivity by year of birth and race/ethnicity. By 1957, about 90%+ of the birth cohorts were considered immune. In a conference call, the work group considered several options: (1) not to change the recommendation, (2) to accept birth before 1957 as evidence of immunity in all cases; (3) to accept birth before 1957 as evidence of immunity only in specific instances or certain groups (felt to be an overly complicated option); and (4) to prioritize implementation of vaccination efforts to ensure immunity first among persons born after 1957, but not accepting birth before or during 1957 as evidence of immunity (again, not a popular option due to complexity).

(1) Pre-1957 birth as acceptable evidence of immunity. The consensus of the work group was to extend the same criteria to rubella as to measles and mumps, with two important caveats: birth before 1957 is not acceptable evidence of rubella immunity for women who might become pregnant; nor does birth before 1957 guarantee rubella immunity.

Discussion
Dr. Katz applauded the group's admirable work in fashioning a very complete statement. But he noted it is not a ringing endorsement of elimination of congenital rubella syndrome (CRS) or measles. For the latter, he thought that ACIP might come to a different conclusion than simply continuing the recommendations as they stand. Dr. Modlin did not disagree, but explained that this document was a compromise effort to balance several contingencies. It sought to do all possible to eliminate rubella despite the expense associated with compelling hospitals and health care facilities to ensure that all workers comply.

He confirmed for Dr. Guerra that this would also apply to individuals born outside of the U.S. before 1957. One argument against this change was the possibility of pockets of such ethnicities/individuals, but data on this is lacking. For example, certain Hispanic groups had rubella in disproportionate numbers, including CRS, which is of concern.

Dr. Hayward concurred that some compromises are necessary in an epidemiologic discussion of rubella elimination, but observed that some populations such as the aged are unlikely foci of rubella transmission. Although elimination would suggest immunization of all the susceptible populations, he would be permissive for control, to allow leeway for such aged populations. However, Dr. Davis noted that the language in the draft is responsive to the comments received by CDC, and called for a vote.

VOTE: Those in favor of the resolution and its caveats were Sherrod, Guerra, Thompson, Glode, Schoenbaum, Davis, and Modlin. There were none opposed, and three absent.

(2) Immunity of health care workers. The work group revisited the ACIP's vote that all health care workers should be immune to measles and rubella. The advantage of that resolution is that health care workers have the responsibility to do no harm; that the acute side effects of rubella vaccine are mostly self-limited; that recent studies do not confirm earlier reports of chronic arthropathy after rubella vaccine; that high absenteeism is not expected after health care worker vaccination (about 1-6 health care workers absent per 1000 vaccinated); and that rubella transmission from health care workers to nonimmune woman resulted in CRS. On the other hand, the risk of CRS in infants born to nonimmune health care worker is unlikely (3 were born to health care worker moms since 1979); acute transient joint symptoms occur in 25-33% of vaccinated nonimmune adult females; and there are some reports of chronic arthropathy after rubella vaccine in nonimmune women.

The work group's options included (1) that all health care workers should be immune to rubella (the status quo); (2) that only health care workers considered at high risk of exposing pregnant women or other women of childbearing age should be immune; and (3) that only female health care workers of childbearing age should be immune to rubella.

The work group's consensus was that (1) all workers in medical facilities should be immune to measles and rubella; (2) all medical facilities should ensure measles and rubella immunity among those working in their facilities; (3) adequate vaccination for persons born during or after 1957 is defined as two doses of measles-containing and one dose of rubella-containing vaccine; and (4) stepwise implementation (e.g., addressing Abeginning@ vs. Acurrent@ workers) should not be addressed (passed by a slight majority).

Discussion

Dr. Zimmerman pointed out that this resolution discusses rubella, not measles. AAFP=s policy encourages that all women of childbearing potential be vaccinated. Those who could expose such women also need to be vaccinated. But he noted that not all of the over 6 million health care workers pose a threat. He felt there no need to ensure immunity, risking potential chronic arthopathy, among such personnel as nursing home staff with geriatric patients or a back-office secretary.

Dr. Modlin responded that the problem arises in defining who has and has not important patient-care contact, pointing out that a Boston outbreak stemmed from a dietary worker distributing trays in a hospital. Dr. Zimmerman had no problem focusing on hospital employees, but demurred that all out-patient settings should be covered.

Dr. Halsey asked if the work group considered a compromise to focus only on those workers with direct patient contact or who work in hospital wards with patients present. He suggested a softer recommendation for those working in medical facilities without direct patient contact, copying the adult recommendations for varicella. This might allow for some flexibility, and still encourage screening for those who might be susceptible. Though there are some instances of airborne rubella transmission, most cases are from direct contact. He advocated a two-tiered approach, mandating immunity for all health care workers who might expose women of childbearing age, and encouraging immunity for others.

Dr. Watson noted that a statement had been added that elderly care facilities could probably be exempted. Dr. Schoenbaum supported immunity among health care workers with or without direct patient contact, but preferred that this be the health care worker=s individual responsibility rather than a mandate. Dr. Thompson advocated a focus on those with direct patient contact to avoid involving support staff like maintenance workers. However, Dr. Schaffner would include everyone for just that reason, since in the current health care milieu many people with varying education levels may work with patients. Dr. Schaffner advised not making "health care workers" and "workers in medical facilities" synonymously.

VOTE: Those in favor of all health care workers in medical care facilities being immune to measles and rubella were Modlin, Schoenbaum, Glode, Guerra, Sherrod and Davis. Those opposed were Ward and Thompson. There were no abstentions and two absent. The motion carried. Dr. Snider clarified that ACIP cannot mandate anything, only recommend, but also acknowledged that other bodies could perceive these recommendations as mandates.

(3) Should physician-diagnosed measles and mumps be considered acceptable evidence of immunity? The ACIP was asked to reconsider its recent acceptance of this, as opposed to rubella. At issue is that measles diagnosis may be less reliable now than in past, since the positive predictive value of clinical diagnosis declines as measles and mumps become less common. Some jurisdictions' immunization programs do not accept physician-diagnosed measles and mumps as proof of immunity, though many if not most do.

Among the options considered by the work group were to continue to accept the diagnosis as evidence of immunity, to accept it only if it occurred before a specified date (e.g., 1965 or 1970), or to accept it with the caveat that some jurisdictions may require other more stringent evidence of immunity to meet school-entry requirements or other regulations. The last seemed the most reasonable, and became the work group's consensus. However, they specified that prior clinical diagnosis of rubella continues to be unacceptable evidence of immunity.

Discussion
Dr. Thompson asked that the statement specifically ensure that the diagnosis is made on the occurrence of the condition through a physical examination, not retrospectively.

Dr. Plotkin thought the little data available to suggest that the diagnosis of past measles history in the health care setting is 95% reliable. But the data was questioned on current accuracy/sensitivity of physician measles/mumps diagnosis. It was agreed that diagnosis must be in the parameters of acute illness, but noted that school nurses and nurse practitioners also can do so. This recommendation was expected to impact historical diagnosis.

Dr. Watson reported the states' desire for the flexibility to not accept a physician diagnosis for school entry requirements, especially since correct diagnosis is less likely in presently-trained physicians. Dr. Gardner warned that public health epidemiologic errors could results by allowing such exceptions as he cited on the draft's page 16 (line 22 on). Another opinion was that adding a suggested footnote to define "physician-diagnosed measles" would be micromanaging health care, a perhaps unwarranted specificity.

Dr. Chin Le advocated mandating serological support to ensure a good physician diagnosis and support eradication of disease. Dr. Matus reported 66000 measles cases in 1919 Mexico epidemic, but only 1700 suspicious cases last year, only one of which was determined measles by laboratory testing. Many of the balance cases had received measles vaccine.

Dr. Modlin reminded the committee that discarding physician-diagnosed measles would leave a sizable number of people with no other evidence of immunity. Dr. Hadler agreed that past physician diagnosis would be more reliable, but questioned where in time the line should be drawn. He suggested inserting a statement that these currently-uncommon diseases make diagnosis less reliable so that every case now should be serologically confirmed, but to leave the table as it is.

VOTE: The proposal was to continue to recognize physician diagnosis of measles and mumps as acceptable evidence of immunity, but for the specified caveats, and to continue to not accept prior physician diagnosis of rubella as evidence of immunity. Dr. Thompson offered an amendment that the diagnosis be by the physician who actually saw and diagnosed measles in a patient during the illness, to avoid retrospective medical record diagnoses. However, there was no second. Voting in favor of the original motion were: Modlin, Davis, Schoenbaum, Ward, Glode, Thompson and Guerra. None were opposed. Dr. Sherrod abstained; two were absent. The motion carried.

Measles and Encephalopathy
Dr. Chen introduced Dr. Vitaly Pool, the first Epidemic Intelligence Service (EIS) officer from the former Soviet Union. He reported the 1991 Institute of Medicine (IOM) definition of encephalopathy as a generalized disturbance in brain function. Acute Encephalopathy (AE) occurs in 1-2 of 1000 cases of wild measles infection, with a 10-20% mortality rate, and a

50% occurrence of permanent central nervous system impairment. It pathologic mechanism is unknown, but is presumed to be an autoimmune reaction, as the virus is absent from brain.

The question has been posed whether live attenuated measles vaccine virus can also cause AE. However, AE was not shown in prelicensure or postlicensure testing, but rare neurologic sequelae could not be detected until wider post-licensure use. Between 1963-1971, CDC received 84 reports of neurological illness within 30 days of measles vaccination. Of these, 26 of 36 (76%) cases of AE began between days 6-15 of measles vaccination, peaking on days 8 and 9. It was then concluded that since the reported frequency of <1 per million was below the background rate for AE, there was no causal relationship. But the distribution of onset cases was clearly nonrandom, and nonreporting was not considered. In 1994, the IOM found the uncontrolled data inadequate to establish a link to measles vaccine.

The only large controlled study has been the British National Childhood Encephalopathy Study (NCES), which found a relative risk of 3.9 for AE or seizures between 7-14 days after measles vaccination (1:87,000 vaccinations). But no separate analysis for AE was done, and the study power may have been inadequate (624,000 doses). In new data since 1994, a 10-year follow-up to the cases classified as "abnormal" in the NCES found a relative risk of 0.8 for permanent neurological sequelae in children after measles vaccination. This rose to 1.2 for death, educational or behavioral sequelae, seizures or other neurological disorders. However, again, there were only a small number of cases.

In 1995, over 6 million children received measles-rubella vaccine in the United Kingdom. Over 1200 reports of adverse events were received, of which 91 were serious neurological reactions including 61 convulsions. While the rates were lower than background prevalence, again, there was no estimate of nonreporting. Most children were already immune to measles and therefore not susceptible to measles-induced encephalitis.

Fifty new cases of AE of unknown etiology after measles vaccination were presented to the Vaccine Injury Compensation Program. These patients' symptom onset peaked at day 8-9 after vaccination. Analysis of the VICP data prompted a CDC review of 1991-1996 data in two other independent passive reporting systems (Monitoring System for Adverse Events Following Immunizations, formerly a CDC program) and the Vaccine Adverse Events Reporting System (VAERS -- CDC/FDA). A total of 299 AE cases had been reported since 1979. A chart of the passive surveillance systems showed a similar nonrandom bell-shaped curve of AE peaking on days 8 and 9 after vaccination.

The program concluded that there is a known random distribution of AE, peaking on days 8-9 after measles vaccination. While the pattern may be partially attributed to consistent biases, it also could indicate a causal relationship between measles vaccine and encephalopathy. From 1963 to date, 166 AE cases out of 313 million doses were reported between days 6-15 after measles vaccination; a reporting rate of 1:1.89 million doses. Dr. Pool noted that this attributable risk is profoundly smaller than that after wild measles infection.

Dr. Chen reported that a review of the Vaccine Safety Datalink (VSD) shows about 500,000 doses. Although there are too few cases for proof, this is generally consistent with the possibility of this pattern, particularly in view of a passive surveillance system's potential underreporting. He also noted that since the IOM review, two publications based on the UK MMR mass campaign and the Pan American Health Organization (PAHO) measles vaccination mass campaign both found no certain association. A paragraph summarizing this late data was added to the draft.

Dr. Chen asked the committee whether the draft's page 42 longer or shorter discussiong of the NCES should be used. Dr. Davis exercised his prerogative as Chair and selected the longer version and requested the members' comments on the MMR draft within two weeks. Any language conflicts would be resolved by the work group, and the committee informed; this would be published before the next meeting.

Update on the Status of HIV Vaccines

After a short break, Dr. William Heyward, the HIV Vaccine Coordinator for the National Center for HIV, STD and TB Prevention (NCHSTP) addressed the committee. He reported an estimated 28 million HIV infections. Currently, about 22 million people are living with HIV, about 98% in developing countries. The epidemic seems to have plateaued in the U.S. and Europe in groups where age is the most common cause of death, or in certain age groups. There are about 45,000 new HIV infections annually in the U.S. and about 8500 new infections a day worldwide.

There are three impediments to developing an HIV vaccine: the unknown correlates of immune protection, the unknown significance of HIV variability on vaccine-induced protection, and the unknown correlation between in vitro and animal tests.

Dr. Patricia Fast, the Associate Director for the Vaccine/Prevention Research Program within the Division of AIDS at the National Institute for Allergies and Infectious Diseases (NIAID) reported that the development of vaccines to prevent HIV/AIDS infection has not been too successful to date. Vaccine research is underway in academic and pharmaceutical laboratories, much of it sponsored by the government. This includes not only the design and evaluation of vaccines, but also placing them in the context of other vaccine strategies.

The overall NIH effort is funded primarily by NIAID and the National Cancer Institute (NCI). Dr. Fast discussed NIAID's laboratory and epidemiologic research. The NIAID program acknowledges the uncertainty about HIV vaccine. It strategy is to use multiple concepts to assess diverse approaches, and to use standardized evaluation in preclinical, animal, and clinical trials.

