DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

Advisory Committee on Immunization Practices

June 27-28, 2007

Atlanta, Georgia

Record of the Proceedings

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
June 27-28, 2007
Atlanta, Georgia

Minutes of the Meeting

The Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC), National Center for Immunization and Respiratory Diseases (NCIRD) convened a meeting of the Advisory Committee on Immunization Practices (ACIP). The meeting was held on June 27-28, 2007 at CDC's Global Communications Center in Atlanta, Georgia. The list of participants is appended to the minutes as Attachment 1. [Note: the list only includes persons who introduced themselves for the record, presented, made public comments, or registered prior to the meeting.]

Day One, June 27, 2007

WELCOME AND INTRODUCTION

Dr. Abramson welcomed attendees to the June 2007 ACIP meeting. Dr. Pickering introduced several international visitors, including Dr. Christine Ding-Ping Liu, Director of the Vaccine Center for the Centers of Disease Control in Taiwan, and members of the Turkish Adult Immunization Advisory Board. In addition, he welcomed the new liaison representative from Canada's National Advisory Committee on Immunization Practices, Dr. Joanne Langley from the Division of Infectious Diseases of the Department of Pediatrics, the Canadian Center for Vaccinology at Dalhousie University in Nova Scotia, and thanked Dr. Monika Naus, who was replaced by Dr. Langley. He noted several people who could not attend the meeting, including ACIP member Dr. Robin Womeodu. Dr. Geoff Evans was not present, but Dr. Indira Jevaji took his place; Dr. Norm Baylor was not present, but Dr. Florence Houn attended on his behalf; Dr. Wayne Hatchey from the Department of Defense was represented by Dr. Ted Cieslak; and neither Dr. Paul McKinney from the Association of Teachers of Preventive Medicine nor Dr. David Salisbury from the Department of Health in London were able to attend. Finally, Dr. Pickering announced that Dr. Sam Katz had been awarded a 2007 Pollin Prize for his contributions to pediatric infectious diseases and vaccine development, particularly his role in developing the measles vaccine with Nobel laureate Dr. John Enders.

Dr. Pickering noted that the CDC web site had been revised and that the ACIP site is updated frequently with the current version of the meeting agenda, meeting minutes and presentations, ACIP recommendations and other ACIP activities (http://www.cdc.gov/vaccines/recs/acip/default.htm).

Dr. Pickering explained that the goal in appointing members to the ACIP is to achieve the greatest level of expertise while minimizing the potential for actual or perceived conflicts of interest. To summarize conflict-of-interest provisions applicable to the ACIP, as noted in the Policies and Procedure manual, members of the ACIP agree to forgo participation in certain activities related to vaccines during their tenure on this committee. For certain other

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interests that potentially enhance a member's expertise while serving on the committee, CDC has issued limited conflict-of-interest waivers. Members who conduct clinical vaccine trials or serve on safety data monitoring boards may serve as consultants to present to the committee on matters related to those vaccines. However, they are prohibited from participating in the deliberations or votes of the committee on issues related to those specific vaccines. Regarding other vaccines of an affected company, a member may participate in discussions with the proviso that he or she abstains on all votes related to the vaccines of that company. ACIP members who may have a potential conflict of interest should make it known by disclosing all of their vaccine-related financial interests and work.

Dr. Abramson noted that the terms of four members, including himself, would expire on June 30th. He presented those members with a certificate of appreciation and thanked them for their many contributions to ACIP over the years. Dr. Ban Allos, Dr. Janet Gilsdorf, and Dr. John Treanor all spoke briefly about what working on the committee had meant to them.

Dr. Abramson added his appreciation of the incredible talent found among the ACIP committee members, the liaisons, and particularly the full-time CDC staff. He then pointed out some of the accomplishments he had witnessed, starting in 1999, when thimerosal was becoming an important topic and rotavirus vaccine was causing problems over the issue of intussusception. Influenza vaccine has gone to an age-based rather than a risk-based recommendation and appears to be moving toward a universal recommendation for all children, if not for adults. Progress has been made on the ACIP-HICPAC joint statement on immunization of healthcare workers, but that needs further emphasis.

In 1999 the committee voted to stop the use of rhesus rotavirus vaccine in the U.S., with the understanding that the risk-benefit ratio differed tremendously from that of developing countries. However, manufacturers developed other safer rotavirus vaccines, which will be introduced into developing countries in the next few years.

The committee approved varicella zoster recommendations that now include the use of a routine second dose and will be looking at its impact on decreasing the occurrence of varicella disease and fixing the age shift in the occurrence of the disease. The recommended use of MMRV, despite occasional vaccine shortages, will help decrease the number of injections that children need. The herpes zoster vaccine is aimed specifically at older adults and is now recommended for routine use.

The development of an adolescent platform was a major move forward, especially use of a conjugated meningococcal vaccine. Tdap was recommended for use in adolescents as well as adults and healthcare providers. The pertussis component of this combination vaccine will have more impact now that it is being used in adolescents and adults. The impact of the human papillomavirus vaccine, the first vaccine specifically created as an anticancer vaccine, will be great; the issue of how to implement it remains to be solved.

The recommendation for use of hepatitis B vaccine in adults has been expanded, and perhaps should be expanded further. The hepatitis A recommendation also has been expanded to include all children 12 months of age and older, which has already shown a marked impact due to the high-risk part of the recommendation. The committee has continued to make recommendations based on good science and the best interest of the United States, without regard to cost. However, there is much to be done in the area of vaccine financing.

Dr. Pickering thanked Dr. Abramson for all his work as chair of ACIP and as a

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member of the influenza work group. He praised Dr. Abramson's intellect and insight, as well as his compassion and integrity – particularly his concern for children and adults.

Dr. Abramson asked committee members to state any conflicts of interest.

Dr. Allos: no conflicts.

Dr. Baker: no conflicts.

Mr. Beck: no conflicts.

Dr. Gilsdorf said she was an independent safety monitor on an NIH-sponsored vaccine trial for which she receives no compensation.

Dr. Hull: no conflicts.

Dr. Lett: no conflicts.

Dr. Lieu: no conflicts.

Dr. Morita: no conflicts.

Dr. Neuzil: no conflicts.

Ms. Stinchfield: no conflicts.

Dr. Treanor said he was doing clinical trials of influenza vaccines for Protein Sciences and for Merck, and had laboratory support for influenza work from GlaxoSmithKline.

Dr. Morse: no conflicts.

Dr. Abramson said he had no conflicts, but was on an NIH data safety monitoring board for the use of oseltamivir in children less than one year old.

Dr. Pickering announced that there would be four new members joining the ACIP beginning July 1st and a fifth new member would be appointed in the very near future. The new members are Dr. Lance Chilton, a pediatrician with the Young Children's Health Center and Professor of Pediatrics at the University of New Mexico in Albuquerque; Dr. Paul Cieslak, Medical Director of the Oregon Immunization Program, Oregon State Public Health Division and Clinical Assistant Professor in Public Health and Preventive Medicine and Iinfectious Diseases at the Oregon Health and Science University; Dr. Allen Craig, State Epidemiologist from the Tennessee Department of Health, trained in family medicine; and Dr. Janet Englund, Associate Professor of the Division of Pediatric Infectious Diseases at Children's Hospital, the University of Washington and Fred Hutchinson Cancer Research Center in Seattle. As of July 1st, the new ACIP Chair will be Dr. Dale Morse, who has been an ACIP member since July of 2005. Dr. Morse is Director of the Office of Science and Public Health at the New York State Health Department. He will be assisted by Dr. Carol Baker, who will serve as the Vice Chair. Dr. Baker has been an ACIP member since July of 2006 and is Professor of Pediatrics, Molecular Virology, and Microbiology at Baylor College of Medicine.

HEPATITIS A VACCINE: POSTEXPOSURE AND TRAVEL PROPHYLAXIS

Dr. Tracy Lieu, ACIP, WG Chair
Dr. Ryan Novak, CDC/NCHHSTP/DVH

Dr. Lieu began with a reminder that the ACIP had considered draft recommendations for postexposure prophylaxis for hepatitis A in February and at that time it was apparent that more clarification and discussion were needed. An ACIP hepatitis working group was formed and was able to reach consensus on the wording of the recommendations with the hepatitis

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group within CDC. For postexposure prophylaxis for persons 12 months to 18 years old, vaccine is preferred to immune globulin (IG). For persons 19 to 40 years old, vaccine is preferred to IG. For persons over 40 years old, IG is preferred although vaccine can be used if IG cannot be obtained. Lastly, for patients with chronic liver disease, those who are immunocompromised, and children less than 12 months old, IG should be used.

These recommendations also affect the recommendations for hepatitis A travel vaccinations. Based on new data on vaccine effectiveness postexposure, the recommendation is that the first dose of vaccine at any time before travel should protect most healthy persons. Another recommendation is to add immune globulin for high-risk groups who are traveling in less than two weeks to areas of high transmission and to use IG for persons less than 12 months old or who cannot receive vaccine.

Dr. Novak summarized the conclusions from the February ACIP meeting when these data were first introduced, as well as the activities of the hepatitis work group. In February, Dr. John Victor presented the results of a clinical trial comparing efficacy of hepatitis A vaccine and immune globulin after exposure. This was followed by a discussion of these data and the policy implications of using hepatitis A vaccine alone postexposure. The work group reviewed the available data with respect to vaccine age groups and patients with chronic liver disease and other underlying medical conditions. It considered patient characteristics associated with more severe outcomes, response to vaccine, and the risk of transmission in common scenarios where postexposure prophylaxis is given in the U.S., and then drew on the experiences of those countries currently using hepatitis A vaccine post exposure.

Potential benefits of being able to use vaccine include long-term protection, ease of administration, acceptability, and availability. There is currently only one U.S. supplier of immune globulin, and the cost of IG has risen considerably over the last five to ten years, making it similar to that of hepatitis A vaccine. A single adult dose of IG is now about $20, and the pediatric vaccine dose under government contract is about $12. The adult dose is about $19. Another benefit of being able to use hepatitis A vaccine is that it brings U.S. practice in line with many other countries that recommend vaccine as postexposure prophylaxis.

In the randomized clinical non-inferiority hepatitis A vaccine postexposure trial conducted in Almaty, Kazakhstan, 4,524 households or day-care contacts aged 2 to 40 years were enrolled. Contacts had been exposed to index cases within two weeks after the index case symptom onset and had no history of hepatitis A or receipt of hepatitis A vaccine or IG within the last six months, chronic liver disease, or contraindications to vaccine or IG. There was a 1-to-1 randomization within households or day-care centers to receive vaccine or IG within two weeks after the index case symptom onset. The primary outcome was clinical hepatitis A among contacts that met the following three criteria: Positive for IgM anti-HAV, ALT level at least twice the upper limit of normal during an episode of illness with no other obvious cause, and symptoms consistent with viral hepatitis.