Dr. Fast reported the HIV virus' variability, both in the envelope and in the internal components, as the greatest obstacle to developing a vaccine. Such recombinations vary both within people and between geographical regions. However, there some simple general principles have been learned from the animal model experiments. First, vaccines can work

against HIV; in the animal they may prevent detectable infection, and affect chronic infection and disease onset. But there is no universal "correlate of immunity". Because of this, the preclinical trials have assessed immunogenicity without any real certainty of what that means, and she expected this to continue into the efficacy trials.

Two NIAID networks are evaluating the vaccine. One is the AIDS Vaccine Evaluation Group (AVEG), six academic centers which have run 25 different Phase I studies with about 15 vaccine candidates, and with 2115 uninfected volunteers without HIV risk factors. The small number of participants in the only Phase II trial are at high risk of HIV infection.

The vaccine design strategies are to prevent viral entry, prevent viral replication in side cells, and to destroy infected cells. Some vaccines focus more on one hypothetical mechanism or another. In general, the recombinant subunit protein vaccines focus on inducing neutralizing antibodies; the recombinant pox viruses seek to induce T-cell immunity to block replication within cells or to destroy infected cells.

Dr. Fast outlined a variety of different vaccine concepts. Using peptides as immunogens has been relatively unsuccessful to date. Subunit recombinant envelopes are addressed in the GP160 and GP120 cells. The GP120 vaccines have been made in yeast or mammalian cells; the GP160 cells in insect or mammalian cells. NIAID has tested and incorporated some form of the envelope into eight different adjuvants. However, none have shown outstanding imunogenicity, and some are very toxic. Those now in development are very bland.

NIAID is just beginning to work with recombinant particles, to develop something like HIV virus with without its genetic material and ability to replicate. They hope to have such a material in the next year or two. Whole-killed HIV has not been tested in humans; only part of the difficulty with this approach is the challenge to kill the virus and yet maintain its structure. They have worked with about 20 vectors (genetically modified vaccines [e.g., polio, pox virus] modified to include some HIV material) in animal models. Only pox viruses have proceeded to human testing.

DNA immunization is of great current interest; the first two human trials are on influenza and HIV, using an HIV envelope vaccine. However, this is initial work without any data available. There is much community interest in the live attenuated HIV vaccine, since the success of the live attenuated SIV vaccine in the animal model. The challenge is to design appropriate safety trials to rule out the potential harm from the live attenuated vaccines.

The recombinant proteins GP120 and GP160 have been found to be good immunogens if they are handled properly and well, producing antibody and neutralizing viruses. But there are an enormous number of HIV isolates. To test them all to see if they are neutralized is a daunting task, so the breadth of protection is unknown. But NIAID has varied several envelope vaccine factors (strain, formulation, antigen size, etc.), and selected mammalian GP120 as the most effective immunogen so far of this type.

Vaccinia virus can be modified to carry the HIV envelope or additional components. It induces good T-cell immunity in some people, but not much antibody. It is recommended by nonhuman primate protection and it is increased by a protein boost. It is safe for use in HIV-uninfected volunteers, but cannot be used by those with prior smallpox vaccination.

To overcome some of these problems, Paster-Merieux and Connaught developed a vaccine based on canarypox. It replicates well in humans, and is about equally immunogenic as vaccinia in a vaccinia-naive person. It is safe even in HIV-infected volunteers, and not limited by prior smallpox vaccine. The leading candidates now are a combination of canarypox (including both envelope and structural protein) and GP120 made by Chiron, the envelope to boost the neutralizing antibody.

Dr. Fast showed data from many clinical trials, in which the smaller GP120 vaccine (versus GP160) showed excellent results in producing neutralizing antibody. If expressed in a mammalian system, the GP120 was highly effective. In the combination of canarypox and vaccinia with a booster of GP120, everyone again responded with neutralizing antibody. In the prime-boost combination with the two vaccines, the titers were at least as good as any other regimen tested, if not better. Finally, she showed data from a research study of T-cells, demonstrating that the canarypox-GP120 booster improved the body's ability to recognize HIV and kill it. This would presumably be helpful in early HIV disease.

Dr. Fast concluded with the NIAID upcoming Phase II trials to assess the broadness of protection afforded by this approach. They will provide 1/3 of the study population (total 420 participants) with a placebo, 1/3 with canarypox and 1/3 with both in months 1, 3, and 6. One problem with vaccination now is that multiple vaccines will be necessary to induce appropriate immunity, and adult compliance is a general vaccine issue. The vaccine community also needs help in educating the public about the length of time needed to develop a vaccine.

Discussion

Dr. Fast confirmed for Dr. Ward that two GP120 vaccine candidates had been compared and shown similar in performance, but having adequate study power has been a challenge. They are now comparing canarypox alone versus the combined regimen, with the latter appearing better for antibody formation. T-cell activation is now being assessed.

Dr. Halsey noted that in past, manufacturers have tested vaccine in other than the target populations. He suggested that Dr. Fast read ACIP's statement on adolescent immunization, which focuses on age 12 as the target for introduction of STD vaccines. Having planned studies parallel ACIP's direction toward universal adolescent vaccine would be beneficial. Dr. Fast appreciated that, noting that there is not as strong an effective range in adults (18-60) for HIV vaccine. The GP120 vaccines have been tested in a small number of infants of HIV-positive mothers.

Dr. Katz asked how effective against fresh isolates were the antibodies and cytotoxic lymphocytes (CTLs) generated in vitro by volunteers. Dr. Fast reported that most of the

vaccinees' sera were not effective. However, she expected that with further knowledge of the second receptor for HIV, they may be able to move forward. Duke's and Harvard's CTL approaches suggest that in infected and even vaccinated people, there is an extremely broad range of viruses that can be killed by the CTLs. They hope that by turning more to T-cell responses and adding additional core virus antigens, they will make more headway against the variation problem.

Vaccination of HIV-Infected Persons

Dr. John Kaplan presented the revised USPHS/IDSA Guideline revisions for pneumococcal influenza and measles vaccines which were discussed in November 1996. The members' comments were solicited. The strength of the recommendations were rated from A (the standard of care, always done) through E (good evidence to advise against use; never to be offered). The changes included (1) upgrading the pneumococcal vaccination from B to A, except for persons with CD-4 counts <200; (2) leaving influenza vaccine as a "B" level recommendation, but inserting footnotes discussing the issues of increased HIV plasma RNA which may follow influenza vaccination; (3) clarifying that measles vaccine should not be given to severely immunosuppressed people; (4) presenting a vaccination schedule for HIV-infected children consistent with the schedule for immunocompetent children, which also applies to children of indeterminant status. It recommends annual IPV and influenza vaccinations and pneumococcal vaccination at age 2. It also indicates that MMR should not be administered to severely immunocompromised children.

Discussion

Dr. Modlin was uncertain that the MMR recommendation was consistent for the second dose, which ACIP now encourages to be given as early as one month after the first dose. Dr. Kaplan responded that the footnote specifies that. Dr. Heyward advocated labelling the MMR doses by number, as is done for hepatitis vaccinations. However, Dr. Modlin was uncertain that the implication was correct that the second MMR dose could be given to up to 12 years of age.

Dr. Halsey reported that the Redbook Committee discussed this, but thought that inserting another column for 13 months would be even more confusing. They looked at several versions of this document. They were concerned at possible misinterpretation of this statement if posted on a clinic wall because it is so similar to the universal schedule. He suggested the HIV schedule title be "Modified" Immunization Schedule and that a bar be placed below Haemophilus influenza to indicate that everything above that bar is identical to the harmonized schedule. That area should be labeled as "Modifications for HIV-Infected Children". They also suggested that there be no bar for varicella, just an indication that it is indicated or contraindicated. With that, he thought the confusion between this and the harmonized schedule would be addressed.

Dr. Modlin persisted that immunity will most likely develop if a child is vaccinated early in life, (e.g., given vaccine at 12 rather than 15 months) and wished to apply the same philosophy to the second dose. Indicating a wait to 12 years of age is inconsistent with that philosophy.

Dr. Kaplan thought that refining the footnote might help in that regard; this bar was to target the unvaccinated child between 1 and 12 years of age.

Dr. Davis feared that calling this a "Modified" immunization schedule for HIV-infected children may indicate that there us another immunization schedule for HIV infected children. He suggested instead more clearly entitling it a "Modified Immunization Schedule Recommended for HIV-Infected Children".

Dr. Peter asked if this schedule would be updated yearly as is the U.S. schedule. Dr. Kaplan said no, since the guidelines themselves are not modified annually. They know this must be addressed. He added that they are working on another guideline on preventing infections in bone-marrow transplants recipients. A March 19-20 meeting will be held in Atlanta between USPHS, IDSA and the American Society for Bone Marrow Transplantation, and he invited ACIP participation.

Serogroup C Menigococcal Conjugate Vaccine Cost Update

Dr. Brad Perkins introduced an update on the development of meningococcal conjugate vaccine in the U.S. and a cost-effectiveness analysis of their routine use. Feedback was requested on a questionnaire distributed to the committee. It asked whether additional immunogenicity data was desired; if other strategies should be evaluated (e.g. other vaccine regimens' assumptions or costs); if an ACIP position statement should be drafted about further development and use of serogroup C meningococcal vaccines in the U.S.; whether a draft ACIP statement should address other than serogroup C; and what other studies, data, and information might be needed for ACIP to develop a position.

Neisseria meningitides is unique among bacterial meningitis in its ability to cause epidemic as well as endemic disease. That, its dramatic clinical progression and presentation of meningococcal disease, and its mortality rate of 10-15% has created much fear in the U.S. Serogroup C has caused about 1500 cases each year, and about 150-200 deaths. It is also the most common cause of meningococcal outbreaks in the U.S., and both these outbreaks and the use of polysaccharide vaccine to control them has increased.

Dr. Perkins outlined the U.S.' history of meningococcal disease, which has been a notifiable illness since 1920. Routine large epidemics decreased after World War II, but stabilized at endemic levels of 1-3 cases per 100,000 over the last 20 years. Serum therapy introduced in 1913 reduced the mortality from 90% to 30%, and antibiotic use lowered it further to a stable 15-20%. In 1968, the polysaccharide capsule of meningococcus produced protective bacteriocidal antibody; by 1971, all the military forces were vaccinated. In the 1970s, official public health recommendations called for chemoprophylaxis for those in close contact of meningococcal disease cases. After the first successful HIV conjugates were tested in 1992, the first meningococcal conjugates were produced.

The current obstacles to improved prevention of meningococcal disease in the U.S. include the polysaccharide (PS) vaccine's poor immune response and short duration of protection in infants

and children; that there is no licensed serogroup B vaccine in the U.S.; that development of better chemoprophylaxis is unlikely due to rare secondary cases in the U.S.; that improved outbreak control with PS vaccine will not affect overall incidence because it represents a small proportion of all cases; and that the other know meningococcal risk factors are not susceptible to public health interventions.

There are several issues related to serogroup C meningococcal conjugate vaccines in the U.S. The unconjugated PS vaccine is effective in adults and reduces carriage in some settings, but the duration of protection is unknown. Bacteriocidal antibody titer (i.e., functionality) is the best laboratory correlate of immunity. Controlled trials are unlikely of serogroup C conjugate vaccines to estimate efficacy. They likely will be licensed based on immunogenicity data alone, but for what age is unknown. The manufacturers anticipate develop a conjugate C vaccine in the U.S. in about a year.

Dr. Perkins then outlined the four companies testing serogroup C vaccines in humans. Chiron has tested both serogroup C and A conjugate bivalant and monovalent preparations at sites in the U.S., Canada, U.K., and Gambia, in infants, toddlers and adults. It was found safe and well tolerated, and serogroup C showed boostable increases in bacteriocidal antibody. Pasteur-Merieux Connaught has two tracks underway on a bivalent vaccine and a quadravalent conjugate preparation. The bivalent A/C was tested in the U.S. and Niger in infants (2,3,4 months in the U.S.; and 6,10,14 weeks in Niger). It is safe and well tolerated and elicited good bacteriocidal antibody response that appears to be boostable. The quadravalent conjugate vaccine had not been tested in humans but is planned for Phase I study.

The monovalent Wyeth Lederle Vaccines and Pediatrics vaccine has been tested in infants in the U.S. and the U.K. It is similarly safe, well tolerated and provides good levels of immunogenicity. North American Vaccine has a variety of vaccines in development. A monovalent vaccine conjugated to tetanus toxoid tested in U.K. adults, and a monovalent in preparation with a B polysaccharide (e coli) conjugate, have had good results in nonhuman primates.

Dr. Perkins then presented the issues now arguing against routine serogroup C meningococcal vaccination. The efficacy, duration of protection and effect on carriage is not known; there is a relatively low rate of disease in the U.S.; there are other important meningococcal serogroups that would not be covered by the C vaccine; it would further complicate the immunization schedule; and compared to Hib, it has a broader age range at risk of transmission. But in favor of a serogroup C vaccine is the disease's severity, its epidemic potential, the need for a public health response for every case, and the expense and disruption of outbreak response. Antimicrobial resistance also is rising overseas, and conjugate vaccines may provide a herd immunity.

Dr. Orrin Levine then presented the cost analysis which evaluated the advantages and disadvantages of the vaccine. First, they charted the epidemiologic data to see at what age the meningococcal vaccine made sense as compared to Hib. Unlike Hib, where 40% of cases

occur in the first 12 months, only 13% of meningococcal C occurs then; but nearly 25% occurs between 1-5 years. This indicates that a toddler vaccine could significantly impact disease.

They considered several possible approaches to mengicoccal C vaccination. An additional injection in the first year of life would be very unpopular, so the number of necessary doses in a toddler program were assessed. Three doses are likely to provide long-lasting protection, but without a combination with meningococcal C, these must be separate vaccinations from 1-5 years. Or, a two-dose schedule might be sufficient, and it could be combined with DTaP at two and at pre-school entry.

The objectives of the cost analysis were to assess the cost-effectiveness of meningococcal conjugate vaccine (specifically comparing the infant/toddler programs and the separate and combined vaccine issues), and to compare this cost effectiveness to other new vaccines. The infant program would have four doses (2, 4, 6, 12-15 months) of vaccine; the toddler program could have two doses (12-18 months and pre-school) or three (two doses at age 2 and the third at 4-6 years).

The vaccination costs/estimates included the 1995 cost per dose of Hib conjugate, $4.17; plus $5 for a separate toddler vaccination (as done for hep B/varicella). The birth cohort was 3.98 million, the vaccination coverage was 89%, and the efficacy was 90% for the first two years of life and 85% thereafter. The direct costs per meningococcal case were $13,431 for a hospitalization and $44,000-864,000 for direct lifetime costs of sequelae. Two perspectives of costs considered the health care payer (direct costs only) and society (direct and indirect costs). The indirect costs include only productivity losses due to premature mortality or severe retardation. Caretaker costs were not included.

Dr. Levine summarized the serogroup C incidence rates/cases expected in the birth cohort to age 30 years. The cumulative incidence (incidence x number of person years) was 26.46, with a projected 1,353 cases expected. Of those, 88 deaths and 126 children with severe sequelae were anticipated. The total direct costs for meningococcal disease in this cohort without vaccination were over $107 million, and $24 million in indirect costs. The infant program would prevent 685 cases (65% of expected illness without vaccination), preventing 61 deaths and 82 sequelae. The toddler program would prevente 615 cases.

The cost-effectiveness measures calculated from the model were then summarized for benefit in net savings and costs. For the toddler program with 3 separate doses, the net program costs were $4.5 million (cost of vaccination program minus cases prevented). The direct and indirect costs per life year saved were $2482; the direct costs were $43,420 per life year saved. Both the infant and toddler immunization schedules presented direct and indirect cost savings.

An important concern in developing this model was the number of doses necessary, so they varied the duration of protection in the model. Assuming protection to age 30, the benefit cost

ratio was 3.15. If it only protected to 15 years, there were still cost savings, but only at 2.63; a similar trend was shown to 5 years of protection. This indicated that the two-dose projections were robust.

The second objective was to put the results of the cost analysis in the context of other routine or new vaccinations. The toddler program (3 doses) had a cost per life year saved of $65,199, higher than the cost effectiveness of infant immunization of hep B. A combination vaccine was even more efficient. The infant program had a similar cost effectiveness.

The analysis conclusions were that (1) the modeled meningococcal vaccine program would prevent 615-685 cases, 55-61 deaths, and 74-82 sequelae, and save up to $62 million; (2) the cost-effectiveness and potential impact of meningococcal conjugate vaccine were consistent with other new vaccines such as hepatitis B; (3) the toddler vaccination is epidemiologically justifiable and can have a significant impact on disease; and (4) an infant combination drug would be programmatically less complicated and provide cost savings.

Discussion

When questioned, Dr. Perkins reported no vaccine effect expected on otitis media. Dr. Glezen noted that herd immunity was not modeled, but he thought that immunizing the toddlers would protect the infants as well, as occurs with Hib. Dr. Perkins responded that this conservative model had no data on which to base an assumption about herd immunity. The dynamics and age groups involved in meningococci transmission differs from Hib, with carriage mostly among older adolescents and young adults. It would be a challeng to address those populations to assess an impact on herd immunity.

Dr. Ward appreciated this provocative but still speculative analysis. He cited the limited data on immunogenicity and its duration in both infants and toddlers. The incidence of Hib is 10%-20% with carriage is concentrated in infants, while the meningococcal reservoirs are adults unaffected by this program. The immunization schedule would be more complicated than that for Haemophilus, with a separate infant/toddler plan spanning five years; there is more than one serotype (perhaps 9); and there is a potential for shifting patterns of disease. He worried about raising expectations too high before there is more published data. Finally, efficacy data on these vaccines, as Hib had, are unlikely. Dr. Perkins related his impression that the manufacturers were looking for ACIP direction for acceptable combinations, and even a speculative analysis can help guide these issues. Dr. Davis agreed with both men. He suggested that the model be refined with Dr. Ward's points and also consider a reasonable vaccine cost. He also asked that the overheads about the analysis be provided for the members to study and thereafter advise.

Dr. Chin Le thought this vaccine to be most likely for clinical efficacy or field trials in endemic or epidemic areas like India and Africa, and advised ACIP to keep markets beyond the U.S. in mind. Dr. Thompson asked why the data were limited to group C and excluded vaccines against groups A, Y, and W-135. Dr. Perkins responded that two tracks of

development targeted group C for use in developing countries to prevent endemic disease, and the A track was pursued mostly to prevent epidemic diseases in Africa.

Dr. Halsey appreciated the manufacturers coming to ACIP to see how other vaccines to be developed could fit in an immunization schedule. He suggested submitting the cost-benefit analysis to peer review, particularly since he thought the vaccine cost low. He also noted the lack of an analysis for any alternative strategies, e.g., for geographic areas or subgroups at higher risk for whom a phased approach could be used. This would also provide some experience with these vaccines first.

Dr. Ward noted that the bacteriocidal assay for meningococci offers an excellent serological marker for protection which could help the efficacy trials. And, if meningococci can be linked to Haemophilus or the pneumococcal conjugates, its cost could be reduced. But he did caution CDC to keep their analyses conservative, as such can suggest vaccine costs for the manufacturer.

Dr. Howard Six asked for comment on recent publications projecting a 30% reduction in meningococcal disease. Dr. Perkins responded that the proportion of meningococcal disease due to serogroup Y in the U.S. had increased dramatically in the last two years, causing 30% of disease for unclear reasons. It was seen regionally in New York state about 20 years ago earlier, and resolved in a couple of years. However, regarding vaccine development, it must be recalled that serogroup Y occurs in older populations than other serogroups. With that, Dr. Davis requested that committee comments be returned within a month.

Guillain-Barre Syndrome and Influenza Vaccination Investigation Report

Dr. Chen reported on a possible association between Guillain-Barre Syndrome (GBS) and the influenza vaccinations of 1992-1993 and 1993-1994. VAERS data indicated a doubling from the background rate in a non-random pattern different than other adverse event reports which appear to peak in the first week and then decline.

CDC commissioned a study done by the University of Maryland/Baltimore by Lasky and Stolley. Dr. Tamar Laski reported the initial data of the study, done in collaboration with NIP, to estimate the risk of GBS associated with the 1992-93 and 1993-94 influenza vaccines. GBA is a rare neurological disease characterized by symmetrical paralysis beginning in lower extremities and accompanied by loss of reflexes. There is eventual recovery with rare exceptions.

They studied persons over the age of 18 in four states, with total populations of 21.2 million in 1992-93 and 21.4 million in 1993-94. Case ascertainment occurred from hospital discharge summary databases (with IRB approvals). These produced 1201 discharges appropriately ICD-9 coded during the study periods. They requested, reviewed and analyzed 1109 (92%) of those charts. This resulted in 273 "definite" and "probable" cases, for which 180 patient interviews were conducted with a 69.5% success rate for patients or proxies. The verbal reports received of influenza vaccine were confirmed with health care providers for the exact vaccination date.

No vaccination was reported by 116; 8 unrecorded reports were considered unvaccinated. Thirty reported influenza vaccine, but outside the 6-week study period. Sixteen patients reported influenza vaccination within 6 weeks of GBS onset. Ten reported influeza vaccination, but the provider was not accessible.

A random survey of vaccine coverage in those states estimated over 10 million vaccinated persons, producing 60.8 million person-weeks of exposure for the study denominator. This was then added to an estimated 32.5 million unvaccinated persons to produce a sum of 1.05 million person-weeks of non-exposure. The study then calculated incidences and relative risks. The overall unadjusted relative risk of GBS within 6 weeks after influenza vaccine, compared to the risk at other times, was 2.02, with a confidence interval of 1.21-3.39. Adjusting for age group and study year, the relative risk was closer to 1.0 (1.45) with an overlapping confidence interval from 0.86 to 2.42.

There are three possible explanations for the VAERS increase: (1) an increase in GBS incidence; (2) an increase in vaccine coverage; and (3) and increase in risk associated with the vaccine. The data showed an independent increase in GBS cases over the two study years that they are just beginning to explore. They also found a constant number of definite cases and a fair increase in probable cases. The difference between the two is thought to be a diagnostic difference, the availability of CSF measurements.

There is evidence for each of the posited explanations. There is a definite increase in GBS cases, from 118 to 155 in one study year, and the survey showed an increase in vaccine coverage from 20.9% to 26.6% over the two study periods. However, the study data did not indicate an increase in risk by study year (relative risk of 1.73 and 1.28).

Dr. Lasky showed the plotted data from vaccine-associated cases, which had the characteristic curve of the swine flu study, with vaccine-associated cases peaking in week 2-3. That supports some kind of vaccine-associated risk, but the study's data showed a relatively small risk of disease onset relative to influeza vaccination.

The study's preliminary conclusions were that the relative risk is about 1.45 with a confidence interval from 0.86 to 2.42 after controlling for age group and year. There may be small increase in risk associated with the influenza vaccine, but the confidence interval is 1.0. Finally, the distribution of cases in a 6-week period after immunization seems to support a small increase in risk, but further analysis is needed to understand the variation in background rates. This is similar or less than the risk observed in earlier years, except for 1976. They concluded that the increase in VAERS reports did not indicate an increase in risk associated with GBS for that year.

Discussion

Dr. Ward asked if there is any seasonality pattern to GBS. Dr. Lasky reported that the rough data from September to February indicated some variations within those months, but this has

not been analyzed. Dr. Ward about any correlation between GBS and influenza. Dr. Davis asked of any data on bloody diarrhea, which could indicate a correlation to campylobacter infection, and also reflect seasonality. Dr. Lasky confirmed that they are looking at some campylobacter-related questions.

Dr. Glezen reported a survey indicating that any seasonal GBS clustering would occur in late summer or early fall, times not normally associated with influenza. He urged investigation of other possibly associated etiologies or infections. Dr. Halsey was concerned that the study's methodology of adding the vaccinated group's 20-week window of risk to the unvaccinated group's six week window could inflate the relative risk. Dr. Lawrence Schoenberger said the risk was concentrated primarily in the first five weeks, then approached background for the next 7-10 weeks. Subsequent state studies did not show any increase after 6 weeks, but definitely did within the first 6 weeks of GBS after swine flu. He agreed that wild influeza is not associated with an increases of GBS.

Dr. Christopher Drew from Evans Medical in England asked if the study worked the figures to include the 93 unlocated cases, and what impact their inclusion would have had on the conclusion. Dr. Lasky expected that applying the study's proportions of other patients would not affect the relative risk, though it would result in an underestimation of overall GBS incidence. Dr. Drew asked what proportion of VAERS GBS cases are over 6 weeks post-vaccination. Dr. Chen thought it to be $<10\%$. Dr. Drew then inquired what proportion of GBS was non-vaccine related. Dr. Lasky responded that most were not vaccine related. The study did not confirm the 116 reports of no influeza vaccination, but she expected the bias to be more of a vaccination report than otherwise. The 30 who reported it but were outside the 6-week period is another consideration; other investigators have used an 8-week period.

Dr. Paul Copland of Merck asked if the 8 unrecorded rejected cases and 30 cases outside the 6-week period were within the denominator. Dr. Lasky responded that these were the numerator of the denominator. Dr. Copland suggested taking those out of the analysis. Since they are probable cases falling between the definite cases and non-cases, removing them would give a cleaner comparison.

Other Studies

Dr. Chen appreciated this study as lies at the margin of the epidemiologic method's feasibility. He also welcomed the apparent lack of increased risk, and that VAERS fulfilled its design by indicating a potential increase. However, although VAERS is sensitive to changes in incidence of rare serious adverse effects, it cannot sort out the different causes.

He reviewed several controlled studies of GBS and influenza within the military and civilian populations. In general, the military are vaccinated more frequently than the general population; in their studies, the background rate of GBS was 2-4 times higher, perhaps due to such factors as closer living quarters. However, if the civilian cases are plotted for onset intervals, a non-random pattern emerges, requiring updated language in the recommendation. (insert text??)

Regarding this, Dr. Chen presented the long version of the suggested addition to the influenza statement (page 9 of the influenza draft), and noted that younger persons could also be added to the risk groups, though there are less data on them. There was also another proposal to stop the statement after the "100,000 adult vaccinations" text. The balance of the draft insert discusses the VAERS data, the subsequent study and its conclusions.

Discussion
Dr. Glezen thought that the relative risk would generally be around 1.0, and that higher risk years would balance out. But Dr. Chen reported that the 1992-93 season was picked at random and produced the same relative risk as the 1991-92 cluster and the 1993-94 VAERS spike. Dr. Glezen reiterated his call for systematic surveillance of flaccid paralysis to answer such questions of vaccine-related illness.

Dr. Nichol thought the presented data provocative and of some concern. However, he advised that relative risk can be hard to interpret without good incidence rates, and suggested discussing the increases in absolute rates (e.g., the increase above background might be an additional one per 100,000 individuals), particularly since these studies are not statistically significant.

Dr. Schoenberger suggested that as these potential statements are reviewed, ACIP consider dropping out the two sentences referring to the VAERS increases. This would more accurately provide the present situation in the absence of data on absolute/relative risks. Dr. Davis asked the members to review the statement without that text to discuss it further on the following day.

Recently Licensed Acellular Pertussis Vaccines
Dr. Peter Strebel presented an overview of the work on acellular vaccines. At the October ACIP meeting, a draft statement was presented and a vote taken on the timing of the fourth dose, and language was presented on the fifth dose and vaccine interchangeability. Since then, new draft statements were written in response to the release of two new acellular pertussis products (ACEL-IMUNE7 and Infanrix7).

Dr. Barbara Howe of SmithKline Beecham presented the safety data for Infanrix7, which was licensed in January 1997. Infanrix7 has three pertussis antigens, as well as diphtheria and tetanus toxoids, added to .05 mg of aluminum. Its efficacy was evaluated in two independent prospective blinded trials in Germany (which found 89% efficacy) and in Italy (84%. as opposed to 36% for DTPw). She also showed results from the Swedish trial, which evaluated a bicomponent DTPa which was less effective (59%). Infanrix7 is now licensed in more than ten countries, including Canada and the U.S.