The results of that study indicated that the efficacy of hepatitis A vaccine was similar to that of IG, i.e., the noninferiority criterion was met. Because of the study design, the point estimate for vaccine efficacy required an assumption about IG efficacy. Assuming 90 percent IG efficacy, the point estimate of vaccine efficacy was 86 percent with a 95 percent confidence interval of the upper bound of the relative risk of 76 percent. If 85 percent IG efficacy was assumed, the point estimate of vaccine efficacy was 80 percent with the upper

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bound of 64 percent.

Despite showing statistical noninferiority, the proportion of outcomes among vaccine recipients was slightly higher than among IG recipients, however the difference was small. Putting this in context, the risk of hepatitis A among vaccine recipients was never more than 1.5 percent greater than among IG recipients. This study provided evidence consistent with many previous studies that IG might attenuate clinical illness when given after exposure.

Looking at clinical endpoints by age, most cases were among children, so that was where the most inference was made, however the estimates for adults were similar. For the primary endpoint, 26 cases of laboratory-confirmed hepatitis A occurred among vaccine recipients and 18 occurred among IG recipients, yielding a relative risk among vaccine versus IG of 1.32. The one-sided 95 percent confidence interval upper bound of relative risk was 2.3, which was well within the prespecified margin of 3.0.

When stratified by age, the risk of hepatitis A was slightly higher among adults than in children in both the IG and vaccine groups. The point estimate of the relative risk for adults was very similar to that among children, but because of the relatively small number of adult participants, this stratified analysis has low power, so the confidence interval is wide. Similar findings were found when considering all suspected hepatitis A cases.

After considering these results, the consensus of the work-group members was that there was sufficient evidence to support equivalency of vaccine and IG in both children and adults 40 years or younger. Because of the advantages of vaccine and equivalence to IG, the work group decided to state a preference for vaccine in this age group: *"For healthy persons age greater than or equal to 12 months to 40 years, hepatitis A vaccine at the age appropriate dose is preferred to IG because of vaccine's advantages, including long term protection and ease of administration."*

At the time the Almaty study began, hepatitis A vaccine was not yet licensed down to 12 months in the U.S., thus children aged 12 to 24 months were excluded from the study population. The work group decided to include 12- to 23-month-olds in the vaccine recommendations. There is no evidence to suggest persistence of maternal antibody past 12 months, and the immunogenicity of the vaccine at 12 months is similar to that of 24 months. Currently, vaccine is licensed for use from 12 months in every country with a hepatitis A vaccine immunization program. Finally, current ACIP recommendations include this age group for pre-exposure vaccine use.

Unfortunately, results of the current study and previous information cannot answer all questions about how hepatitis A performs postexposure. First there is the question of age. Eligibility was restricted to age 40 and under in the Kazakhstan study. Most of the cases and study participants were fairly young, which is not surprising, given the epidemiology of hepatitis A in a country like Kazakhstan. All adults over age 40 are immune to hepatitis A, as are many young adults. No additional data are available to support preference for vaccine in these risk groups.

Considering the clinical characteristics of reported hepatitis A cases by age in 2005 received through the National Notifiable Disease Surveillance System (NNDSS), the severity of hepatitis A disease increases with increasing age, as evidenced by the proportion of hospitalizations and deaths due to hepatitis A. Because of the absence of data about vaccine performance in persons older than 40 years and the risk of hepatitis A increasing with age, the work group made the following recommendation: *"For persons greater than 40 years, IG is preferred because of the absence of information regarding vaccine performance and the more*

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severe manifestations of hepatitis A in this age group. Vaccine can be used if IG cannot be obtained."

The next population addressed was persons who were diagnosed with chronic disease, immunocompromised, and people with other medical conditions. The Almaty study excluded patients who reported a diagnosis of chronic liver disease based on the concern about the increased severity of hepatitis A. It did not explicitly exclude people with other medical conditions, but in general the study population was young and healthy. Patients with chronic liver disease or other chronic medical conditions are known to have poorer response to vaccine pre-exposure. In addition, patients with chronic liver disease have a higher risk of more severe disease outcomes.

Dr. Novak then presented available data with respect to immune response to a single hepatitis A dose in selected populations. Among HIV-infected patients, the three relevant studies report a wide range of seroconversion after one dose of hepatitis A: from 10 percent to 78 percent. Hepatitis A vaccination is recommended for patients with chronic liver disease, so there has been a fair amount of interest in studying the immunogenicity of the vaccine in these patients. In the three published studies of immunogenicity in these patients, the percent positive at four weeks ranges from 63 to 93 percent. It appears that the response rate is lowest in patients with decompensated cirrhosis. Finally, a few studies in liver and kidney transplant patients showed a much lower percent positive at four weeks.

A number of studies have indicated that the risk of severe outcomes from hepatitis A is higher among people with chronic liver disease (CLD). In a recent analysis of national death certificate data from 1999 to 2004 among 511 hepatitis A deaths, 229, or 45 percent, of deaths included a CLD-related ICD-10 code. The median age was 55 among CLD-related deaths and 69 among non-CLD-related deaths. Because of the suggestion of a suboptimal response to hepatitis A vaccine and the increased risk of severe hepatitis A outcomes in CLD patients, the work group decided to leave the current recommendation for IG in these groups: *"IG should be used for children age less than 12 months, immunocompromised persons, persons who have been diagnosed with chronic liver disease, and persons for whom vaccine is contraindicated."*

The work group also reviewed the risk of transmission of hepatitis A virus and the common scenarios in which postexposure prophylaxis is given in the U.S. The most common setting for IG use as a postexposure prophylaxis currently is among household and other close personal contacts. Outbreaks in childcare centers used to require IG, but now these outbreaks are rare. In these settings, secondary attack rates of 15 to 30 percent are common, with higher rates of transmission occurring from infected young children than from adolescents and adults. This is probably the setting in which the risk of transmission is highest.

Another common scenario is after exposure to an infected food handler. Based on surveillance data, 3 to 7 percent of reported hepatitis A cases are food handlers. About 5 percent of food handlers worked while they were infectious and were felt to pose a transmission risk, i.e., people who might have been exposed to this food handler should be notified. However, the majority of food handlers do not transmit to patrons, as attack rates are generally low. In the context of these public notifications, an average of 350 IG doses per episode were administered. But there is a very broad range, and thousands of people received IG. The ability to use a vaccine might be quite beneficial in these circumstances.

Thus the working group recommended the following language: *"Decisions to use vaccine or IG should take into account patient characteristics associated with more severe*

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manifestations of hepatitis A. Additionally, the magnitude of the risk of hepatitis A virus transmission from the exposure should be considered."

At the last meeting the committee heard about postexposure policies of Canada, the UK, and other European countries. The work group looked for new data, and reconsidered available data with respect to the experience in Canada and the UK. In Canada, vaccine without IG is the preferred method of postexposure prophylaxis, while IG continues to be used for infants and the immunocompromised. The work group reviewed one report of possible breakthrough infections, but it was found to be a transmission chain involving outbreaks in several child day-care settings. It also tried to get additional information about the rationale of the U.K. recommendations, which limit vaccine to exposures within the previous seven days and IG for exposures greater than seven days or involving people older than 50 years with cirrhosis or chronic HBV or HCV infections. But the data available to inform these recommendations were very limited.

In summary, vaccine offers a number of advantages over IG, and the flexibility to use vaccine in some circumstances would be beneficial. Available data suggest that vaccine is efficacious postexposure, but not all populations were studied. Pre-exposure immunogenicity data suggest that there are suboptimal responses to vaccine in persons with chronic liver disease and other chronic medical conditions. Any recommendation the committee might make about the ability to use vaccine would be an off-label use, as it is not approved through FDA for this indication. Additional data are not likely to be forthcoming, and additional studies would be logistically difficult. So the committee needs to balance the practical public health implementation considerations against the limitations of the available information.

Among the materials provided to the committee was a copy of the current postexposure prophylaxis ACIP statement to provide background, as well as the new recommendations for postexposure prophylaxis. This document is meant to be a stand-alone MMWR 'notice to readers' with links to and from the current ACIP hepatitis A statement, thus it contains an introduction to the recommendation language to provide background information to the reader as to what changes were made and their rationale. These recommendations were clarified by appending the language from the current statement concerning common settings in which postexposure prophylaxis is given in the U.S. The only language change is the substitution of *"IG or hepatitis A vaccine"* for *"IG."* In addition, the committee was provided with new travel recommendations for timing of pre-exposure vaccine dose.

The draft language for postexposure prophylaxis with hepatitis A vaccine is as follows: *"Persons who recently have been exposed to hepatitis A virus and who previously have not received hepatitis A vaccine should be administered a single dose of vaccine or IG as soon as possible. Information about the relative efficacy of vaccine compared to IG postexposure is limited, and no data are available in persons aged greater than 40 years or those with underlying medical conditions.*

"Therefore, decisions to use vaccine or IG should take into account patient characteristics associated with more severe manifestations of hepatitis A, including older age and chronic liver disease. Additionally, the magnitude of the risk of hepatitis A virus transmission from the exposure should be considered."

The next paragraphs deal with specific groups. *"For healthy persons age greater than or equal to 12 months to 40 years, hepatitis A vaccine at the age appropriate dose is preferred to IG because of the vaccine's advantages, including long-term protection and ease*

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of administration.

"For persons greater than 40 years, IG is preferred because of the absence of information regarding vaccine performance and the more severe manifestations of hepatitis A in this age group. Vaccine can be used if IG cannot be obtained.

"IG should be used for children age less than 12 months, immunocompromised persons, persons who have been diagnosed with chronic liver disease, and persons for whom vaccine is contraindicated.

"Persons administered IG for whom hepatitis A vaccine is also recommended should receive a dose of vaccine simultaneously with IG. For persons who receive vaccine, the second dose should be administered according to the licensed schedule to complete the series. The efficacy of IG or vaccine when administered greater than two weeks after exposure has not been established."

Discussion

Dr. Allos asked whether adults over 40 who received IG as postexposure prophylaxis could also receive the vaccine and, if so, whether that should that be made part of the recommendation.

Dr. Neuzil was concerned about not having comparative randomized-controlled data on persons over 40. Looking at the hospitalization rates from the 15 to 39 group and the 40 to 59, the real jump seemed to occur at 60 and over. Thus she wondered what data would be sufficient to recommend vaccine above the age of 40 or whether there were immunogenicity data in immunocompetent healthy people between 40 and 59 that could be used as a bridge. Dr. Novak replied that there were not enough data to inform that decision currently, nor are there any data in the pipeline. Dr. Neuzil added that if immunogenicity data would be helpful, those are relatively easy and inexpensive studies to do.