Infanrix7 is indicated in infants and children from 6 weeks to 7 years of age as a 3-dose primary series, and then as a fourth dose in those who received three doses of Infanrix7. It can also complete a five-dose series in those who received one or more doses of DTPw. The

overall safety database includes more than 30,000 subjects in clinical trials of safety, immunogenicity and efficacy. Of these, 28,000 received the 3-dose primary series, about 6000 received the fourth dose, and 22 have received a fifth dose after priming with Infanrix7 or DTPw.

Dr. Howe showed a chart of the local adverse events (%) for Infanrix7 or DTPw at 2, 4, and 6 months of age. These included redness; redness >2.4 cm; swelling; and swelling >2.4cm. All the local adverse events were less frequent following vaccination with Infanrix7 as compared to whole-cell vaccine. The same was true for the general adverse events (fever, irritability, drowsiness, loss of appetite, vomiting, crying >1 hour).

She then presented data on U.S. infants at 2,4,6 months of age, which is included in the ACIP statement's Table 3. Of the 120 infants who received the three-dose primary series, 76 received a fourth dose at 15-20 months. The rates of some symptoms like redness, swelling and fever increased with successive dose administration, from the first to the third dose as well as on to the fourth. This was also true of other acellular vaccines in this trial. But compared to four doses of DTPw, the rates were lower for Infanrix7. They are still collecting data on five consecutive doses.

Dr. Howe then showed data from trials where infants were primed with three or four doses of DTPw (Table 4 in the draft statement). Again, Infanrix7 produced lower rates of adverse events after vaccination, with significant differences for many reactions (pain, fever, restlessness, decreased appetite, unusual crying). For moderate to severe adverse events within 48 hours of vaccination, there was a much lower incidence in the Italian trial for Infanrix7 than for DTPw for high fever, hypertonic hyperresponsiveness (HHR) and crying >3 hours. Severe adverse events were similar to DTPw. Of the 66,000 German doses, only one case of HHR occurred, and none of febrile seizures, etc.

The conclusions were that Infanrix7 was shown to be followed by fewer local and systemic adverse events than those commonly associated with DTPw. There were significantly lower rates of moderate to severe adverse events such as high fever, HHE and persistent crying. Infanrix7 is highly efficacious with vaccine efficacy of 89% and 84% in two independent prospective trials. Finally, post-marketing experience outside the U.S. confirmed an excellent safety profile.

Discussion

Dr. Anthony asked about the follow-up protection data. Dr. Howe had shown the Stage I trial data, an average 17-month follow-up with 84% efficacy after three doses. Children were still followed after a booster dose of DTP at 15 months. They also have efficacy data from Stage II of the trials, an additional 9 month follow-up (absolute vaccine efficacy of 78% for children averaging 33 months of age). They are continuing to follow them to four years of age. A control group consists of children whose parents refused the acellular vaccine. They are being

boosted and serving as a control, but they are not the same control group as the original efficacy trial.

Presentation on the Status of Acellular Pertussis Statement
Dr. Melinda Wharton recalled that the initial discussions of the acellular pertussis statement only addressed the single licensed product available. However, the new products introduced since then demand the discussion of interchangeability of acellular pertussis vaccines for the first three doses. The FDA has rapidly overtaken CDC's ability to finalize this statement. She recommendation text on interchangeability was very similar to that on Hib conjugate. It read: "Whenever feasible, the same brand of DTaP vaccine should be used for all doses of the vaccination series. Data do not exist regarding the safety, immunogenicity, and efficacy of using DTaP vaccines from different manufacturers for successive doses of the primary or booster vaccination series. However, if the vaccine provider does not know or does not have available the type of DTaP vaccine previously administered to a child, any of the licensed DTaP vaccines may be used to complete the vaccination series. These recommendations may change as data become available regarding the safety and immunogenicity of interchangeable ("mix and match") administration of different DTaP vaccines."

Dr. Wharton stated that there are known differences in acellular pertussis vaccines. The antigen contents vary, and the antigen preparation method varies greatly; the immunogenicity to the antigens contained varies somewhat; and there is some evidence that of a difference in the immunogenicity of specified epitopes. However, the significance of this regarding conferred protection is unclear.

One difference between the Haemophilus influenza type B conjugate vaccines is that those have an accepted good correlate of immunity. Such is not widely accepted for pertussis, making protection of disease the outcome of interest. Immunogenicity study of mixed sequences is not interpretable in the absence of a serologic correlate of protection. Since an antibody response cannot be measured to determine protection, there is no way to judge if a child receiving these vaccines would be suboptimally protected.

However, there are some possible approaches to study the interchangeability of pertussis vaccines. There are some studies in the animal model which seek to identify serologic correlates of immunity by using the clearing of the organism as an endpoint, and some models appear to correlate in a general way with efficacy (e.g., the mouse model at FDA). However, it is likely that the data from post-licensure surveillance will be important input.

From a policy point of view, Dr. Wharton saw no alternative to the language proposed. It is permissive, finding even a mixed sequence preferable to an unvaccinated child.

Discussion
Dr. Halsey noted that the last sentence of the statement applies to every recommendation, and proposed instead that the statement indicate that studies are underway and might be reviewed.

It was suggested that perhaps mix and match studies could be done. Though there is no correlate of protection, he thought that bridging data could enable comparison of the vaccine consistency, scale-up, manufacturers' consistency, combinations of vaccines within populations, etc. Dr. Wharton agreed that this could be done, and that FDA has accepted bridging data. But in her opinion, the bottom line was the absence of a correlate to make it clear if the child is optimally protected.

Finally, Dr. Peter Strebel reported that the program has a scheduled publication date of March 14, for which the final version must be ready by March 1. He requested any comments be sent to him by the middle of the following week. With that, the meeting adjourned at 7:00 PM.

FEBRUARY 13, 1997

Opening Comments

On the following day, Dr. Hadler noted that a compendium of recommendations from other statements regarding health care workers would be sent to the members before the next meeting. Dr. Davis requested that comments on the draft statement on the use of combination Hib-Hep B vaccine (Comvax7) be provided to the program. This will be reworded for publication as an advisory in *MMWR*. Dr. Snider reported that the anthrax discussion resulted in the formation of a work group of CDC staff and DOD personnel. They will meet to discuss the data on the use of anthrax and may present that at the next meeting.

VFC Vote

Dr. Hadler read the revised recommendation on the use of combined Haemophilus influenzae type b (Hib)-hepatitis B vaccine (Comvax7). This will be published in Spring 1997 with the ACIP recommendation "Hepatitis B Virus Infection: A Comprehensive Immunization Strategy to Eliminate Transmission in the United States; 1997 Update". The recommendatino would become effective upon the completion of ongoing vaccine contract negotiations. The recommendation and resolution that resulted from discussion were:

"On October 2, 1996, the FDA licensed a combined Hib-Hep B vaccine (Comvax7) for routine immunization of children born to HBsAg negative mothers.

"Combined Hib-Hep B vaccine should not be given before 6 weeks of age.

"Combined Hib-Hep B vaccine may be used as a three-dose series at 2, 4, 12-15 months in infants, regardless of the mother's HBsAg status. Combined Hib-Hep B vaccine may be used as a three-dose series at 2, 4, 12-15 months in infants who have received a dose of Hep B vaccine within the first month of life.

"Combined Hib-Hep B may be used interchangeably with Hib and hepatitis B vaccines produced by other manufacturers as previously defined in VFC resolutions 6/94-14 (consistency of use of Hib vaccines) and 2/94-9 (interchangeability of other vaccines).

"The contraindications to the combined Hib-Hep B vaccine are the same as those for the individual component vaccines (see VFC resolutions 6/94-9 and 6/96-10)."

Resolution:

"The ACIP recommends inclusion of combined Hib-Hepatitis B vaccine with the number of doses, schedules, qualifications and contraindications as noted in the text above in the Vaccines for Children program, effective February 13, 1997."

Discussion
The words "inclusion of" were added to the resoluation when Dr. Halsey worried that using the word "recommend" would indicate a preference for this vaccine. He also anticipated confusion when two more combined products are released next year, presenting a potential of three different regimens.

Dr. Karen Minton of FDA wished to avoid the perception that a three-dose series of Comvax7 would obviate the need for a dose at birth of hep B vaccine and HBIG for infants of HBsAg antigen-positive mothers. However, Dr. Davis noted that this vote was only to include this vaccine in the VFC, and was intended to be permissive.

Dr. Sherrod was concerned at potential confusion since the statement first notes the product's licensure for surface antigen-negative mothers, then allows its use regardless of antigen status. Dr. Hadler reassured her that this resolution only sought to delineated the vaccine, the number of doses, the schedule and contraindications. This is consistent with what has been done in the past.

VOTE: The members voted on the resolution as amended. Those in favor were Glode, Schoenbaum, and Davis. None were opposed. Abstaining were Sherrod, Modlin, Guerra, and Ward. Three were absent (DeBuono, Griffin and Thompson). The motion carried.

Influenza Updates
Influenza in the U.S.
Ms. Nancy Arden of NCID's Influenza Branch provided an update on H3 and H2 influenza activity in the U.S. There were no H1 influenza isolates reported. State morbidity reports indicated the first regional activity in early November in Montana. By mid-December, 17 states reported regional activity, and 13 reported widespread influenza. The prevalence peaked in early January, and regional and widespread influenza gradually declined. An increase of Influence B isolates were seen in the last month, constituting 30% of the overall total in the last week. This was an early influenza season, but the Pneumonia and Influenza (P&I) Mortality curve was typical for a predominantly H3 and H2 season. The activity began in the northeastern states and was less severe in the southeast. However, there was an unusually large number of reports of outbreaks in nursing homes and other institutions.

When asked the influenza season's time frame, Ms. Arden responded that it varies from year to year. Surveillance begins the first week of October. Sporadic activity is normal the first week of November, and the peak can span from December to as late as March.

Global Influenza Surveillance

Dr. Nancy Cox reported that moderate to severe influenza epidemics were seen in Europe and North America. The outbreaks in France and the United Kingdom (U.K.) paralleled those in the U.S.; Germany and the Czech republic had later activity. Influenza A (H3N2) viruses predominated in North America, Japan, and most European countries. A rising number of Influenza B viruses have been isolated in recent weeks; isolation of influenza A (H1N1) viruses has been infrequent worldwide since October 1996.

Dr. Cox stressed that all the viruses charted were similar to the 1280 vaccine strain antigens. Had last year's Johannesburg 33 vaccine strain virus reemerged, coverage would have been poor. The current vaccine strain is genetically typical of current virus strains. All the viruses received by CDC's laboratories are being distinguished genetically, which is more accurate than antigenic analysis. Over 94% of these were the H3N2 strain.

The H3N2 virus is similar to the vaccine strain, and predominant in Europe North America. Virologic surveillance in China and the U.S. military populations stationed in Asia was critical to the selection of last year's vaccine strain, the A/Nanchang/933/95 strain. Antigenic drift in the H3N2 strains circulating worldwide has been moderate. However, genetic and serologic analyses suggest there may be a new genetic strain emerging (the South Africa 96 strain), which is being carefully monitored.

In the H1N1 viruses, the antiserum to the Texas vaccine strain was homologous to the Texas virus. Other strains isolated from around the world show that a number of viruses have decreased fourfold in titer from the Texas antiserum, showing some antigenic drift. However, there is a dramatic reference change (not well inhibited) in the A/Beijing262/95 strain. Viruses similar to the Beijing strain had been circulating in China for several months.

Genetic examination of those viruses shows a clear correlation between those of the lower antigenic profile to the Texas and Taiwan antiserum. The viruses are all from Asia (until recently all were from China; a new virus was reported in Singapore). The rest of the viruses fit in another genetic loop. Analysis indicates that the summer H1/N1 virus activity in Asia fell into the minority virus group.

Dr. Cox summarized that there are two distinct genetic groups of influenza A virus (H1N1) viruses, one group predominating worldwide, while the second circulated only in China. The HA genes of the H1 viruses have continued to evolve, with a number of amino acid changes noted. The molecular correlate of the reduced HI titers of the lower reacting viruses is known.

Influenza B viruses have circulated at low levels world-wide, but the numbers of reported isolates have increased in several countries. Their antigenic drift is insignificant, but the distinct Victoria B viruses (not represented in the vaccine) are circulating in China. However, they have not circulated in the U.S. since the 1991-92 season.

For vaccine selection, the Influenza B component of the 1997-8 influenza vaccine was selected by FDA's Vaccines and Related Biological Products Advisory Committee. The Antigenic, genetic and serologic data support retaining the previous type B component (B/Harbine/7/94 -- B/Beijing-like). Decisions for Influenza A components were deferred pending additional data and WHO's recommendation of February 19.

Vaccine Recall

Dr. Carolyn Bridges then provided an update on the CDC study of nursing home residents who received a recalled Parke Davis influenza vaccine. In November 1995, Parke Davis voluntarily recalled 11 lots of influenza vaccine due to the decreasing potency of its A/Nanchang component. Neither CDC nor FDA recommended revaccination. The New York state health department then requested CDC assistance to determine whether several nursing homes which had administered the recalled vaccine should revaccinate. Six nursing homes participated in the study; three had used the recalled vaccine, and 3 another manufacturer's. In all, 172 vaccinated nursing home residents participated, evenly divided between recalled nonrecalled vaccine. None of the nursing homes had an influenza outbreak to that point in the influenza season.

Medical chart abstraction data included information on age, sex, date of vaccination, prior influenza vaccination, chronic disease and activity levels. Blood samples were collected three weeks post-vaccination. Hemoglobin inhibition testing was done for antibody against all the 1996-97 vaccine components. Of the two groups, the recall group was significantly older (88 versus 82.5 years of age). The non-recall group also had two more days between vaccination and blood sample collection than the recall groups (23.5 days versus 21 days). There were no differences in chronic illness, higher influenza vaccination history, sedentary or bedridden status.