Dr. Barbara Kuter reported that Merck did look at immunogenicity in individuals greater than 40, and in fact their dosage is different from individuals less than 40 because the response with the 25-unit dose was not as good. They moved to the 50-unit dose, for which there are data in individuals over 40, and seroconversion rates are comparable to those less than 40.

Dr. Lett expressed concern about having so many age stratifications, which complicates the public health response when clinics have to rapidly vaccinate hundreds or thousands of people, particularly for restaurant exposures. The data about lack of transmission to patrons were interesting in that respect. Dr. Novak said those data were partly why the recommendations state a preference for IG , but that vaccine could be used if IG was not available. With situations such as restaurant exposures where the risk of transmission is believed to be low, vaccine could be used in older individuals. The worry is that older individuals with potentially underlying medical conditions that predispose them for more severe manifestations really need to receive IG. Dr. Abramson suggested that since serologic bridging data would not be published until October, that specific issue could be voted on October and put in the final document.

Dr. Hull asked whether only a single dose was being recommended postexposure. Dr. Novak clarified that a single dose was sufficient for postexposure prophylaxis but the second dose should be administered according to the licensed schedule to complete the series. Dr. Baker pointed out that exposed individuals who had had the vaccine series would not need postexposure prophylaxis. Dr. Abramson added that having had proven hepatitis A should

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also preclude needing vaccine.

Dr. Treanor asked whether having been involved in an outbreak or other situations where prophylaxis was required, such as travel, would identify one as being at higher risk of subsequent exposures to hepatitis A than the general population. In other words, why would it matter whether they got the second dose? Dr. Treanor responded that it was just a question of logic.

Dr. Schuchat noted that this country had already moved to a universal hepatitis A strategy, so the issue of high risk and low risk has changed because of the safety, effectiveness, and long-term protection of the vaccine.

Dr. Hull said he was confused by the statement indicating that the intensity of exposure should be considered in making the decision for IG versus vaccine. Dr. Novak replied that the recommendations needed to be seen in context. They include definitions for different settings where hepatitis A postexposure is often used in the U.S. and this provides some guidance as to the magnitude of risk. Household or close contact might be considered high risk versus the low risk of transmission in the case of an exposure to an infected food handler. Dr. Hull asked whether someone with high-risk exposure should get IG or vaccine. Dr. Novak explained that the magnitude of risk question pertains only to those individuals over 40 years of age, for which there are no efficacy data. For those people, one might use IG if there was a household or close-contact situation and vaccine if it was an exposure to an infected food handler, except where contraindicated. The recommendations are clear that persons at higher risk for more severe complications of hepatitis A should be receiving IG. Dr. Hull agreed with the context idea, but still felt the recommendation should be more explicit.

Dr. Morse asked whether one would be able to get data on safety and efficacy for people over age 40 from other countries. Dr. Abramson said he felt most people would feel comfortable with serologic data as a bridge.

Dr. Treanor pointed out that the statement actually says one should take into account the magnitude of the risk of transmission independently of the magnitude of the severity of disease and asked how that would be used to decide between the vaccine or IgG. Dr. Novak commented that the most common interactions with the state health departments were around helping decide the risk to those exposed. Dr. Bennett added that the decision was complex, but that it came down to whether or not to give prophylaxis and the statement needed to be simpler for the people giving the vaccine.

Dr. Bennett asked a related question about the timing of immune globulin and vaccine and whether immune globulin can be given after the vaccine if it is not available initially. Dr. Novak replied that that the work group had not specifically addressed this issue, but the important thing would be to get some kind of postexposure intervention put in place right away if it was a high-risk exposure. Dr. Hull pointed out that the language should clarify that this applies only to high-risk individuals. Dr. Pickering restated the previous question: If a person gets vaccine and then gets immune globulin, will the immune globulin inactivate the hepatitis A vaccine such that the whole series would have to be repeated? Dr. Bell responded that when vaccine and IG are administered simultaneously, the data indicate that the geometric mean concentrations from vaccine are somewhat lower. Other situations also suggest that when antibody is given, immunogenicity is reduced. Nonetheless, the antibody concentrations are still quite high, so there is no problem giving vaccine and IG at the same time. She speculated that there might be fewer problems giving IG after vaccine than giving

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IG with vaccine.

An unidentified speaker commented that the stratification seemed rather complicated and suggested having one broad recommendation, with a guide for practitioners regarding the quality of evidence for one age group or another.

Dr. Bell said she appreciated the concern about bridging immunogenicity data, but felt the committee would need to be clear about what pre-exposure data would be relevant to the performance of vaccine postexposure. There are few data available with respect to pre-exposure immunogenicity in people older than 40. One could argue that the relevant information is response at two weeks after the first dose of vaccine, and that available evidence showing seroconversion at four weeks after a single dose of vaccine with differences in geometric mean concentrations in older versus younger adults might not be adequate bridging immunogenicity data to confidently recommend the equivalence of vaccine versus IG in people older than 40. She added a word of caution about whether bridging immunogenicity data in people over 40 would address the concern about the performance of vaccine in that age group. It is not as simple as stating that since there is 90 percent seroconversion at four weeks, vaccine works as well as IG postexposure.

Dr. Lieu asked whether the immunogenicity data presented for the older-than-40 age group in February were the same as that from Merck. Dr. Bell replied that the Merck data were not published, and that the data she presented used the previously licensed GlaxoSmithKline formulation, which is a three-dose series at half the dosage per shot, so they were not helpful for looking at the postexposure performance of a single dose at double. One published study explicitly looked at less than age 40 versus over 40 and at two weeks after the first dose; there was a difference in the percent positive between people less than 40 and older than 40, as well as a difference in the GMT. By four weeks, that difference closed up to about 70 percent positive at two weeks after one dose of vaccine in people older than 40, as opposed to 90-plus percent positive. One could argue that this is relevant when considering using vaccine in a postexposure setting. Dr. Kuter confirmed that the amount of data at the two-week time point was limited. The information at four weeks is much more substantial.

Dr. Abramson asked whether anyone still wanted to look at those data and to see if the recommendation as far as age cutoff should be changed. When there was no response, he felt the committee was ready to vote on the recommendation to preferentially vaccinate one-year-olds to 40-year-olds and to use IG in the other settings.

Vote

Dr. Morse made a motion in favor of the recommendation, which Dr. Baker seconded.
Dr. Morse: yes.
Dr. Treanor: abstain.
Ms. Stinchfield: yes.
Dr. Neuzil: yes.
Dr. Morita: yes.
Dr. Lieu: yes.
Dr. Lett: yes.
Dr. Hull: yes.
Dr. Gilsdorf: yes.
Mr. Beck: yes.
Dr. Baker: yes.

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Dr. Allos: yes.
Dr. Abramson: yes.

Dr. Abramson reminded the committee members they would have a chance to look at this document before it was finalized and published and make comments about specific issues. Dr. Baker commented that, with respect to the over-40 group, it would be nice to get convincing data because that would make it easier operationally for everyone.

Travel Recommendations

Dr. Novak presented the travel recommendations, which needed to be revised to bring them in line with the changes just voted on. The current ACIP travel recommendations for preexposure protection against hepatitis A state that travelers departing in more than four weeks should receive vaccine. If departure is within two to four weeks, then IG may be given for optimal protection. IG is recommended for children less than 12 months old, and persons allergic to or electing not to receive vaccine.

The work group found that the Almaty study findings and the new postexposure recommendations were relevant to preexposure vaccine use among at-risk travelers. The data regarding postexposure use suggest vaccine administered any time prior to departure should adequately protect most travelers, but may not be generalizable to all populations.

The actual recommendation begins, *"The first dose of hepatitis A vaccine should be administered as soon as travel is considered. Based on limited data showing equivalent postexposure efficacy of IG and vaccine among healthy persons aged less than or equal to 40 years, one dose of single-antigen hepatitis A vaccine administered at any time before departure may provide adequate protection for most healthy individuals.*

"However, no data are available for other populations or other vaccine formulations. For optimal protection, older adults, immunocompromised persons, and persons with chronic liver disease or other chronic medical conditions traveling to an area where risk of transmission is high less than two weeks after the initial dose, may also be administered IG, but at a different anatomic injection site. Completion of the vaccine series according to the licensed schedule is necessary for long-term protection."

There is no change in the rest of the recommendation, which reads as follows: *"Travelers who elect not to receive vaccine or are less than 12 months of age or allergic to a vaccine component should receive a single dose of IG, which provides effective protection against hepatitis A for up to three months. Travelers whose travel period is greater than two months should be administered IG, and administration must be repeated if the travel period is greater than five months."*

Discussion

Dr. Mobeen Rathore noted that there was a time period of greater than four weeks for first line, then another one of two to four weeks. He thought just saying ‘less than four weeks’ would be easier for people in the field, unless there were specific differences between two and four weeks.

Mr. Beck asked about people who have liver disease or are immunocompromised, as covered in the previous recommendation. Dr. Novak said they should receive IG.

Vote

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Dr Abramson asked for a motion to accept the travel recommendations. Dr. Hull so moved and Dr. Gilsdorf seconded the motion.

Dr. Allos: yes.
Dr. Baker: yes.
Mr. Beck: yes.
Dr. Gilsdorf: yes.
Dr. Hull: yes.
Dr. Lett: yes.
Dr. Lieu : yes.
Dr. Morita: yes.
Dr. Neuzil: yes.
Ms. Stinchfield: yes.
Dr. Treanor: abstain.
Dr. Morse: yes.
Dr. Abramson: yes.

VFC Vote

Dr. Calugar reminded the committee that the vaccine-specific resolutions for the Vaccines for Children Program, or VFC, are revised any time there is a new or updated ACIP recommendation. For the just-approved postexposure use of hepatitis A vaccine, there were changes relating to eligible groups, but the recommended hepatitis A schedule and dosage intervals remained unchanged. A new section was incorporated in the VFC resolution, *"Recommendation for use of hepatitis A vaccine for postexposure prophylaxis,"* which is similar to the just-approved ACIP recommendations.

The first paragraph includes general information about administering immune globulin and a statement about limited relative efficacy data when administrating hepatitis A vaccine compared to IG post exposure. The complex picture of a person's health condition, including age and chronic liver disease, as well as the magnitude of the risk of hepatitis A virus transmission, should be considered in this decision process.

Specifics are needed for postexposure prophylaxis in selected special categories. Immune globulin should be used in healthy persons younger than 12 months of age, immunocompromised persons, persons who have been diagnosed with chronic liver disease, and persons for whom vaccine is contraindicated. For healthy persons aged 12 months through 18 years, hepatitis A vaccine at the age-appropriate dose is preferred to immune globulin because of the vaccine's advantages, including long-term protection and ease of administration.

The last paragraph emphasizes the importance of administrating hepatitis A vaccine simultaneously when IG is used for postexposure prophylaxis. For persons who receive vaccine, the second dose should be administered according to the licensed schedule to complete the series. The efficacy of IG or vaccine when administered later than two weeks after exposure has not been established.