The geometric mean antibody titers (GMT) for each group was shown. The recall group had a statistically significant difference in GMT (33 versus 55 in the non-recall group) for the A/Nanchang component; but there was no difference for the A/Texas or B/Harbin strains. Comparisons of titers $\exists 40$ showed the recall group's lower titer (54%) versus the non-recall group (67%) for A/Nanchang. Again, there was no difference for the A/Texas or B/Harbin strains.

To see if age was a significant confounder for the A/Nanchang component results, CDC stratified the participants into four different groups from ages 60 to >90. Each age group showed higher GMTs for the non-recall vaccine group. The recalled vaccine participants showed increasing GMTs with increasing age. To assess the impact of the differing number of

days between vaccination and blood collection, the groups were stratified for blood collection 2, 3, or 4 weeks after vaccination. The data showed little difference in GMTs.

They concluded that nursing home residents receiving the recalled vaccine had significantly lower A/Nanchang antibody titers, but the A/Texas and B/Harbin strains did not differ between the two vaccine groups. CDC recommended first to immunize the unvaccinated high-risk persons. Second, they advised consideration of revaccinating the high-risk persons, especially those with a chronic medical conditions, who received the recalled vaccine. Follow-up studies in January 1996 were done in two of the three nursing homes which administered recalled vaccine. Serum samples were collected three weeks post-revaccination, and results are pending.

Discussion

Dr. Ray Strickes asked if any of those receiving recalled vaccine became ill. Dr. Bridges reported an influenza outbreak in one nursing home in the first week of December. Of 300 residents, three persons in the original study who became ill did not have the case definition of illness; they had titers of #320.

Dr. Modlin asked if there were any consideration of re-dosing for those with low titers. Dr. Bridges responded that only those patients who did not have influenza-like illness were revaccinated.

Dr. Peter asked how the study could know that such illness does not occur continuously with suboptimal vaccine lots. Dr. Bridges reported the vaccine companies' routine post-release testing of vaccine to check the viruses' stability and amount of antigen. Dr. Six confirmed that vaccine stability testing is done each year; if a strain is changed, stability studies are done to follow-up.

Dr. Halsey commented that the recall created a preventable problem. AAP found out after the fact, resulting in enormous pressure for a quick decision on whether to advise revaccination. He asked that in similar situations, the manufacturers share the information with the AAP as soon as possible, even if only 24-48 hours in advance.

It appeared to Dr. Glezen that FDA left the recall decision to the manufacturer, and they only notified the physicians to whom the lots were delivered. Dr. Anthony did not know of any other way this could be done. Dr. Bridges added that previous studies' data indicated no reason to re-vaccinate, and that the investigation's mid-November results were quickly released through the press, faxing, and Parke-Davis' letter.

Dr. Glezen asked if another prototype strain could be used to represent the Nanchang antigen. Dr. Cox agreed that this question is of concern, and reported CDC's search for alternative vaccine candidates. Parke-Davis is testing to understand what happened and to prevent it in future. Dr. Six was unsure a change in the strain was the root cause, as it was not encountered by all manufacturers.

Impact of Influenza Vaccine on Pregnant Women

The impact of influenza on pregnant women was presented by Dr. Katherine Neuzil of the Vanderbilt University Medical School. The current ACIP recommendation states that health care workers should consider administration of influenza vaccine to all women who would be in the third trimester of pregnancy or early post-partum/purpurium during the influenza season, or to any pregnant woman who has a concomitant high-risk condition.

Dr. Neuzil noted that historically, influenze risk in pregnancy was high until 1957. Though data is scant on inter-pandemic periods, Schoenbaum et al found among women in late-stage pregnancy or the early post-partum period only four mortalities associated with underlying risk factors. There also are many isolated case reports of mortality in influenza season, most of them among women. But the more sensitive measure of influenza impact is morbidity, such as acute respiratory hospitalization rates in the third trimester.

The study used acute cardiopulmonary hospitalization to assess influenza impact on women. The objectives were to assess the appropriateness of ACIP recommendations for immunization of pregnant women, to determine the relative risk of influenza-related hospitalizations for pregnant women, and to determine the incidence of influenza morbidity and mortality among women of childbearing age.

The study used a Medicaid database on outcomes of pregnancy developed by Vanderbilt University. For the period 1974-1993, it included all Medicaid enrollees' demographic characteristics, enrollment dates, hospitalization and outpatient diagnoses, detailed information on prescriptions filled, and all other services billed to Medicaid. The database was linked to birth certificates and to fetal and maternal death certificates.

The population consisted of women aged 15-44, black or white, enrolled for more than 180 days in the Tennessee Medicaid program. The time period was picked to optimize the background information, to identify if a woman was high-risk or to include those enrolled due to pregnancy.

Influenza season was defined as the day of Vanderbilt's first and last influenza virus isolation. The study included seasons; two with very low activity (<5 isolates) were excluded. The rest had a mean duration of 10.6 weeks. Peri-influenza season was the period from April 30 to November 1 with no influenza activity. Whether the season was short or long, the morbidity and mortality peak matched the influenza season definition.

The narrow study outcome was a hospitalization or death from pneumonia or influenza. A broad study outcome was a hospitalization or death from all cardiopulmonary conditions. These were defined by ICD-8 and ICD-9 costs.

They began with a nested case-control study, defining a case as the first study-defined hospitalization during influenza season. Five controls for each case were randomly selected

from the same population. They found 2061 cases (hospitalizations or deaths) in all women in influenza season (10,000 controls). In the broader definition of all events, they had 4,369 cases and 22,000 controls. Dr. Neuzil explained the demographic breakdown by age, race, urban/rural population, AFDC, pregnancy, etc. They also looked at selected medical characteristics: any high risk condition, recent hospitalization, influenza immunization (0.7%), non-pregnant (85%), pregnant (7%), and almost 6-months post-partum (8%).

The results showed an increased risk of about 2% per year of increasing age for being hospitalized for the broadly-defined acute cardiopulmonary conditions. There was a slightly increased risk (odds ratio of 1.34) for white women and for rural women (2.15). For all study events, the risk status for women with pulmonary conditions was highest (8x risk of being hospitalized); cardiac conditions and steroid use were next in line, followed in decreasing order by renal conditions, cancer, and diabetes.

Dr. Neuzil then outlined the association of pregnancy status with all study events. There was a relative risk of more than 4.5 for women in the last half of the third trimester. This risk was statistically significant at 21 weeks when compared to non-pregnant women. Therefore, only women with chronic pulmonary disease had a higher risk of being hospitalized than women in the third trimester.

They investigators then did a retrospective cohort study for the entire year, rather than just in influence season. The population was all eligible women (1.393 million women); the study outcomes were the same.

With crude rates of hospitalizations for high-risk (as defined medically) nonpregnant women of childbearing age, a bar chart showed a much higher risk for hospitalization or death in non-influenza seasons. If the woman was both pregnant and high-risk, the rates of hospitalizations increased. The risk of nonpregnant and first-trimester women was about the same; it rose in the second and third trimester. The post-partum period was the lowest. Dr. Neuzil acknowledged that the hospitalization rates may reflect a bias to hospitalize a pregnant woman.

Dr. Neuzil then showed a bar chart of low-risk women. Their hospitalizations increased with the stages of pregnancy, and increasingly with non-influenza, peri-influenza and influenza season. And, after subtracting out the peri-influenza baseline, there were increasing numbers of hospitalizations with stages of pregnancy. There were no deaths among pregnant women during influenza season.

To determine how many study events could be preventable, they took the excess rate of events attributable to influenza by subtracting the peri-influenza season incidence rates in the third trimester from the influenza-season incidence rate. This produced 10.5 excess events per 10,000 women-months. The average exposure time to influenza virus was about 2.5 months, making the attributable events 2.5 per 1000 in third trimester women. Using an 80% vaccine efficacy rate, they concluded that immunizing 500 women should prevent one hospitalization.

The study limitations were that there were no chart reviews, and an unknown morbidity or cost associated with hospitalizations. There could have been a selection bias, as a physician is more likely to hospitalize a pregnant woman than a non-pregnant healthy woman. It was not known if the study findings are generalizable to other populations, since most subjects came from low-income groups. Dr. Glezen's studies indicate that middle- and high-income women may have an increased risk.

They concluded that the risk of acute cardiopulmonary hospitalizations during influenza season for third-trimester pregnant women is comparable to that of high-risk groups for whom the vaccine is recommended. Influenza immunization of 1000 women beyond 14 weeks of pregnancy should prevent 1-2 influence-related hospitalizations.

Discussion
Dr. Glode agreed that there could be a selection bias favoring the hospitalization of a pregnant over a non-pregnant woman, and wondered if other measures of morbidity could be assessed from the database. Dr. Neuzil responded that a follow-up study will conduct a chart review for the length of stay, fetal issues, etc.

Dr. Glezen found that "selection bias" to hospitalize a pregnant woman well founded, to ensure the avoidance of a bad outcome. Dr. Gall agreed that physicians justifiably over-react to treat woman in the third trimester, particularly in the influenza season. He lauded this study and looked forward to new data on morbidity statistics, expecting the information on excess emergency room or office visits to be as revealing as admission statistics.

Dr. Chin Le thought the study made a convincing case for increased morbidity in pregnant women, and asked if they should be vaccinated. Some data show that the vaccine is not very protective prior to six months before the season, and there is no field clinical data to prove otherwise, except for serological evidence. Dr. Neuzil said that this is a challenging decision for the ACIP. Since pregnant women have frequent contact with the health care system, an ACIP statement could greatly help reach an accessible population. Dr. Gall agreed, noting that the previous ACIP statement was very helpful in advancing immunizations or other treatments in pregnant women.

Dr. Glezen recalled that vaccine was recommended in pregnancy until 1966 and that over 52,000 such women received influenza vaccine through 1959. In fact, a large perinatal study including all trimesters of pregnancy showed a relative risk of 0.9, indicating a better outcome with vaccines. This also was at a time when vaccines were less purified and potent than they are now. Subsequent studies show that maternal protection crosses to babies, protecting them in the first months from influenza-type illness. There is no concern about safety, and physicians just need to be reeducated on that fact.

Proposed Changes to the 1996-97 Influenza Recommendations re. Vaccination of Pregnant Women

The ACIP members discussed the option of changes to the 1996-97 influenza recommendations regarding the vaccination of pregnant women. The proposal read as follows:

"Influenza-associated excess mortality among pregnant women has not been documented except during the pandemics of 1918-1958. However, because death certificate data often do not indicate whether a woman was pregnant at the time of death, similar studies conducted during interpandemic periods may underestimate the impact of influenza in this population. Case reports and limited studies suggest that pregnancy may indeed increase the risk for serious medical complications as a result of increases in heart rate, stroke volume and oxygen consumption, decreases in lung capacity and changes in immunologic function. A recent study of the impact of influenza during 17 interpandemic influenza seasons found that the relative risk of hospitalization for selected cardiorespiratory conditions among pregnant women increased from 1.4 during weeks 14-20 of gestation to 4.7 during weeks 37-42, compared to rates during the period 1-6 months post-partum. The risk during the third trimester was comparable to the risk for non-pregnant women with high-risk medical conditions for whom influenza vaccine has traditionally been recommended. It was estimated that immunizing 500 women who would be in their third trimester during influenza season would prevent one hospitalization.

"In view of these and other data which suggest that influenza infection may cause increased morbidity in women during the second and third trimesters of pregnancy, health-care workers who provide care for pregnant women should consider administering influenza vaccine to women who will be beyond 14 weeks of gestation during the influenza season. Pregnant women who have medical conditions that increase their risk for complications from influenza should be vaccinated before the influenza season, regardless of the stage of pregnancy. Although definitive studies have not been conducted, influenza vaccination is considered safe at any stage of pregnancy."

Discussion

Dr. Modlin asked for any data on the efficacy of the influenza vaccine in pregnancy. Dr. David Fedson reported calculations on individual risk within specific illness. The vaccine's effectiveness in preventing all pneumonia and all respiratory condition hospitalizations was 35-40% or higher in the elderly. If half of these are attributable to influenza-virus specific illness, then vaccine efficacy itself is twice the effectiveness in preventing this microbiologically imprecise outcome. So while he did not know of data supporting efficacy at 80%, it may well be close to that efficacy. However, he agreed that there are no hard data, and was not comfortable with using surrogate data to support a recommendation. Ms. Arden saw an assumption in the immunogenicity data that the vaccine was just as immunogenic in pregnant women as it is in healthy younger adults, and the latter is known, allowing an extrapolation to the pregnant women.

Dr. Zimmerman asked why, when the recommendation wording mentions 14 weeks, the study used 20 weeks' data. Dr. Neuzil responded that while risk started to increase at week 14, the increase was not statistically significant until week 21.

Dr. Siegel noted the last sentence and asked if the data were definitive. Ms. Arden reported that a number of studies have been done, but that FDA preferred this language. Dr. Six stated that this is of concern to the manufacturers. Though the data clearly show an effect in pregnant women, there have not been controlled safety studies in pregnant women. The package inserts state that there may be an increased risk to pregnant women, and the potential benefit to vaccination, but that there is no safety data available.

Dr. Glezen thought that CDC's current inclusive policy on pregnant women would not allow them to be excluded without specific reasons. Any danger ought to be cited; since several studies of pregnancy have shown benign outcomes, he thought pregnant women should be included. Dr. Snider clarified that CDC's recent policy on women is to include women in studies without a compelling reason not to include them. Dr. Glezen questioned whether any vaccine has "definitive" safety data, and thought excepting influenza vaccine was unfair.

Ms. Arden thought that influenza vaccine was not singled out. In the past, there were even more caveats about safety, some of which was almost contradictory regarding pregnancy. All these ACIP caveats regarding pregnancy were removed, but FDA thought that going too far. Many drugs are Category C, with no reason to expect harm, but which have no controlled studies. FDA felt that this had to be included in the recommendation to be minimally consistent, particularly with the package insert cautions.