Dr. Abramson asked for a motion to approve the VFC resolution. Ms. Stinchfield so moved and Dr. Baker seconded the motion.

Dr. Lett: yes.
Dr. Hull: yes.
Dr. Gilsdorf: yes.

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Mr. Beck: yes.
Dr. Baker: yes.
Dr. Allos: yes.
Dr. Abramson: yes.
Dr. Morse: yes.
Dr. Treanor: abstain.
Ms. Stinchfield: yes.
Dr. Neuzil: yes.
Dr. Morita: yes.
Dr. Lieu: yes.

Discussion

Dr. Amy Middleman from the Society of Adolescent Medicine asked if TWINRIX was recommended as one of the hepatitis A formulations that can be used postexposure on travel, even though there are no data. Dr. Bell clarified that the wording on TWINRIX for the travel recommendation was unchanged from the previous statement. The antigen content of hepatitis A in TWINRIX was only available for adults and it is half of that in the single-antigen vaccine. Since there is no information about the use of TWINRIX for postexposure prophylaxis, TWINRIX is not included in the hepatitis A vaccine postexposure prophylaxis recommendation. The VFC vote is the postexposure vote, not the travel vote, and so it has to do with hepatitis A vaccine, not TWINRIX. But TWINRIX currently is in the VFC language for preexposure prophylaxis for hepatitis A for 18-year-olds.

VACCINE FINANCING

Dr. Grace Lee, Harvard Medical School, Boston Children's Hospital
Dr. Walter Orenstein, Emory Vaccine Center
Dr. Guthrie Birkhead, New York State Department of Health, NVAC

Underinsured Children

Dr. Lee presented research looking at gaps in vaccine financing for underinsured children in the U.S. The number of vaccines routinely recommended for children and adolescents has more than doubled over the past decades; in 1985 there were vaccines to prevent seven diseases, whereas now there is protection against 16 infectious diseases. However, the cost has risen over 20-fold, from about $45 in 1985 to almost $1200 to fully vaccinate a female child in 2006. Many of the newer vaccines, such as HPV vaccine, rotavirus vaccine, meningococcal vaccine, and PCV7, are significantly more expensive.

In the U.S., financial coverage of childhood vaccines depends on whether or not a child has insurance and if so what type of insurance. Most private health insurance plans cover the cost of recommended vaccines, but some privately insured children are underinsured for vaccines. In those cases, patients either pay out-of-pocket or are referred to the public sector to receive publicly purchased vaccine from the state. Even that depends on whether a state has adequate 317 or state funding available. Publicly insured children (e.g., Medicaid) and the uninsured receive vaccines free of charge through Vaccines for Children (VFC).

The private sector accounts for 46 percent of vaccine purchase. Two federal funding sources, VFC and 317, account for 43 percent and 6 percent of the total vaccine purchase in

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the U.S., respectively, and state funding contributes to about 5 percent.

VFC is a federal entitlement program linked to ACIP, so when ACIP votes to include a vaccine the funding must be provided to purchase vaccine for eligible children, including the uninsured, Medicaid insured, American Indian or Alaskan natives, and the underinsured, but only if they are served at a federally qualified health center (FQHC) or a rural health center (RHC). Unfortunately, there are a limited number of these centers, so access is not readily available to all. In contrast, 317 funding is a discretionary annual appropriation that can be used for both children and adults.

As the number and cost of vaccines increases, VFC funding increases accordingly. In 2007, nearly $2 billion will available for vaccine purchase from VFC funds. However, 317 funding has remained level, which means additional funding for new vaccines is not available for those who depend on 317 funding, such as the underinsured.

After the VFC program came into effect, there were three different types of state vaccine financing policies: universal, VFC enhanced, and VFC only. VFC-eligible children can receive vaccine in the public sector, in the private sector, or in FQHCs or RHCs. Underinsured children can receive vaccine in the public sector or the private sector. Fully insured children typically receive vaccine in the private sector.

In universal-purchase states, all vaccines recommended by ACIP are given to all children in all settings. In VFC-enhanced states, all vaccines are provided to VFC-eligible children and underinsured children in the public sector and the private sector, but not to insured children. In VFC-only states, all vaccines are provided to VFC-eligible children, but underinsured children in the public and private sectors do not necessarily have access to vaccines unless there happens to be adequate 317 or state funding available.

Historically, vaccinating underinsured children was not a problem because many of the vaccines were inexpensive and there was adequate 317 funding. The gap began to widen in 2000 when the pneumococcal conjugate vaccine was recommended for use. The addition of PCV7 actually doubled the cost of immunizing a child. Even though PCV7 was covered by VFC, many states could not cover it for other children, resulting in the creation of two new vaccine financing policies: universal select and VFC-enhanced select. The universal-select and VFC-enhanced-select states could provide some but not all vaccines to the underinsured, whereas they could provide all recommended vaccines to VFC-eligible children, including PCV7.

The objectives of the two-phase study presented by Dr. Lee were to describe the variation among states regarding access to new vaccines for underinsured children and to identify barriers to state implementation of new vaccines. In the first phase, one-hour qualitative telephone interviews were conducted with nine state immunization managers from November to December of 2005. States were chosen to include different types of vaccine financing policies. Phase 2 was a national survey; those not previously interviewed were sent written surveys and had one-hour semi-structured phone interviews. Surveys and interviews included questions about the status of the implementation of new vaccines, barriers encountered, and any changes in their vaccine financing policy.

The overall response rate was 89 percent; 48 of 50 state grantees participated in Phases 1 and 2 and two of six city grantees participated in Phase 2. The immunization program managers had been in their positions from six months to 27 years, with a median of five years. Fourteen percent of grantees were considered universal, 12 percent were universal select, 20 percent were VFC-enhanced, 16 percent VFC-enhanced select, and 38 percent were

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VFC only.

There have been many changes regarding state vaccine financing policies since 2004. In general, states found that they needed to restrict their policies further, in part because of the number of new vaccines approved. Two states went from universal to universal select, five states went from VFC-enhanced to VFC-enhanced select, and three states went from VFC-enhanced select to VFC only. Interestingly, one state temporarily went in the other direction because they were able to secure state funding to purchase of Prevnar for the underinsured. However, they expecte to go back to VFC-enhanced select as soon as new vaccines became available.

States and cities were asked whether they were able to provide vaccines to the underinsured in the private sector; 35 percent of underinsured children could not receive varicella vaccine in the private sector, 50 percent for Prevnar, nearly 70 percent for Menactra, 50 percent for Tdap, and 56 percent for hepatitis A. Approximately half of underinsured children could not be vaccinated by their regular provider unless they could pay out of pocket. These underinsured children would typically be referred to the public sector.

When program managers were asked if they were able to provide vaccine for underinsured children in the public sector, nearly 40 percent of programs were unable to supply Menactra to those children. Nearly 15 percent were unable to supply Prevnar and hepatitis A, and 4 to 5 percent of the states were unable to supply Tdap or varicella. This is a significant concern because the public sector has been a safety net for these vulnerable children. Many public health practitioners voiced discomfort about turning away children who could not afford to pay for new vaccines.

Questions about barriers to implementation in the underinsured population were directed at states or cities that were not able to implement these vaccines for all underinsured children. Barriers cited included limitations on 317 funding and insufficient state funding, by which they meant they could not secure additional state funds for new vaccine purchase or, more commonly, their states had no money for any vaccine purchase.

Finally, program managers were asked about strategies used to address limitations in vaccine financing. Twenty-seven states had limited provider vaccine choice as a way to purchase the least expensive vaccine and be able to buy more vaccine. Twenty-five states received additional annual state appropriations to augment their budgets and thirteen states had expanded the designation of FQHCs or RHCs. Nine of 32 states with adult vaccination programs had to decrease the amount of adult vaccine purchased in order to assure enough money to purchase childhood vaccines. Four were fortunate enough to have had some health-plan appropriations and one state billed insurance companies for vaccines given to insured children in the public sector.

Those 13 states that expanded the designations of FQHCs or RHCs essentially increased the number of sites where underinsured children could receive VFC vaccine, which increased the number of underinsured children considered VFC eligible. Nine states have been able to designate some public VFC providers as FQHCs or RHCs. Three states have designated all public VFC providers so that underinsured kids could receive vaccine anywhere in the public sector and one state was able to designate all private and public VFC providers as FQHCs or RHCs, so underinsured children could receive all vaccines in either the public or the private sectors.

The study found that the current vaccine financing system was increasing the gap for underinsured children in the U.S. Given the estimate of about 14 percent of underinsured

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children in the U.S., about 3.9 million children are unable to receive Menactra in the private sector and another 1.1 million underinsured children are unable to receive Menactra in the public sector. Limitations in 317 and state funding are clearly contributing to this gap. State immunization program managers are finding creative solutions to try to address limitations, but expanded access through funding and/or legislation is needed to protect this increasingly vulnerable population.

Discussion

Dr. Hull asked what the birth cohort size was, to put the number of children unable to get Menactra in context. Dr Lee replied that there were usually 4 million children in a U.S. birth cohort. She added that there was an increasing number of high-deductible health plans or catastrophic health insurance plans, which do not necessarily cover the cost of preventive care, so this may increase the proportion of underinsured.

Mr. Phil Hosbach of sanofi pasteur commented that the fact that 27 states had limited provider choice was not a new phenomenon; it has existed since the implementation of the VFC program. From this manufacturer's perspective, it is a public health policy that stifles competition and innovation. He added that it was useful to know the number of children not being covered for different vaccines by state, since they vary in size, scope and socioeconomic status.

Mr. Beck asked whether the gap could be expressed in terms of dollars. Dr. Lee replied that the calculation for Menactra would be $83 times the 1.1 million children who could not receive vaccine in the public sector. If one were to consider the 15 percent that were unable to receive Prevnar or hepatitis A, the total could easily reach $100 million. Dr. Schuchat added that CDC submitted a report to Congress about unmet needs in the underinsured and the cost of vaccine purchase had an estimated dollar figure for vaccines that were not reaching the underinsured.

Dr. Schaffner noted that HPV vaccine was not included in this estimate. Dr. Lee explained that HPV vaccine had just been introduced at the time of the study and many states had not yet implemented it. This will of course increase costs. Dr. Schaffner also pointed out that insurance that does not cover vaccines is not health insurance and that the study ended at the 19th birthday. Adult vaccination is also a concern.

Dr. Temte of the American Academy of Family Physicians commented that just because private insurers cover vaccine does not mean that private providers will be fully reimbursed for the cost of vaccine. For those involved in VFC, there are a lot of regulations around reimbursement and many private physicians are no longer willing to incur the costs. Dr. Abramson added that even human papillomavirus vaccine was being implemented in stages. The fact that VFC is an entitlement does not mean everybody has the money to implement the full recommendation.

Dr. Rodewald said that the Office of Management and Budget had provided sufficient funding to implement VFC for HPV. After 3 or 4 months of HPV implementation and availability of the contract, all of the state programs and all of the urban-area grantees had begun the HPV vaccine. Any limitations would relate to the degree to which a state wants to launch a catch-up campaign and variation in the amount going to adults. About a month ago, approximately 5 million doses of the vaccine had been sold and the VFC program had purchased about 60 percent of those doses.

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AMA/AAP Immunization Congress

Dr. Orenstein shared information from an Immunization Congress sponsored by the American Academy of Pediatrics and the American Medical Association, which focused on concerns about the need to remove financial barriers to access, particularly for newly recommended vaccines. The first day was devoted to financing of vaccines recommended for children, within existing legislation as well as potential new legislation. Attendees included private providers, medical societies, public health societies, insurers, employers, manufacturers, and representatives from government at the federal, state, and local level. Nine recommendations were made, which have been under consideration by the National Vaccine Advisory Committee Vaccine Financing Working Group.

There was consensus on a number of points. Stakeholders supported universal access to all ACIP-recommended vaccines without financial barriers, although it was recognized that just removing financial barriers was not sufficient to ensure high immunization coverage. The private and public sector collaboration in vaccine delivery should be maintained. Through the VFC and other efforts, an army of private providers has been enlisted to decrease vaccine-preventable diseases by immunization. The medical home can add more medical benefits to children than vaccines alone, so vaccination of children by private providers ought to be supported. The best way to assure continued private-sector participation is to assure some reasonable return on that investment beyond costs.

There was consensus that vaccines are different from most other preventive measures. Vaccinees receive direct protection, but because the vast majority of vaccine-preventable diseases are spread person-to-person, vaccination also indirectly protects other members of society. Solutions need to solve problems in every state, otherwise some states may become reservoirs for disseminating diseases to other states. Problems include under-insurance, inadequate or non-timely reimbursement, costs for vaccine ordering, storage, handling and paperwork, and the actual administration of vaccines. Unfairness of Medicaid reimbursement for administration was another big concern, with a range from $2 to more than $18.

The first working group recommendation was to work with federally qualified health centers and rural health clinics to delegate authority to public health clinics to serve underinsured children through the Vaccines For Children program. This decreases the pressure on the need for increased 317 appropriations and moves children from discretionary funds to entitlement funds. It also offers a safety net for referring underinsured children to public clinics for vaccines if other solutions to underinsurance are not found. All stakeholders represented at the meeting supported this effort, including manufacturers, provided it did not decrease the private sector market. Recent data from the Association of State and Territorial Health Officials indicate that 22 of the 64 immunization grantees have now implemented this delegation authority, including sixteen states, four urban areas, and two territories.

The second recommendation was to obtain as soon as possible the actual cost of delivering vaccines in private practice settings, using gold-standard methods so that all stakeholders, including CMS, business groups and insurers, could accept the information as valid. Input from these stakeholders should be obtained prior to initiating the study and the AAP and AAFP could use that data to educate insurers and advocate for better reimbursement rates. Providers indicated that their number-one concern was inadequate administration fees, not vaccine fees. They also felt that the medical societies should advocate with insurers to have contracts that covered changes in mid contract, such as vaccine price increases or new vaccines added to the schedule.

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A third recommendation was that the medical societies should work with manufacturers and distributors to obtain more favorable terms for payments for vaccine inventories. This is a major cash outlay, especially for smaller practices and for new vaccines. Solving this issue should be in the interest of the manufacturers and, if necessary, could be built into pricing.

A fourth recommendation was that medical societies work with the AMA to better define all of the components that go into CPT codes for vaccine and vaccine administration.

A fifth recommendation was that the National Vaccine Advisory Committee Vaccine Financing Working Group examine the potential role of tax credits for insurers and/or employers in eliminating underinsurance. The group felt there were not yet enough details to endorse such a recommendation, but it could be a positive incentive.

A sixth recommendation was to convene a working group of key stakeholders, including manufacturers, to determine whether some form of universal federal vaccine purchase or funding should be pursued. This option has been vigorously opposed by the vaccine industry in the past, but it might be designed in such a way as to gain their support.

The seventh recommendation was that the societies should obtain data from the Centers for Medicare and Medicaid Services that led to the current influenza administration fee and use that data to advocate at the state level for enhanced Medicaid reimbursement. There has not been sufficient publicity given to the tremendous variation in Medicaid reimbursement rates for administration, and the data from Recommendation 2 should be used to advocate for higher rates.

Recommendation 8 dealt with the cost of obtaining and administering combination vaccines, compared to individual vaccines. If they are shown to be more costly, there should be better reimbursement for combination vaccines.

The last recommendation was that the American Academy of Pediatrics and the American Academy of Family Physicians should collect data on best business practices to minimize vaccine and vaccination costs and disseminate them to their members.

NVAC Financing Working Group

Dr. Birkhead presented an update from the National Vaccine Advisory Committee Vaccine Financing Working Group. New vaccines added to the schedule and new recommendations have created a crisis in the delivery system. However, the problem is not readily visible because there has been no resurgence of vaccine-preventable diseases due to failure to vaccinate and morbidity from the diseases prevented by the new vaccines may not yet be recognized as a problem.

NVAC has a long history of looking at vaccine finance issues. In 2006-2007, a working group was charged with obtaining information from stakeholders on the challenges in creating optimal approaches to vaccine financing in both the public and private sectors and their impact on access; establishing a process for selecting and addressing two to three topics per year; developing specific targeted policy options in these areas; and presenting the findings and policy options to the full NVAC for discussion. Members of the working group included a number of NVAC members, as well as representatives from insurance, pharmaceuticals and academia.

The primary focus in the first year was childhood immunization. In the public sector, although vaccine is available through the Vaccines For Children program, administration fees are a problem. The Medicaid administration fee is very inadequate and the base rate has not

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been updated since 1994. Uninsured children are eligible for VFC vaccine, but there is no mechanism to supply an administration fee. However, providers who participate in VFC cannot turn anyone away for inability to pay. The 317 program has not kept pace with the new vaccines that have come along.

In the private sector, providers are stressed in terms of the cost of maintaining an inventory. It becomes a cash-flow problem, along with loss of vaccines due to power failure or other reasons. There are concerns on the insurance side about the adequacy of reimbursement for vaccine costs and/or administration costs.

The working group obtained input from the various other NVAC subcommittees and stakeholders and commissioned a number of surveys to obtain data on the actual impact at the practice level. There are also other studies of cost of vaccination in process. Members of the working group attended the AMA-AAP vaccine financing congress. CMS is represented on the working group, and has helped the group understand the current system of Medicaid and Medicare reimbursement for vaccination. Individual vaccine manufacturers will be interviewed to gain their perspective, and something similar is planned for insurers.

Dr. Birkhead reported on two studies commissioned by the working group. The first was an assessment of charges and reimbursement for vaccines and administration fees in private practices. The purpose was to determine the range of prices paid for childhood and adolescent vaccines, the administration fees charged, and the reimbursement paid by three large insurers. Thirty practice managers were surveyed by telephone, from five non-universal purchase states, medium, small, and large, with metropolitan and non-metropolitan areas. Results are expected in the fall.

The second study looked at private provider attitudes regarding vaccine financing and to what extent they influence their willingness to adopt new vaccines. This is a cross-sectional survey through the mail of a random sample from the AMA master file. Results are anticipated by the fall as well.

Meanwhile, work has begun on a draft of a white paper laying out the issues and making some recommendations. There is overall agreement on the goal: to ensure universal access to all vaccines recommended by ACIP for children and adolescents without financial barriers, and there are a number of conclusions. One is that the current public and private sector mixed-financing system for purchase of pediatric and adolescent vaccines has the capacity to deliver the currently recommended vaccines but it may not assure access to all children and adolescents without financial barriers. Financial incentives can play a major role in strengthening the system to deliver current as well as future recommended vaccines.

There appear to be wide variations in vaccine costs and reimbursements to providers. It is not clear that CPT codes take into account such factors as the need to enter data in the vaccine registries, time for parental counseling and discussion, maintaining reminder systems, and insurance policies against catastrophic loss of vaccine.

The group felt that HRSA and CDC should encourage federally qualified health centers and rural health clinics to work with their local public health departments to serve underinsured kids who cannot be served at the federally qualified health centers because of lack of access or availability. The Association of State and Territorial Health Officials is already working with states around this point.

The maximum allowable reimbursement rates for administration in the Medicaid program should be re-examined. Once those rates are set, states need to contribute maximally to the vaccine administration fee and then draw down federal dollars to create the full

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administration fee. CDC should collect data on actual non-vaccine costs of vaccinating in private practices, using a method that is accepted by the major stakeholders and passes muster with CMS and insurers, so that it can potentially form the basis of the new administration fee amounts.

Medical and other relevant societies should work with the AMA to be sure that the CPT codes used for billing contain all necessary elements. Medical societies should collect data on best-business practices to help practices design their work load.

Vaccines may be recommended by ACIP in the middle of an insurance policy cycle, and so provider and insurance contracts should allow for increases in new vaccines or increases in existing vaccines mid contract. Vaccine manufacturers and third-party distributors should work with providers to reduce financial liability for initial inventories of new vaccine. There should be a mechanism to increase Section 317 funding when new vaccines become available and mechanisms to utilize the 317 funding to support administration fees.

NVPO should convene key stakeholders, including manufacturers and insurers, to talk about these issues in light of data from the surveys and other studies. The idea is to look outside the box and find solutions that would be mutually agreeable to all parties. For example, is there a way to design a federal vaccine universal purchase that has not been thought about yet, perhaps around a voucher system?

Regarding next steps, the practice and cost survey along with the draft white paper will be submitted to NVAC for consideration and potential adoption. Discussions will continue around the administration fees and Medicaid, to either increase those or improve state participation. Another option is to look at the Medicare influenza administration rate and see if that can be adopted in the Medicaid setting. Vaccine economic evaluation projects are encouraged. Finally, there will be a stakeholders meeting in the winter or early next year.

Discussion

Dr. Lett asked whether anyone had thought about how to identify and address the ERISA problem. Dr. Birkhead replied that it had come up in the beginning. Self-Insured plans or ERISA plans are not regulated through state insurance departments, so it is more of a third-rail issue. Dr. Orenstein added that there has been legislation in the past that offered to open up ERISA, but it never went anywhere. It would be important to know how big the underinsured problem actually is. Old IOM estimates ranged from about 5 percent of the birth cohort up to about 13 or 14 percent. More recent data indicate about 7 percent.