Dr. Gall defined two involved issues: the teratogenicity of the vaccine and the background rate of spontaneous abortions. The latter will always occur in the first trimester, but there is no teratogenicity data on killed vaccine.

Dr. Chin Le noted that the risk does not increase at a significant level until week 21. This would make giving the vaccine to patients later more acceptable. He thought the better option for science and the patient was to recommend immunization for women at or beyond 21 weeks gestation during the influenza season.

Dr. Karen Goldenthal of the FDA reported requests in recent years to study pregnant women for several Investigational New Drug (IND) vaccines. The presumption is that inactivated vaccine will not cause reproductive toxicity; but this is a difficult area in the absence of data. Therefore, FDA asked the IND drug sponsors to do some limited reproductive toxicology testing. Those results have always been negative for influenza vaccine, but this remains a difficult and evolving policy area.

Dr. Snider suggested changing the text to "although definitive studies have not been conducted *and are needed…*" Dr. Gall reported rising national acceptance to immunize women, and supported a strong statement to encourage health care providers to provide this service.

Dr. Davis found consensus to add "and are needed" to the last sentence. In another issue, based on the limitations of data on making the cut point at 14 or 21 weeks, he preferred to err in favor of the earlier age to provide a safety cushion rather than being scientifically precise. The risk begins at that time, and that is beyond first trimester. Dr. Gall supported using the trimester reference, as this is obstetricians' time frame. He also recommended deleting the last sentence in the first paragraph on the benefit of immunizing 500 women.

Dr. Fedson suggested qualitative language such as "It is beneficial to vaccinate to prevent influenza in second trimester of pregnancy and especially in the third trimester."

Dr. Schoenbaum observed that the current language indicates that a pregnant woman who also has a high-risk condition should be immunized at any stage of pregnancy. If the members were uncomfortable with vaccinating pregnant women without high-risk conditions, then he offered two suggestions: recommending vaccination in the second trimester of such women without other underlying conditions, or at any stage of pregnancy if they did.

A gentleman in the audience noted an almost straight-line relationship through gestation to cardiopulmonary events. Since the confidence level rises two-fold, he found the data clear that all women at 14 weeks of pregnancy and later are at risk.

Dr. Guerra asked about pregnant woman not under an OB/GYN's care, who might receive influenza vaccine, e.g., in a community outreach vaccination campaign. Dr. Gall was comfortable that they could be vaccinated, with no vaccine teratogenicity or impact on pregnancy. He also noted that this study was retrospective and only of hospitalized women. Many women will have less severe forms of influenza during the influenza season that the study would not pick up, nor did it pick up outcomes that occur other than hospitalization.

Dr. Modlin asked if stronger language should be considered, e.g., "ACIP recommends influenza immunization for health care workers", rather than "should consider administering" influenza vaccine. Dr. Guerra advocated deleting wording on those "who provide care for pregnant women", because this would probably be considered restrictive to such workers as OB/GYNs, nurse midwives, etc. He recommended a text of "health care workers providing care to pregnant women", as this would include the many more providing vaccines in the community, etc.

On the last sentence of paragraph one, Dr. Fedsen advised specific language that this immunization would prevent hospitalization due to virus infection, not other causes. Dr. Gall agreed, also noting that saving one in 500 does not seem significant enough to inspire compliance. Dr. Davis agreed that if such text is included in future, it should be clear that this is a substantial impact. Ms. Arden thought it a nonessential sentence and advocated eliminating it altogether. Dr. Modlin advocated strengthening the language to "ACIP recommends".

VOTE: There was unanimous approval to delete the last sentence of the first paragraph ("It was estimated that immunizing 500 women who would be in their third trimester during influenza season would prevent one hospitalization"). Voting members were Sherrod, Modlin, Guerra, Glode, Ward, Schoenbaum and Davis. However, Dr. Davis noted that should this be included in future, its benefit should be clearly stated.

VOTE: There was unanimous approval to amend (as italicized below) the second paragraph to read: "In view of these and other data which suggest that influenza infection may cause increased morbidity in women during the second and third trimesters of pregnancy, *ACIP recommends immunization of women who will be beyond the first trimester of gestation (beyond 14 weeks gestation)* during the influenza season. Pregnant women who have medical conditions that increase their risk for complications from influenza should be vaccinated before the influenza season, regardless of the stage of pregnancy. Although definitive studies have not been conducted *and are needed*, influenza vaccination is considered safe at any stage of pregnancy."

Balance of Recommendation Change
Ms. Arden noted to no comment the addition of a section on the draft's page 7 regarding mothers who breast feed: "Influenza vaccine does not affect the safety of breast-feeding for mothers or infants. Breast-feeding does not adversely affect immunization and is not a contraindication for any vaccine." Dr. Glezen reported data soon to be published that breast feeding increased the infant's titer. There also were no further comments on the minor changes on page 8 about side effects and adverse reactions.

Guillain-Barre Recommendation
The draft's page 9 addressed the Guillain-Barre (GBS) recommendation. Dr. Davis recalled Dr. Schoenberger's suggestion on the previous day that the two sentences referring to the VAERS increases be dropped. Dr. Chen agreed that since no increased risk was found in the 1993-94 season, that could be deleted. But for consistency with other recommendations, he argued that the data on the non-random patterns should be retained. Dr. Peter agreed, citing ACIP's obligation to provide data, even if inconclusive, and to state that the benefits of vaccination outweigh any risk.

Ms. Arden recommended retaining the information about the 1990-1991 study, and all the cautionary language that there might be some slight risk. However, she agreed that data that is neither final nor peer-reviewed perhaps should not be published in this way. Dr. Chen was comfortable to not include this section.

Dr. Davis asked to what the point estimate of relative risk equated. Ms. Arden suggested adding text that "in some but not all seasons since 1976, inconclusive data suggest that there may be an increased risk among younger people. But this is still less than the risk observed following a swine influenza campaign, such that the absolute increase in rates is probably #1-2 per 100,000 vaccinees." There was general agreement to this, with the committee to work on the wording with Ms. Arden.

Dr. Glezen noted the lack of a positive statement that no increased risk has been detected in persons aged 65 and older. Dr. Hadler stated that a data re-analysis will require still more statement editing. Dr. Davis suggested crafting language consistent with Ms. Arden's suggestion, adding the test about ages 65+ years and older, and that ACIP will be responsive to further analysis. The committee could be informed thereafter; if further discussion is needed, it could be done by a work group and still meet the necessary turnaround time for influenza recommendations.

Discussion
Dr. Schaffner asked for greater text emphasis on the substantial progress made in delivering vaccine to persons 65 and older. He also advised strengthening the discussion about vaccinating HIV-positive patients to match that about pregnant women, especially the data to support its statement of vaccine benefit to HIV-infected patients. He noted the emphasis (page 11) on immunizing nursing home residents, but cited the proposal in the January issue of the *Journal of Infectious Diseases* that immunizing the care givers is more important than immunizing the residents. He advised referencing that paper, and an equal emphasis between extended care facilities and others.

Dr. Fedson supported convening a regular (but not necessarily annual) work group to review the influenza statement. In future, he also advocated more concise tables to shorten the statement, and an emphasis on avoiding missed immunization opportunities.

Dr. Gardner thought that the statement finding adverse events to amantadine Ararely severe@ to be too relative. While the vaccine saves lives, administering prophylactic amantadine and rimantadine is not a common practice. He asked if there were any data on prophylactic use in influenza season to prevent transmission to patients. Ms. Arden responded that some facilities offer that treatment and prophylaxis to their workers for outbreak control, and noted the great variety in the use of antiviral agents.

Dr. Davis appreciated these comments. Although he recognized that the GBS text was still undecided, he requested the members= recommendations to be returned to the program by the end of the following week.

Programmatic Strategies
Dr. Edward Hoekstra recalled two ACIP recommendations to improve immunization coverage: linking WIC vouchers and immunizations and conducting clinical assessment and feedback. He presented two slides of data demonstrating that such WIC/immunization linkage was effective. After the May 1996 WIC/immunization linkage, data showed up-to-date vaccination compliance in Chicago to rise from 64% to 74% within seven months. Provider vaccination rates also rose over four years of clinical assessment/feedback. In Missouri, public clinics= percentage of median coverage increased from 45% to 81%.

Dr. Hoekstra presented a third strategy to improve immunization rates, the use of reminder/recall systems. NVAC had recommended these for all public and private providers in their 1993 Standards for Pediatric Immunization Practice. These standards were endorsed by ACIP, AAP and AFP.

In the reminder component, mail and telephone messages remind parents of both their children medical appointments and their vaccination needs. The recall component uses mail and telephone message contact to the parents/guardians of children past-due for immunization. These methods can be manual (i.e., a paper "tickler" file) or computer-generated (mailing or telephone calls). The messages can be modified as needed, e.g., for special language needs or to address preventive health services and well-child visits. Though the cost-effectiveness varies according to practice size, level of computerization and degree of use, consistent implementation of a reminder-recall strategy can help achieve high, sustainable vaccine coverage levels. This can help decrease vaccination drop-out rates and help reduce the time children are at risk for vaccine preventable disease.

Over the past 20 years, studies have demonstrated these methods= ability to significantly improve patient compliance for a variety of scheduled health visits. The median increase in appointment keeping in one previously presented study was 13%; the median increase in vaccination rates, 17%.

A large clinical trial measuring the effectiveness of multiple computer-generated telephone immunization reminder/recall messages showed that 41% of those contacted kept vaccination appointments versus 28% not telephoned. In another study, vaccination visit compliance was 57% after an autodialed reminder call versus 20% not so reminded. A 1992 national survey showed 8% of pediatricians and 5% of family physicians using manual immunization reminders, and 6% and 5%, respectively, using a computerized system. By 1995, use of reminder systems had leapt (42% pediatricians, 33% family physicians) as had recall systems (27% and 20%).

Dr. Hoekstra summarized that reminder/recall messages are simple, effective, and inexpensive, particularly when automated. Implementation of these can improve vaccination rates and sustain high rates in vaccine-provider sites. He proposed that ACIP recommend that all providers utilize a reminder message before each vaccination due date, and that recall messages be used for past-due children immediately after each vaccination due date has passed without a vaccination documented.

Discussion

Dr. Ward believed the effectiveness and utility of reminder-recall systems, and thought that an ACIP recommendation expanded to high-risk groups including adults could prevent more mortality and morbidity. He asked if studies had been done in adult high-risk populations. Dr. Hoekstra was not aware of such, and agreed to check on them. Dr. Schoenbaum knew of many reminder studies for influenza vaccine, although perhaps not of other adult vaccines.

Dr. Snider commented that veterinarians and dentists find this strategy effective. Dr. Hoekstra agreed; particularly with the difficulty for patients to remember to return longer 2-6 months after an office visit, reminders are immensely important for both practitioner and patient.

Dr. Guerra advocated a central immunization registry to help track the population, particularly with the movement of patients from provider to provider. Dr. Hoekstra concurred but thought this a future issue; it was not now now included to avoid providing that as an excuse for noncompliance.

Dr. Fedson thought that a programmatic ACIP strategy to increase immunization should include adults as well as children, especially since a focus on children is not reflected in the document's title or the first paragraph. The effectiveness of Reminder/recall in boosting influenza vaccinations is well supported by the literature. Dr. Davis agreed that such studies on high risk and adult groups should be added to the statement.

Dr. Peter suggested approving the statement as it is and then finalizing it with additional information. The challenge is in its implementation, for which endorsement by AAP, AAFP, and ACP might have a greater impact than a single ACIP recommendation. However, Dr. Ward feared that such multiple endorsement could slow down the process, requiring cost assessments regarding the implications to standards of care. Dr. Halsey agreed. He would request this be put on the Academy's May agenda, and asked CDC to present the information.

VOTE: The was a unanimous vote in favor of this approach, with two members absent. In another vote to seek additional endorsement, Davis, Glode, Guerra, Modlin, and Sherrod voted in favor. Voting against were Ward and Schoenbaum, because the process could take too long and because the more difficult adult immunization issues require a more sophisticated reminder/recall system. The vote carried.

Dr. Snider suggested adding value to this statement by addressing how it could be implemented with the AAP and AAFP. Dr. Schoenbaum asked if the ACIP would be consulted about the adult immunization issues, and Dr. Davis thought that possible.

Dr. Zimmerman suggested dividing this up into two statements, one for children and another for adults, to be run through different organizations.

Dr. Hadler noted that this text was the last of three intended short statements by ACIP to endorse known-effective practices. NVAC had focused on this more than ACIP, and he was concerned that changing the statement's scope too much would duplicate their work. He noted that there was no representative from the NVP present at the time, and wished for their input. Nonetheless, ACIP's endorsement would give this prominence.

Dr. Fedson thought the statement fine as it was if the title specified childhood immunization. Dr. Hadler suggested that a statement at the end could read that Asuch strategies are also likely to work and should be used for adult vaccinations.@ However, since there was no rush for this statement, Dr. Ward preferred to address it definitively. He advocated an ACIP leadership role (rather than burying a sentence here and there) in how to increase immunization across the board. This would not compete with NVAC and would likely be well received.

Dr. Davis requested that the committee's return its comments to Dr. Hoekstra within two weeks. He anticipated that at least another sentence or two would apply these strategies to adults and people at high-risk, and the title would be reassessed. The document would them be returned to the committee within 45 days for their further comments. Dr. Snider added that it would be presented to NVAC at its next meeting to coordinate the science and policy involved, and to consider its implementation.

Rotavirus Vaccine Presentation

Dr. Roger Glass introduced an update on licensure data for the first rotavirus vaccine, which was submitted to the FDA in January 1997. A sample recommendation on this was developed for the ACIP. New analytical data on epidemiology and cost-benefit would be presented at the next meeting.

Dr. Joseph Camardo of Wyeth-Lederle Research reported that since the reassortant and tetravalent vaccines were developed by Albert Kapikian in 1986, 27 studies in over 8 countries had been conducted. The breadth of the research program was large, involving U.S. pediatricians, health centers and clinics, Native American reservations, Finnish well-baby clinics, and public hospitals in Venezuela, Thailand, Peru and Turkey. There were more than 147 investigators at over 320 investigational sites. Of 17,000 infants, 10,000 had received Rotashield; of those, 6000 had received three doses.