Dr. Rodewald commented that vaccines and vaccine coverage constitute a relatively small proportion of the total healthcare cost, so point estimates are difficult to obtain. They are not included in most surveys of insurance coverage. However, the point estimates from the IOM seemed to hover somewhere around 10 to 11 percent. The National Immunization Survey has added an insurance module that will include adolescents and help obtain underinsurance information. The 2001-2002 module was in the 10 to 11 percent range as well.

Dr. Freed, as chair of NVAC, emphasized that this was all only draft language, which has not been approved by the working group. Once the full NVAC receives the recommendations from the working group, there will be a process of deliberation, which includes comments from federal agencies, the public, and the members themselves. NVAC has no statutory authority to enforce its recommendations; its role is to make specific

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recommendations to the Assistant Secretary for Health and stimulate public debate. Then people can use those recommendations in their own way.

Dr. Abramson asked if there was any sense about what the Undersecretary of Health might do. Dr. Gellin replied that the Assistant Secretary for Health was following the progress of this working group and got regular reports, so the good news was that people are listening to the debate.

PROPOSED REVISIONS TO THE ADULT IMMUNIZATION SCHEDULE

Dale Morse, ACIP WG Chair
Gina Mootrey, CDC/NCIRD, ISD

Dr. Morse explained that the work group's initial task was to add zoster to the adult schedule, but then members asked how they could actually promote and increase immunizations in this population and make the adult schedule more user friendly and consistent with the childhood and adolescent schedule. Potential future activities include revising healthcare worker recommendations and having focus groups review the Medical and Other Indications schedule. The hope is to publish this recommended adult immunization schedule in October 2007, which would correspond with a number of activities to promote adult vaccines, then incorporate the adult immunization recommendations into the next general recommendations for simplification, and eventually look at the adult immunization schedule for HIV-infected persons.

Dr. Mootrey went over the changes made to the schedules and the footnotes. The proposed age-based schedule for 2007 and 2008 was presented. The bar for HPV vaccine has been shortened to show that it only goes through age 26. The bar for varicella vaccine is now yellow throughout. The previous one had yellow for 19 to 49 years and purple for 50 to 64 years, pending zoster recommendations. The zoster vaccine bar is yellow for those 60 years and older. The yellow bar wording has been changed from "age requirements *and* lack of evidence of immunity" to an "*and/or*," so that this schedule would apply if one had age requirements and/or lack of evidence of immunity. Wording has been added giving a reference to the ACIP recommendations and the extent of available data. The URLs for the ACIP recommendations were updated and a note was added that meningococcal vaccine is covered by the injury compensation program.

Dr. Mootrey then presented the proposed revisions to the Medical and Other Indications schedule 2007 and 2008. The working group is proposing a revision to the title of this table, to indicate that the vaccines mentioned do not all have a specific recommendation, but that there is no contraindication and they may be given for these different groups. Mention is made that meningococcal vaccine is covered by the Vaccine Injury Compensation Program. The column for the immunocompromising conditions has been shortened and a footnote added because of the increasing number of conditions. To make things simpler, the immunocompromising conditions column is now adjacent to the HIV column. Because of indications for several of the vaccines, specifically varicella and MMR, the HIV column was split, based on CD4 count.

The chronic liver disease column used to have recipients of clotting factor concentrates as a risk group. Since that now only applies to hepatitis A vaccine, it has been taken out of the column heading but remains in the footnote for hepatitis A vaccine.

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For influenza vaccine, there is now a specific indication that TIV or LAIV can be given to healthcare workers, and there is now a yellow bar as opposed to a purple bar for the asplenia column. For meningococcal vaccine, the table indicates that one or more doses could be given, depending on various risk indications.

Zoster vaccine was added, with a contraindication for pregnancy, immuno-compromising conditions, and HIV CD4 count less than 200. However, Dr. Mootrey said she had just attended a meeting of the DHHS-IDSA work group on revising the guidelines for prevention and treatment of opportunistic infections in HIV-infected persons, where it was felt that it would not be appropriate to indicate any kind of recommendation for zoster vaccine in HIV-infected individuals, regardless of CD4 count, since there are no data on safety, immunogenicity or efficacy in those individuals. There will be data in about a year from an ongoing study. Currently there is a yellow bar for other risk groups, but Dr. Mootrey proposed leaving that portion blank until there could be further discussion.

There were some general changes to enhance the footnotes, based on the harmonized-schedule discussion last year. There is a lot of explanatory language in these footnotes, particularly to describe the indications for use of vaccine. Contraindications are noted by the red bars on the schedule. Several of the vaccine footnotes contained language about contraindications during pregnancy, and that language was removed for those vaccines. For each of the footnotes, a URL has been added that links directly to the vaccine-specific ACIP statement.

The Tdap footnote has been revised to highlight the general statement regarding replacing only one Td with Tdap, just by reordering the footnote wording. The pregnancy language in HPV was taken out and language was added to indicate that HPV vaccine is not specifically indicated, based on the medical conditions mentioned in the Medical and Other Indications table.

At the opportunistic infection meeting mentioned earlier, the group did not want to give the impression that HPV vaccine was actually recommended for HIV-infected adults, even though it is not contraindicated. The footnote in the schedule also indicates that efficacy and the immunogenicity may be lower in certain persons. The new language for HPV says, *"HPV vaccination is not specifically recommended for females with medical indications described in the table 'Recommended Adult Immunization Schedule by Vaccines That May Be Indicated for Adults Based on Medical and Other Indications.' Although, because it is not a live virus vaccine, it can be administered. However, the immune response and vaccine efficacy might be less than that in persons who are immunocompetent or who do not have the described medical indications."*

MMR also had the contraindications language for pregnancy, and that has been removed.

The varicella footnote has been revised to indicate the use of single-antigen varicella vaccine. A phrase regarding an epidemiologic link to a laboratory-confirmed case has been added as a requirement for evidence of immunity in a healthcare-provider diagnosis of a mild or atypical case, and pregnancy language has been removed.

For pneumococcal vaccine, to be consistent with the Medical and Other Indications schedule heading, chronic alcoholism and chronic cardiovascular disease have been added to the text. CSF leaks was deleted from the immunodeficiency column and added to the footnote text. In the footnote for revaccination with pneumococcal vaccine, the listing of the multiple immunodeficiency conditions has been deleted.

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For hepatitis A vaccine, the schedules for the two single-antigen vaccines have been clarified. Single-antigen formulations should be administered in a two-dose schedule, and the specific vaccine based on which schedule was being used has been added. For hepatitis B, persons who receive clotting factor was removed as a risk group. For meningococcal vaccine, the footnote now clarifies that persons who remain at increased risk as opposed to high risk for infection may be indicated for revaccination.

A new footnote has been added for herpes zoster vaccine stating that the vaccine is recommended. *"A single dose of zoster vaccine is recommended for adults 60 years and older whether or not they report a history of herpes zoster and persons with chronic medical conditions may be vaccinated unless the contraindication or precautions exist for their condition."* In the next iteration, more wording may be added.

A new footnote was added to address the growing list of immunocompromising conditions. It says that inactivated vaccines are generally acceptable and live vaccines are generally avoided when there are immune deficiencies or immune-suppressive conditions. For guidance relating to specific conditions, refer to the general recommendations, giving the URL and the specific pages and the table that describes immunocompromising conditions.

Discussion

Dr. Gilsdorf said that the inclusion of "recommended" leaves the impression that everything in the yellow bar is a recommendation for the use of these vaccines, but for chronic disease indications, HPV and Zostavax are not recommended. She suggested adding a different color or texture to those yellow bars that indicate that it is acceptable to use it, but not specifically recommended. Dr. Baker added that if that were done, one would have recommend Tdap in pregnancy, which the ACIP does not do.

Dr. Hull asked if people over 60 should get zoster vaccine rather than varicella. Dr. Mootrey replied that they would not if they have never had varicella. Dr. Hull added that the footnote on the yellow bars on both tables should be re-examined regarding the addition of "or." For example, one would not recommend zoster for healthcare workers younger than 60.

Dr. Neuzil expressed confusion about the bars for HIV and zoster or HPV, since they did not seem to reflect existing ACIP recommendations. Dr. Mootrey explained that the new language for HPV was consistent with ACIP recommendations because, for HIV-infected individuals, it is neither recommended nor contraindicated. Zoster vaccine is not specifically recommended, but it may be considered. Dr. Neuzil recommended pulling out the zoster statement if there had been no specific discussion on CD4 count and HIV.

Dr. Schuchat thought that when ACIP considered the zoster statement, HIV studies were ongoing. Although there is a lot of interest among the HIV providers and patients in getting this vaccine, more information will be forthcoming and perhaps ACIP should wait to make a full statement. A second issue was an inconsistency in the varicella upper-age group. Providers might be confused whether to give varicella or zoster or both if the patient is 65. One of the footnotes talks about evidence of immunity to varicella being 'born before 1980', so that it would not make sense to have this upper-age group.

Dr. Treanor thought that the issue about whether to screen people for evidence of prior immunity to varicella before giving them zoster vaccine had come up and the committee had decided that that was not necessary. But if it was known that someone was not immune, they should receive varicella vaccine. In another discussion, since there is only a small number of HIV-infected individuals who are 60, the issue was not so much the recommendation but

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whether it will be considered a contraindication. He also recalled a discussion of the fact that varicella vaccine is relatively safe in individuals who are immunosuppressed, including those with advanced HIV, and that HIV with a CD4 count of over 200 is not a contraindication in the FDA label.

Dr. Pickering observed that the recommendation for MMR says it can be given to HIV-infected children with CD4-positive counts above 15 percent. Varicella can be given to that same group, but MMRV is not recommended. The zoster vaccine has 14 or 15 times the amount of varicella, and a recommendation with no data is worrisome. Dr. Treanor added that this was a vaccine being administered to people who were already immune to the vaccine virus.

Vote

Dr. Abramson asked whether the committee was comfortable voting on the recommended schedule, given that the comments and suggestions would be dealt with. Dr. Hull moved to accept, realizing there would be minor modifications per the discussion. Mr. Beck seconded the motion.

Dr. Lieu : yes.
Dr. Morita : yes.
Dr. Neuzil: yes.
Ms. Stinchfield: yes.
Dr. Treanor: yes.
(Dr. Abramson noted that clarification was needed whether Dr. Treanor could vote. Dr. Pickering said he would find out and correct the minutes accordingly.)
Dr. Morse: yes.
Dr. Abramson: yes.
Dr. Allos: yes.
Dr. Baker: yes.
Mr. Beck yes.
Dr. Gilsdorf: yes.
Dr. Hull: yes.
Dr. Lett: yes.