The properties of a useful vaccine are its easily administration to infants <6 months old, that it is well tolerated, prevents clinical manifestations of infection, reduces severe disease, shortens the clinical course of the disease and reduces the need for clinical interventions. Rotashield does so, as it prevents gastroenteritis due to rotavirus infection when given in three doses at 2, 4, and 6 months.

Dr. Camardo outlined the vaccine's construction, as well as four efficacy trials held during 1991-1995. Since the vaccine was studied during at least four different epidemics, its efficacy is not limited to a single circulating strain, and its study in different areas and populations demonstrates its broad applicability.

Rotasheild's immunogenicity was assessed by measuring serum IGA. A serologic correlate of protection was not known when the studies began, nor has it been identified. However, he could state that Rotashield raises the titer of IGA when compared with a placebo, and raises the

antibodies to all prevalent human strains. It achieved seroconversion across the board in the studies to IGA, the parent strain, and all four serotypes.

Dr. Margaret Reynolds of the U.S. Rotavirus Efficacy Group described the national multicenter trial of high-dose rhesus-human reassortant rotavirus vaccines. The design was a prospective, randomized placebo-controlled double blind study of 1278 infants aged 5-25 weeks in 24 U.S. centers. The children, aged about 2, 4, and 6 months of age, were equally randomized to receive three oral doses of either the placebo, monovalent or tetravalent serotype 1 rhesus human rotavirus reassortant. Her report emphasized the tetravalent vaccine, since that was licensed.

Concurrent routine vaccinations were permitted but not required. The surveillance for safety occurred from day 1 to day 5 after each dose. The efficacy period was two weeks after dose three through one rotavirus season. Gastroenteritis was defined as vomiting and/or three or more loose stools in 24 hours, and these families were called every week to remind them to report any such symptoms. The stools were tested for rotavirus by ELISA; those positive were serotyped for specific monoclonal antibody. Clinical severity of each episode was graded on a 20-point scoring system. Severe gastroenteritis was defined as >8 points. However, since a previous clinical trial indicated that <9 points was not clinically severe disease, a second cutpoint was added for analysis.

Dr. Reynolds outlined the safety results. There was no significant difference in fever, diarrhea or vomiting among the percentage of children who received tetravalent, monovalent vaccine or placebo over a five day period. There were some differing symptoms on individual post-vaccination days between vaccinees and controls. While such differences would be expected with 135 safety comparisons, all the reactions followed dose 1 or 2, and all occurred on day 3 or 4 post-vaccination, the incubation period for rotavirus. But the rates were very low, except for lots of runny noses. Four vaccinees and no controls were hospitalized for fever, vomiting, diarrhea, and stool positive for rotavirus a week post-vaccination. It could not be determined if this occurred from vaccination or random chance.

She then outlined the trials' efficacy results. There were 1205 episodes of diarrhea or gastroenteritis reported; stools were collected for 85% of those. The vaccine efficacy against all serotype for the monovalent vaccine was 54%, for the tetravalent vaccine, 49%. For serotype 1, it was 55% for monovalent versus 44% for tetravelent. But in serotype 3, it was 45% for the monovalent and 77% for the tetravalent, an important distinction for years when other than serotype 1 circulates, a common occurrence.

Both these vaccines' efficacy increased with increasing severity of disease, especially with the tetravalent vaccine. Against disease of any severity, the efficacy was 54% monovalent and 59% tetravalent; but for severe disease, 56% versus 68%, and for very severe disease, 69% versus 80%. A graph charted an almost linear increase of efficacy with increasing severity of disease.

On another table, Dr. Reynolds displayed efficacy against rotovirus by clinical parameters. There were no cases of dehydration in the tetravalent vaccine versus 13 cases in the placebo group. There were only two hospitalizations in the trial. She showed the cumulative percentage of rotovirus-positive episodes plotted against increasing severity score. This showed that children who had received the tetravalent vaccine and developed rotovirus disease had milder disease than the control children.

To determine the impact of rotavirus vaccination on gastroenteritis overall during the surveillance season, children were compared with episodes of gastroenteritis of all etiologies between the tetravalent vaccinees and controls. There were significantly fewer episodes among the tetravalent vaccinees; significantly fewer went to a physician or had dehydration.

Dr. Reynolds summarized that for there were no significant safety differences for vaccinated or control children in the incidence of symptoms over the entire surveillance period. There was a trend toward higher efficacy of the tetravalent than monovalent vaccine in serotype 3 disease and severe disease.

Dr. Camardo outlined all the other trials over five years, which showed consistently positive and higher efficacy against severe cases of rotavirus.

He began with the efficacy trials. In Finland, a blinded, randomized study was done of 2400 infants vaccinated in well-baby clinics at about 2,3, and 5 months. They began vaccinations in 1993 before the rotavirus season, and recruited infants during the season. A reduction of severe disease and hospitalization was shown for the endpoint, severe rotaviral gastroenteritis. The efficacy for severe rotavirus disease was 91%, and 68% for all disease. The vaccine was 100% effective regarding hospitalization, as no infants were hospitalized. He noted that a hospitalization reduction of only 50% would be very beneficial.

The Finnish study lasted more than two years, and a subset analysis was done of infants vaccinated before the first season and through the second. The efficacy carried over to the second season at a 68% rate. In the Native American study, 1185 infants in 8 clinics were vaccinated at 2, 4, and 6 months against rotaviral gastroenteritis. The overall efficacy was 52%, and 70% against severe disease.

Another study in a poor area of Caracas, Venezuela was conducted with the NIH, Wyeth and the WHO. About 2500 infants were vaccinated at 2, 3, and 4 months, with an endpoint of severe dehydrating diarrhea due to rotavirus. Rotavirus is endemic there, rather than seasonal. The efficacy was measured to 24 months of age, and showed severe disease reduced by 88%; dehydration by 75%; hospitalization by 70%; gastroenteritis >4 days by 71%. Efficacy against overall disease was 48%, and 50% against severe disease. Another measurement showed equivalent efficacy for breast-fed infants.

Dr. Carmado then outlined the safety data from the entire database. This database did not include the Finnish data, as the protocol was slightly different. The incidence of fever there

was slightly different for dose one, but equivalent for doses 2 and 3. Pooled data showed a statistically significant increase in fever after dose 1, but only a 1% increase in higher fevers (>39C). There were no febrile convulsions or long term sequelae; the fever predictably rose in day 3/4 and was gone by day 5. Adding in the placebo groups, they demonstrated similar incidence of diarrhea, vomiting and fever. They believe that their study participant numbers were large enough to accurately indicate the reactogenicity of the vaccine.

In the U.S., the vaccine will likely be given at 2, 4,and 6 months with DTP/Hib, polio IPV/OPV and perhaps others. They tested in placebo studies against DPT/Hib, and showed no differences between the placebo and Rotashield groups. For pertussis (5 different types of tests), DPT/Hib immunogenicity was not affected. Two doses of OPV were given concurrently with Rotashield and an equivalent antibody response developed (87% and 95% placebo/Rotashield) in percentage of antibody to all three serotypes. With three doses, the protective titer reached 100% in infants. There was no difference in percentage of antibody with one dose.

Dr. Camardo summarized the studies' results. After FDA approval, they recommended incorporating this vaccine into the vaccination schedule for infants. It was shown to be safe and well tolerated, is 80-95% protective against clinically significant cases of severe rotovirus and gastroenteritis, and 50-83% effective against all rotovirus gastroenteritis. If rotovirus disease emerges anyway, its duration and severity are reduced, as are dehydration and the risk of hospitalization or needed physician visits. It eliminated dehydration due to rotovirus in the U.S. multicenter study, and was shown in one study to be effective over two seasons. It is compatible with breastfeeding and can be given with DTP/Hib and OPV. It can be given as early as 6 weeks of age; and consistency of manufacture was demonstrated.

They concluded that ARotaShield is indicated for routine administration to infants at 2, 4, and 6 months of age for the prevention of gastroenteritis due to rotovirus.@ Dr. Camardo stated that this vaccine would be licensed by the next ACIP meeting.

Dr. Glass presented the draft recommendations on the rotovirus vaccine, which followed a discussion of the burden of disease and the trials' data:

(1)"… ACIP recommends that all children should be given three doses of rotovirus vaccine at 2, 4, and 6 months, as part of the routine schedule of childhood immunizations;
(2)the vaccine should be administered along with the DTP (or DTaP), Hib, OPV/IPV and hepatitis B vaccines;
(3)the vaccines can be administered to children who are being breast-fed;
(4)Until further data are available, children with known or suspected immunosuppression should not receive this live attenuated vaccine; and
(5)Premature infants should not receive this live attenuated vaccine."

The precautions and counterindications included (1) infants with hypersensitivity to any component of the vaccine (which were listed); (2) infants with known or suspected immune

deficiency disease and conditions (listed); (3) infants who live in households with persons known or suspected to have an impaired immune status; and (4) infants who have an acute illness, evolving a neurologic condition, persistent vomiting or diarrhea, or who have a temperature >37.8EC (100EF).

Discussion
Dr. Halsey clarified that the Redbook committee is reviewing this vaccine, but had not yet decided on any recommendation. Dr. Glode asked if the last recommendation (#5) was based on data not shown on this day. Dr. Glass responded that the role of maternal antibody in the first three months of life is not known, and there is very little data on neonatal children. He was not aware of any studies of premature children given vaccines. Dr. Glode was concerned about extending the recommendation that far because of the potential safety issues in a baby without sufficient maternal antibody. In those children, even fever and diarrhea could be significant adverse events.

Dr. Chin Le asked if there were efficacy data on two versus three doses. He noted that it would be difficult to administer three doses before rotavirus season to an infant born in October, and that two efficacious doses could cut the cost by a third. Dr. Glass reported the availability of some data on two doses given to children who did not complete the vaccine schedule. The study trials which gave single doses showed variable efficacy and low immunogenicity.

Their decision to recommend three doses was to allow consistency with the standard immunization recommendations. A study done with two doses showed it sufficient to produce antibody response, but the WHO suggested a 2,4, and 6 month schedule to coincide with the OPV schedule. Dr. Chen Le urged FDA to consider that.

Dr. Glezen asked if any interaction between wild and vaccine virus had been noted. Dr. Kopicky reported some episodes in Caracas where the vaccine and wild virus were concurrently shed. Although they have not yet found any gene exchange, he would not be surprised if that occurred. However, the wild strain found was similar to that of the vaccine, so he did not expect a super strain to emerge. They are still looking at other strains.

Dr. Ward learned that no premature infants were evaluated in the studies, as severe prematurity was cause for exclusions. He worried that there may be an innate contradiction between recommendations 4 and 5, and advocated waiting for more data before adopting these recommendations.

Dr. Anthony asked about detection of vaccine virus in recipients and spread to their contacts. Dr. Glass reported that there was no evidence of spread except in Venezuela, where both placebo and vaccinated children with rotovirus diarrhea had a low titer of vaccine strain in their stools only detectable by PCR analysis. Dr. Anthony asked the duration of shedding in recipients, and Dr. Glass responded that this depends on the test. PCR can detect it for a week or more.

Dr. Hadler thought it would be helpful to have an age or size cutoff for #5. Although mild or more severe adverse events may be possible, they may be warranted to provide greater protection in a more vulnerable population. That data would be helpful, as would more on simultaneous vaccination with routine vaccines.

Dr. Peter expected that more than one company has a rotovirus vaccine in development, and asked how interchangeability could be addressed with no correlate of protection. He also noted the need for ACIP to decide whether it would adopt the implied concept of universal immunization with this vaccine.

Dr. Modlin thought that the U.S. trial showed virtually no hospitalization in either the rotovirus vaccine or the placebo groups, but those hospitalized had one dose of vaccine. He asked why none occurred in the placebo group. Dr. Reynolds speculated that the study nurses probably prevented hospitalization by counselling the families on how to hydrate the children who developed diarrhea. Dr. Glass observed that even the U.S. placebo group was lower in expected hospitalizations. Aside from the active aggressive follow-up, the rarity of this severe disease in the U.S. probably also ensured low numbers for study.

Dr. Modlin asked about these vaccines' immunogenicity if given to a child with concurrent diarrhea. Dr. Glass reported a reduced immune response if OPV was given to a child with acute diarrhea, and expected a similar response here. That is why the precaution was inserted at the end of the recommendation. The same study should be done for rotovirus vaccine as was done for polio.

Dr. Modlin noted that there was virtually no effect on OPV seroconversion rates, but that there seemed a substantial difference for type 1 polio virus after two doses. He suggested a cautious approach to this, as past rotovirus studies had mixed results regarding polio immunization. It is a future issue requiring further investigation, but ACIP may want to suggest the use of IPV rather than OPV.

Dr. Davis suggested that ACIP work with the rotovirus study team, and requested that comments on this draft be submitted to Dr. Glass within 45 days. A work group representative of committee members, liaisons, CDC staff, vaccine companies and FDA would be formed.

Rabies Vaccination of Ferrets

Dr. Charles Rupprecht first reported that the VFC update for rabies vaccination is still under discussion by ASTHO and the CSTE Executive Committee. He also reported a lengthy process for physicians to access the vaccine manufacturers' indigent care program for those who could not afford post-exposure prophylaxis (PEP). Written approval for indigent care must be obtained prior to vaccine administration. To get this, the physician had to contact the company's toll-free number to request the vaccine and be interviewed about the patient's need. The company would then consider and decide if the patient met their criteria. This implied an

8-9 day lapse before the serum would be received by the physician -- one reason why the indigent care program is so little used in the U.S.

Dr. Rupprecht then advised the committee of emerging information on the issue of rabies in ferrets in the U.S. Only 22 cases of ferret rabies have been diagnosed to date, making them clearly not a major reservoir of the disease.

The problem arises in the conflict between ACIP's 1991 recommendation and the 1997 recommendation of the National Association of State Public Health Veterinarians (NASPHV). In 1991, ACIP recommended euthanasia of biting ferrets regardless of rabies vaccination. At that time, ferrets were considered exotic or wild pets, but now are considered domestic animals. Since then, a vaccine for ferrets has been licensed by FDA, and their popularity as pets has risen. There are now an estimated 8-12 million ferrets in the U.S., which health department regulations demand be euthanized after an exposure bite to humans.

The 1997 NASPHV recommendation now calls for a risk assessment. The appropriate response would depend on the management of the species, the circumstances of the bite (e.g., if provoked), the epidemiology of the area's rabies (epizootic or not), and the biting animal's history (e.g., health status). The current (1991) ACIP status was based on a focus on dogs and cats, and on their shedding period of 7-10 days before clinical manifestation of rabies. Rabies pathogenesis is complex, depending on the virus; equally important are variances in the epizoology, dose, strain, route, host status and species involved.

One study of the shedding period of ferrets has been completed, and work is underway on another. Adult ferrets of both sexes exposed to various rabies variants showed ranges of susceptibility. In one study of 51 rabies-inoculated ferrets, 37% succumbed over incubation periods ranging from 17-63 days. In another, only 8 (47%) of ferrets inoculated with the raccoon rabies variant produced a demonstrable virus.

So far, only ferrets inoculated with a raccoon variant have shown virus in their saliva as early as two days before onset. In a previous study of 33 ferrets injected with a skunk variant, none was found in the saliva. So besides route and dose, variant and species under study are critical considerations. Susceptibility differs depending on the variant in question, as does the ferrets' morbidity period.

The common clinical signs are predictive, but are not furious or aggressive ones; these are passive rabies symptoms, probably detected not by a veterinarian but rather by the owner noting a listless animal. Since that is the time the exposures are likely to occur, there is concern about the lack of obvious clinical signs on presentation.

Dr. Rupprecht summarized that the morbidity periods were similar in each group and averaged 4-5 days. Ferrets showed only moderate susceptibility to raccoon rabies virus. The most common clinical signs of rabies in ferrets are passive, and only two of 19 ferrets exhibited

aggressive behavior. Ferrets have various levels of susceptibility, but depending on the variant, virus is detectable in swabs as is done with dogs and cats.

Dr. Rupprecht hoped that the Morris Animal Foundation will support CDC's proposed study on the last major group of variants (silver-haired bats and others of epidemiological importance). If that occurs, Dr. Rupprecht should have bt the end of this fiscal year more coherent data to inform the recommendations on the shedding period of ferrets to exposed humans.

Discussion
Dr. Modlin asked how domestic ferrets, presumably housed in a cage, became exposed. Dr. Rupprecht reported that no vaccinated ferrets have been reported as succumbing to rabies. All the infected ferrets to date were unvaccinated, and those with histories were free-ranging and not kept according to recommended husbandry. Many ferrets are treated like cats, and like many dogs and cats in the U.S., are not strongly supervised.

Dr. Davis hoped the proposed studies of shedding are funded, to provide more information for a potential ACIP recommendation. This is a very sensitive situation, into which ACIP will enter with more data on hand.

Update on SV 40 Meeting
Dr. Kenneth? Peden of FDA reported on the SV40 DNA issue associated with polio vaccine. This became critical between 1992 and 1996, when papers described PCR detection of SV40 in various human tissues. The frequency of appearance of SV40 varied from 15-18%. But some other groups have been unable to detect SV DNA in tissues. Therefore, NIH convened a panel of experts in the field, funded by NCI, CDC, FDA and others.

Several questions were asked of the experts: what evidence existed that SV40 DNA is present in human tumors; what sensitivities existed in different labs; whether SV40 DNA was found in tumors of the same type; and how the laboratories controlled for PCR contamination. The second set of issues were serological: whether humans have SV40 antibodies; how good are the serological assays (e.g., did they cross react with common other polioviruses of humans); and whether there is any evidence of SV40 in humans before the vaccine. NIH hopes to use DNA and serology studies once they have been proven suitable. Other important questions were whether SV40 is an infectious agent for humans, and whether it is pathogenic in tumors.

Regarding the first set of questions, papers were presented with convincing evidence that SV40 is in a high proportion of coreoplexus tumors, as well as osteosarcomas and others. The presence in laboratory isolates of two or more of the 72 isolate elements indicated that this did not stem simply from contamination. Other researchers found SV40 sequences in a high proportion of epitheliomas, though whether they could be asbestos-related was not determined. It was concluded in this session that SV40 DNA is often found, but inconsistency between laboratories indicates a need for more study.

The second session addressed whether antibodies to SV40 DNA can be found in human sera. Dr. Peden summarized data from a comparison of populations which received IPV and OPV serum contaminated with SV40, to those who received neither. About 5% of human samples cross-reacted with SV40, but JCV and PKV were not assessed. Those who received IPV developed antibodies to SV40, but those receiving the OPV did not, though they shed it in their stool for a short time. It was concluded that due to the inadequacies of serological assays of SV40, it could not be determined if SV40 was in the population before the polio vaccines were introduced.

The third session summarized the mechanism of the transformation of the SV40 T-antigen. Rodents cells can be transformed by SV40, but human cells are refractory to the transformation, perhaps due to a location on chromosome 6. They are now looking whether mesotheliomas and osteosarcomas associated with SV40 have those lesions on chromosome 6.

The fourth session addressed the epidemiologic data as to whether those exposed to SV40-contaminated vaccine had increased risk of cancer. There was an overwhelming conclusion that there is no evidence for increased incidence of either general or specific cancers in those receiving the polio vaccines. Vaccine manufacturers reported their safety measures, and the British National Office of Standards and Controls reported evidence that vaccines from 1970 to 1990 were free of SV40.

Though conclusions could not be drawn, it was agreed that these questions should be pursued to resolve the questions posed in the beginning of the meeting. A mechanism was not decided, but work groups were considered. A panel of coded samples to test the laboratories' techniques is being considered, comparable to that used for reverse transcriptase activities. Also needed is development of an SV40-specific assay, and a standardization of PCR techniques. These discussions will be continued at scientific meetings.

Dr. Peden summarized that though the questions were not resolved, the discussion was useful in providing a more complete understanding of what the issues and problems are. It has certainly been demonstrated by the epidemiologic studies that there was no increase of risk.

Discussion
Dr. Chen added a few minor caveats to this reassuring data. There was one study of a hamster model which showed the same rare tumor type as found in humans. And, the Swedish study period may not have allowed the necessary long incubation periods needed by exposure to asbestos.

Meeting the Challenge of New Vaccines
Dr. Weniger noted that currently licensed vaccines can accomplish vaccination in a 2-month old with two injections, or four if separate vaccines are used. Licensure of a DtaP-Hib combination will provide an alternative three-injection option. But surveys indicate that even three injections are unacceptable to about 40% of parents and 60% of providers.

The immediate challenge is to select a subset "package" among types and brands, to reduce polypharmacy and provide an incentive for continuing innovation and competition in the vaccine industry. Such public sector choices will be made by CDC, the federal government, and state immunization programs, and by HMOs and other provider groups in the private sector.

The NIP's Vaccine Economics Initiative seeks to establish a rational, objective, and enlightened tool with which to choose among the vaccines. They are proceeding from a selection of vaccines based on the overall "best value" in economic terms, while recognizing as many as possible of the costs of disease prevention through immunization. Purchase price alone is only a part of these considerations. The program would reward the differences between vaccines to stimulate continuing innovation and competition by manufacturers. But in the end, the method of vaccine selection should be as transparent as possible.

Dr. Weniger illustrated a sample algorithm to select a vaccine. It involved policy decisions about product-related variables such as the price of vaccine (currently the only variable considered), the number of doses needed, the route of administration, the preparation time to administer a dose, the earliest age of full immunity, vaccine efficacy, the nature and frequency of adverse events, the requirements for refrigeration and transport, and the product's shelf life.

There are also associated cost data, more of which are needed. These could include the average cost of a provider visit, the injection itself, oral dosing and other routes, the cost of a health care assistant to prepare and administer the dose, that of the disease burden among partly immune persons, that of caring for adverse events, and the cost of spoilage and wastage after product expiration. These are all totaled to produce the total cost to protect against a specific disease with a specific antigen and product.

In current usage, for example, this operations research algorithm could assess the cost savings of Merck's three-dose Hib vaccine compared to other manufacturers' four-dose series. Another is the difference between ready-to-use DtaP-Hib vaccines versus those requiring preparation. Valuations of such differences can stimulate continuous product improvement, including studies of greater flexibility in suitable ages of immunization and the number of required doses. For example, the cost of the rotovirus discussed on this day was unnecessarily elevated 33% to match the OPV schedule.

With the Kaiser HMO, the NVP office and NIP are collecting information on the cost of injections and separate provider visits, and what parents/providers are willing to pay to avoid these. The algorithm's next step will assess the associated constraints (e.g., the joining of specific antigens in combination vaccines and the immunization schedule). Linear programming uses that data to examine the thousands of possible permutations to pick the one that minimizes the overall costs.

Dr. Robert Deuson, a health economist, explained how this operations research method could be applied to the economics of vaccines. To do so, he translated some of these challenges into

an economist's terms. The considerations in vaccine development include new vaccines, new combinations, and new packaging; new vaccine delivery options such as sequencing, scheduling, preparation and delivery, and compliance; and vaccine procurement factors such as cost, purchases, and choice of suppliers.

Operations research can help to inform decisions on such variables. This manner of addressing all components of the involved system has been used in wartime and to address such diverse current challenges as those in transportation scheduling, production, inventory management, and financial planning.

As an example of linear planning, Dr. Deuson used the manufacture of furniture involving three competitively priced brands using different process and having the same hourly labor costs. Their production variables were total labor and material costs; their constraints were the production shop hours available. The primary solution considers all these components to maximize the outcome.

He then applied operations research to vaccine selection. The objective may be to minimize vaccine procurement and delivery costs for, e.g., Hep-B, DTP, or Hib. This is subject to constraints such as the ACIP schedule recommendations, limiting the number of injections per office visit, and the available monovalent and combination products.

In setting up the formula to minimize vaccine costs subject to these constraints, related coefficients of objective function variables will be used. These can stem from the imputed costs shown by such cost identification studies as the described Kaiser work, or from econometrically estimated cost functions.

Operations research will then enable an assessment of the status quo in vaccine manufacturing, procurement and purchasing policies. It will guide the design of cost-effective immunization programs, and help forecast the impact of new immunization schedules and programs through sensitivity analysis and mixed integerlineal programming. In the end, it can help to reduce long-term health care costs and assist CDC in assessing new vaccine combinations and delivery technologies.

Subsequently, Dr. Chen discussed alternative solutions to multiple injections, which to date has rested in combination vaccines. While superficially attractive, this approach has its problems. The interaction of combined antigens is unpredictable with each new addition. The development costs are high for a stable combination, and the "desired" combination may not be affordable. Combinations involve problems of polypharmacy and overimmunization. And the merger of manufacturers is leading to monopolization which reduces competition, raises costs and may eliminate smaller producers.

An alternative to parenteral and oral routes could include nasal administration, but that involves logistical questions in a non-mass campaign, and the "all in one" immunization is a

very long term goal. The parenteral approach has proven immunogenicity and efficacy. There is discussion of DNA vaccines, but safety studies to allow public use will take some time.

Dr. Weniger then addressed the other available long-term solutions. One of these is to rethink parenteral vaccination, a system he termed archaic. The pain of delivery is proportional to the dose volume, but the rationale for a 0.5-1.0 cc standard injection was based the ability to accurately measure volume in a glass syringe.

There are several alternatives: to reduce the volume and concentrate the dose, or to develop a standard pre-filled cartridge which would allow the new jet injector designs. These could allow a multi-dose "magazine" of antigens to provide sequential or simultaneous administration. Supportive paradigms from other industries include the movie production firms' agreement on a standard cartridge for film. This still allows competition for quality of film and camera.

WHO and EPI have a similar problem in delivering safe injections, as they deliver more than 550 million injections per year. In the developing world, injection site abscesses are common, a major worry in areas with a high prevalence of HBV and HIV. Adequate sterilization requires fuel (e.g., kerosene, whose market value incites theft). The solution of disposable needles is not adequate for developing countries, where they are recycled rather than disposed. WHO is considering a tetanus and measles elimination campaign, which would impel a solution to these problems.

There are several potential advantages to jet injectors. These would require a minimal technology "leap", potentially reduce vaccine costs by fostering competition. The reduced vaccine volume dose can lessen pain and the risk of blood cross-contamination. Combination products would still be permitted, but medical waste and needle stick injuries would be reduced.

There has been a renaissance in jet injection technology with the recognition that the "needle and syringe" is an archaic delivery method. Demand is being primarily driven by the auto/pen injectors and for use in home parenteral administration. In addition, the widespread relative ignorance of an emerging immunization crisis is being met by planned CDC and WHO meetings.

Dr. Chen showed a single, pen-sized injector being marketed in England, which costs about 33-404 per device and delivers powder. A WHO steering committee on the development of jet injectors for immunizations will meet in March 1997. The focus for short-term needs is to develop a safe delivery device to avoid cross-contamination. A reusable jet injector is needed for multi-dose vaccine vials, particularly for developing country use. The mid-term need is a disposable injector for single-dose liquid vaccination. These have been cleared for drugs; what remains is to determine the market for vaccines. The long term issues would be to address the

development of powder, reduced volume injectors and to examine the synergies between vaccine and drugs in developed and developing countries.

Dr. Chen felt that although this is a theoretical approach, it warrants some exploration to resolve the current immunization problems.

Discussion
Dr. Glode asked if the program had explored patches for transcutaneous vaccine absorption. Dr. Chen was not aware of any such studies.

Dr. Davis thanked all the presenters for the information provided to the committee. He called for public comment, specifying that this is also welcome in the course of the meeting. None was forthcoming. With no further discussion, the meeting adjourned at 3:30 P.M.