PROPOSED REVISIONS TO THE CHILDHOOD-ADOLESCENT SCHEDULE FOR 2008

Dr. Julie Morita, ACIP WG Chair
Dr. Angela Calugar, CDC/NCIRD/DVD

Dr. Calugar's presentation was for information and discussion only, since it is still a work in progress. She showed the current recommended immunization schedule for ages zero through six years and the one for 7 to 18 years, as well as for catch up. The format was based on focus-group discussions conducted last year. Feedback on the current format for 2007 came from participants at the National Immunization Conference and the NIP info hotline of the CDC. Providers say it is easier to read, convenient to print, and useful to separate age groups. The colors are harmonized with the adult schedule, however the green catch-up bars were said to be confusing. The immunization providers claimed that the content of the

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Childhood-Adolescent Schedule for 2007 is clearer, the footnotes are useful and it has the correct level of detail in comparison with prior schedules.

Suggestions on how to improve the schedule were related to the hepatitis B vaccine birth dose, and clarifications for PCV indication, for the zero-to-six schedule and catch-up. More details for children with special medical conditions would be helpful. Options for black-and-white copies would also be very useful, as would the use of brand names, which is normally avoided as much as possible.

The work group analyzed the accumulated information and conducted a joint meeting with the adult immunization schedule work group, which has experience with the best approaches for persons with special medical conditions. After a discussion about synchronizing the timing of the two schedules, it was decided to adhere to the existing time lines, i.e., the adult group will publish in October, and the childhood group will present final drafts in October for the ACIP vote and publish in January next year. Discussing and providing feedback for a draft immunization schedule for HIV-infected children ages zero to six years was another activity reported by the ACIP Childhood-Adolescent Schedule workgroup.

The process of updating the current schedule took into account other new vaccines that had been approved or were being considered by FDA. Sometimes there are new indications for existing vaccines, such as a potential recommendation for a younger age group for FluMist vaccine starting with the 2007/2008 influenza season (pending FDA decision).

Dr. Calugar showed the current schedule for ages zero to six years and pointed out that there were yellow bars for recommended ages, green for catch-up immunization, and purple for certain high-risk groups. Since providers find the green bars confusing and redundant, the hepatitis B series and Hib vaccine green bars will be removed.

Dr. Calugar then showed the current schedule for ages 7 through 18 years. ACIP will be voting on an updated recommendation for Menactra vaccine (MCV4), which would change the indications on the schedule. Previously it was presented as a yellow bar for a range of recommended ages up to 11 or 12, then for certain high-risk groups and yellow for 15-year-olds. Now there will a green bar in the catch-up immunization schedule for ages 13 through 18, which will make MCV4 consistent with the other two adolescent vaccines -- Tdap and HPV series.

The current catch-up schedule is divided, with ages four months through six years at the top and ages 7 through 18 years at the bottom. In all current schedules, the footnotes are bulleted. The minimum age for administration is on the first line for each vaccine, and the updated references are included.

In the footnotes for age groups zero through six years, the work group proposes adding, *"For additional details, see catch-up immunization schedule."*

Regarding the wording for the hepatitis B birth dose, if the mother is HBsAG negative, the birth dose can be delayed in rare cases with a physician's order and a copy of the mother's negative HBsAG laboratory report in the infant's medical record.

The third and the last change proposed is for pneumococcal conjugate vaccine wording. *"Administer PCV at ages 24 to 59 months in certain high-risk groups,*" and then add, "*Consider catch-up for other children aged 24 through 59 months*."

The proposed changes to the footnotes for the age group 7 through 18 years were simple. The group suggested adding a statement saying, *"Catch-up bars highlight the importance of the adolescent platform. For additional details, see catch-up immunization*

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schedule."

For the catch-up schedule, the PCV wording will be updated. "*Administer PCV at ages 24 to 59 months in certain high-risk groups. Consider catch-up for other children aged 24 to 59 months."* And then, as stated, *"Vaccine is not generally recommended for children aged older than five years."*

Updating the immunization schedules requires multiple activities, and the work group recognizes the importance of the feedback from immunization providers, collaboration with different ACIP work group and subject-matter experts, and harmonization with the stakeholders and the childhood and adolescent schedule.

Discussion

Ms. Stinchfield asked to change the wording in the footnotes regarding the hepatitis B dose from “physician order” to "provider order," because many people write orders in birth centers.

Dr. Whitley-Williams, National Medical Association, was confused about whether children who received the meningococcal conjugate vaccine at 11 to 12 years should be revaccinated five to seven years later when entering a dormitory in college. Dr. Messonnier responded that the current thinking was that the duration of protection would be long enough, and the ACIP recommendations for the MVC4 were based on that assumption. However, that will continue to be monitored.

Dr. Abramson said he understood from David Salisbury that the only problems noted in England have been in those who were immunized before one year of age and that they have not seen breakthrough cases in the other age groups to date. Dr. Messonnier said the U.K. vaccines were mening C conjugate vaccines and each of these vaccines is slightly different. However, based on the U.K. experience, one would anticipate that children vaccinated at age 11 would still be protected as they get to college. In the U.K., studies carried out before they began vaccinating suggested that children would be protected because they had memory, but the U.K. data suggest that, at least in infants, memory is not sufficient to provide protection without a booster dose.

Dr. Abramson commented that this also relates to the issue of reimmunization, which needs to be consistent on both the adult and adolescent schedules.

Dr. Wexler, Immunization Action Coalition, was concerned about the catch-up language for PCV, which says to administer PCV at ages 24 to 59 months of age in certain high-risk groups. That language is left over from the original ACIP recommendations in 2001, where the high-risk groups who were 24 to 59 months old were not covered by the 2-, 4-, 6-, and 12-month recommendations. They were written to catch the older kids in high-risk groups so they wouldn't <u>not</u> get vaccinated. She wondered why there was still a need to talk about certain high-risk groups, when these children should have already been vaccinated at 2, 4, 6, and 12 to 15 months. Basically, the wording should say that all children should be caught up, up to age five. Dr. Calugar replied that this was consistent with the last ACIP recommendation on PCV. There are always a few children being seen for the first time, such as an adopted child, so there has to be catch-up guidance for providers. The aim was to have only routine recommendations in the schedule and then refer everyone to the catch-up schedule.

Dr. Wallace reminded the group that when PCV was first recommended, the language about catch-up in those older than two was softened, but right now it does reflect the

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recommendation. Dr. Lett felt it would be important to standardize these recommendations for revaccination and catch-up between the adult and the childhood schedule. Moving back to meningococcal, she said she recalled that the revaccination statement excluded those living in dormitories.

Dr. Decker reported that as far as he knew there were no definitive data anywhere in the world on the duration of protection from any conjugate meningococcal vaccine. From clinical trials, there are some published data showing the lead and rechallenge of children who were immunized at two to three years of age and children four to five years of age. They still had significant elevations of antibody, and they responded briskly and with large rises to challenge. The U.K. had a problem with breakthrough cases in young children who were vaccinated on a 2-3-4 schedule, suggesting, perhaps, a problem with that schedule and the need for a booster. In contrast, the Netherlands implemented a nationwide 0- to 19-catch-up program and routine immunization at 14 months of age, and they have had no breakthrough cases in anyone vaccinated in six years. They are not going to give any boosters until they see epidemiologic evidence of a need to do so.

Dr. Schuchat pointed out that the apparent inconsistency between the childhood and adult recommendation was not an inconsistency. The revaccination comments in the adult recommendation were for those who receive meningococcal polysaccharide, and those are high-risk adults, e.g., asplenic or working in labs. Dr. Abramson added that he had asked for clarification whether it was the polysaccharide followed by the conjugate.

Dr. Baker noted that Menactra was licensed on a correlate of immunity, and that she understood that postlicensure a cohort of adolescents and young adults would be followed for duration of serologic protective correlate.

CDC IMMUNIZATION SAFETY OFFICE UPDATE

Karen Broder, CDC/ISO

Dr. Broder provided an overview of the Immunization Safety Office (ISO) program, described the proposed ISO research agenda development plans, and presented some preliminary key research themes identified during an ISO external scientific consultancy meeting. The mission of the ISO is to assess the safety of vaccines received by children, adolescents, and adults. It works closely with partners nationally and internationally to develop, provide, and support high-quality research in the field of vaccine safety in order to identify adverse events after vaccination and to assess causality and risk factors. In addition, it strives to communicate its work in a clear and transparent manner and to develop scientific methodology and standardize case definitions for vaccine adverse events.

Four main research and surveillance components work together to accomplish this mission. VAERS is an early-warning, national, passive surveillance system. It identifies vaccine safety signals of potential concern and generates hypotheses. The Vaccine Safety Datalink project or VSD is a collaboration between CDC and eight managed care organizations with comprehensive medical and immunization histories of about 5.5 million people per year. VSD tests hypotheses suggested by signals or expert review and also conducts vaccine safety surveillance. The Clinical Immunization Safety Assessment (CISA) network is a collaboration between CDC and six academic centers with vaccine subject-matter experts. CISA strives to study the pathophysiology of adverse events following immunization and identify risk factors, including host risk factors associated with adverse

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events, and also develops evidence-based guidance for clinicians around vaccine safety issues. The global Brighton Collaboration standardizes case definitions and provides a common vocabulary for vaccine safety research and surveillance. ISO also collaborates on a daily basis with other CDC programs and the FDA.

In October 2006, ISO conducted an internal peer review to determine whether the program activities were achieving the mission and identify areas for improvement. Preliminary conclusions were that ISO should strive for transparency, clearly identifiable research priorities, scientific credibility, enhancement of existing collaborations, and identification of new partnerships. In addition, the office needs to ensure that it can perform core public health functions under both routine and emergency situations. Peer reviewers recommended that the development of the ISO research agenda should include input from stakeholders in immunization safety and an external review.

In February 2005, the Institute of Medicine released a report titled "Vaccine Safety Research, Data Access, and Public Trust," which recommended that a subcommittee of the National Vaccine Advisory Committee (NVAC) review and provide advice on the Vaccine Safety Datalink research plan. In response, the Immunization Safety Office is developing a comprehensive, scientifically robust research agenda with extensive internal and external input, in three phases over a three- to five-year horizon.

In the first phase, CDC is already developing a draft ISO research agenda. In the second phase, the National Vaccine Advisory Committee will facilitate a scientific review of the draft ISO research agenda and provide advice, and in the third phase, CDC will respond to the feedback from the NVAC process and finalize the ISO research agenda.

CDC, the National Vaccine Program office (NVPO), and NVAC are currently discussing the approach for the Phase 2 NVAC scientific review, and plans have not been finalized. It is anticipated that this review would include a broad group of stakeholders in immunization safety as recommended by the Institute of Medicine.

To develop this draft ISO research agenda, ISO conducted an external scientific consultancy and also plans to obtain input from CDC programs outside ISO, other HHS agencies, the Department of Defense, and various nonfederal partners. Input from ACIP members will be welcomed through the CDC-ACIP working-group liaisons.

The charge to the individual external scientific consultants was to identify emerging vaccine safety research questions not currently being addressed, propose potential approaches to study each question, and advise on prioritization of research topics. Seven consultants were invited, representing the fields of pediatric infectious diseases, adult infectious diseases, OB/GYN, immunology, genomics, and epidemiology. In addition, there were liaison representatives from Federal agencies, advisory committees, CDC research collaborations, and the ISO, as well as the Office of the Chief Science Officer, CDC.

The framework used to guide brainstorming discussions was the five life stages: infants, children, non-pregnant adolescents, non-pregnant adults, and pregnant women. Cross-cutting categories included the role of public perception in shaping the ISO research agenda, considerations for vaccine safety surveillance, safety of non-antigen vaccine constituents and new vaccine technologies, and adverse events that occur years after vaccination. Six consultants also presented their own perceptions of the most important vaccine safety topics.

During the brainstorming sessions, consultants thought broadly about vaccine safety research without considering infrastructure or programs. Some of the topics that emerged are

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already being addressed in a current research activity, or might be more appropriate for other CDC or HHS programs, for example, studies of risk perception around vaccination.

The ISO is compiling a report that summarizes the full spectrum of the independent advice that consultants provided, but there were some key themes that appeared most relevant to the future ISO safety research agenda. One was the need to better understand the relationship between certain host risk factors and vaccine adverse events. These factors include prematurity and low birth weight infants; the influence of gender on vaccine adverse events; pregnancy; aging; the presence of chronic conditions, including diabetes; as well as genetic factors.

Another key area was vaccine-specific safety. In the case of rotavirus and LAIV, the concern was for a specific adverse event: intussusception for rotavirus vaccine and wheezing after LAIV. But influenza vaccine was of general interest because of the need for pandemic influenza preparedness. HPV was highlighted for a variety of reasons, including public sensitivities about giving the vaccine to adolescent girls widely. Tdap and zoster were listed, in part, because of safety issues regarding off-label use outside the licensed age range.

Other specific reported vaccine adverse events were included for different reasons. Some, like intussusception, are of concern following a particular vaccine (rotavirus), whereas Guillain-Barré syndrome and demyelinating disorders are of general interest. In addition, with increasing focus on adult vaccination, consultants identified a need to understand the incidence of cardiovascular disorders.

Of the other research topics that emerged during the meeting, some are relevant to the ISO research agenda, and some may also be relevant to other research agendas. Topics included the role of novel vaccine adjuvants, which is coming up in an HPV vaccine currently in the pipeline; understanding immune mechanisms for vaccine adverse events; and strengthening surveillance for reported vaccine adverse events, including signal detection. Understanding age-specific baseline rates of conditions reported as adverse events was a high priority. Off-label use of vaccines was another important area, for example, use of LAIV in persons with conditions that place them at increased risk for influenza complications.

Next steps are to work with the individual consultants to complete the consultancy report, gather input from the other vaccine safety partners, and develop a draft ISO research agenda that can be shared with NVPO and NVAC for the scientific review.

Discussion

Dr. Treanor asked whether there had been any interest in exploring the genetic basis of vaccine side effects. Dr. Broder replied that it is such a new area in vaccine adverse event research that detailed discussion was outside the realm of this particular consultancy. Dr. Iskander said his office had been funded by NVPO to conduct a separate meeting on this general topic, recognizing the emergence of data and interest. They will be seeking collaboration and input and hope to have the meeting early in the first quarter of 2008.

Dr. Katz asked why NIH was not in the list of federal agencies with liaison representatives to the ISO external scientific consultancy. Dr. Broder replied that the liaisons represented at the consultancy were there to hear the presentations, understand discussion and provide technical background. As recommended by IOM, there will be multiple stakeholders, including the other HHS agencies, in the NVAC review. The ISO is collaborating with NVPO to obtain input from the other federal agencies as the preliminary research agenda is being drafted, which would include colleagues in the FDA and NIH, as well as other federal

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agencies.

UPDATE: HERPES ZOSTER VACCINE SAFETY

Dr. John Treanor, ACIP WG Chair
Dr. Sandra Chaves, CDC/NCIRD/DVD

Dr. Treanor noted that as of January 2007 approximately 350,000 doses of zoster vaccine had been administered. It is complicated but interesting to look at adverse events in a population with many concurrent medical events.

Dr. Chaves reminded the committee that the vaccine was licensed in May 2006, and by October, it was recommended for adults age 60 years and older. Injection-site reaction was the main adverse event reported during clinical trials, and it was clearly more frequent among those receiving the vaccine. There were no other clinically important or statistically significant differences observed regarding systemic or serious adverse experiences. However, in the adverse event monitoring substudy, where approximately 6,000 people were closely followed, the rate of serious adverse events was higher among those receiving the vaccine compared to those receiving placebo, but no clinical pattern was identified.

This safety update was based on data from VAERS, which uses a coding system to computerize reported events and as a way of standardizing complaints. A report is classified as serious if a patient reported having been hospitalized or if the patient died or had any life-threatening or disabling illness or any other medically important condition.

VAERS received 590 reports through June 1st, which represents an overall reporting rate of 73.3 per 100,000 doses distributed. These rates are based on preliminary data provided by the manufacturer. Among those, 44 reports were characterized as serious, for a reporting rate of 5.5 per 100,000 doses. Two were deaths.

Among the 590 reports, over half were women, and for reports classified as serious, 43 percent, 19 out of 44, occurred among those ages 70 to 79 years. It is important to note that 14 percent of all reports represented people younger than 60 years. This younger group would represent off-label use or administrative error; many were children under five, and 50 percent were adults aged 21 to 59. In 90 percent of the reports, Zostavax was administered alone. The others referred to concomitant administration of other vaccines that were part of the childhood immunization program.

The most common adverse events were injection-site reaction, rash and zoster. The majority were female and the median age was 65 to 68 years. The interval between vaccination and event onset was a median of one day for injection-site reaction, three days for rash, and five days for zoster. The interval ranged from less than one day to eight to nine months or up to a year for rash. None of the zoster cases tested so far has been confirmed to be due to Oka strain, but very few have actually been tested.

There were reports of allergic reactions and anaphylaxis occurring soon after vaccination. Although hospitalization was required, which automatically classified these reports as serious, they offered very good outcomes.

One pregnant woman was inadvertently vaccinated with Zostavax; the patient actually requested to be vaccinated and then, ten days later, was found to be pregnant. She is being followed by the pregnancy registry, but there is no further information on pregnancy outcome.

There were three cases of encephalitis. One started with disorientation within the first

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24 hours of vaccination. The MRI did not show any abnormalities, and CSF was negative for herpes simplex, but no test was done for VZV. The other two encephalitis cases had very limited data available.

Eight events were coded as secondary transmission, five of which were reports of people developing zoster after being exposed to a spouse who had been vaccinated with Zostavax. Of the other three, one was a child who was exposed to his grandparents and developed chickenpox a few days later. A man was exposed to his wife who had been vaccinated with Zostavax, and ten days later he developed chickenpox, but it is unlikely that his chickenpox was a result of this exposure. There was also a physician who was exposed to a patient who had zoster after being vaccinated; two weeks later, she found two vesicles that she assumed could be chickenpox and started antiviral treatment, even though she had a history of chickenpox during childhood.

Some of the events were coded as varicella and varicella post vaccination. Eleven were varicella-like rash occurring after vaccination with Zostavax, with one case hospitalized due to the extent of the rash, but no lab data are available for any of these cases. Four reports classified as varicella post vaccination were actually zoster. Among the zoster cases, there was a 63-old-woman hospitalized with acute retinal necrosis and zoster in her right eye, but no further lab information was available.

Most of the events coded as medical error or wrong drug administered were presented as human error or unintentional use of Zostavax instead of other vaccines, such as Varivax and ProQuad. There were two reports of immunosuppressed individuals who were inadvertently vaccinated, and two reports of local injection-site reactions in persons under age 60, which could represent off-label use.

Two deaths were reported as temporally associated with the receipt of the zoster vaccine. Both persons were 80 or older, but clinical-lab information was not available. For one of the cases, the cause of death was sepsis and pneumonia, occurring six months after vaccination. The other had a heart attack a week after vaccination.

To summarize, Zostavax seems to have a very good safety profile, very much as expected during clinical trials pre-licensure. The most frequent reported event is injection-site reaction, although herpes and rash were very common. There is no way to establish any association with the vaccine virus without support of laboratory information. It is also possible that all the zoster captured in the system was a reflection of vaccine failure since vaccine efficacy was around 60 percent. Many of the reports describe events related in time, but that is likely caused by other factors, especially in this age group, where co-morbidity is common.

Surveillance is extremely challenging for this vaccine. VAERS is a good system for providing signals, but a better understanding of administration errors and off-label use of the vaccine will come from specific studies. VAERS data are passive surveillance, subject to underreporting, lack of clinical and laboratory information that would establish causality, and lack of denominator data. Post-licensure safety studies are expected to be undertaken, which would add to the safety profile of the vaccine. CDC, through the Vaccine Safety Datalink and Kaiser Permanente and Group Health Cooperative, will look at adverse events among adults 50 years and older. This cutoff age may provide a better assessment of off-label use of the vaccine. Also, Merck has agreed to conduct a post-licensure, randomized, placebo-controlled clinical trial in approximately 12,000 subjects, where half will be receiving the vaccine and the other half placebo. They will also assess the use of high-potency doses of Zostavax and

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the use of lower doses for people taking corticosteroids.

Discussion

Dr. Allos noted that 34 of the administration errors involved children who were supposed to be receiving Varivax. She wondered if those were all in just a few sites or if they were randomly distributed, whether packages looked similar, and whether anything could be done to make them look more distinctive. Dr. Chaves responded that packaging and labeling did not seem to be the major issue in the reports. It was really just unintentional, human mistakes. She did not have any information about how many sites were involved.

Dr. Pickering commented that when meningococcal conjugate vaccine first came out, it was inadvertently given subcutaneously instead of intramuscularly as was recommended. However, a study of about 100 people who had blood drawn showed the titers were low but still acceptable, and they did not need to be immunized again. He wondered what the recommendation would be for children who get this vaccine, at 14 times the dose of Varivax, with regard to a second varicella immunization. Dr. Chaves replied that there was no official recommendation. A two-dose recommendation was in place for varicella, and one would need to assess if a higher dose was as efficacious as a two-dose vaccination. Dr. Kuter from Merck added that they had actually looked at material as high as 50,000 platform units in healthy children and safety was comparable to their typical dose in the five to 10,000 dose range PFU. However, there was a plateauing of the response, i.e., the seroconversion rates and GMTs were comparable whether children were given 5,000 or 50,000 PFU. Off label, she still recommended that a second dose be given.

COMBINATION VACCINES

Patricia Stinchfield, RN, MS, CPNP, ACIP WG Chair

Ms. Stinchfield explained that the combination vaccine working group (WG) was reinstated to develop a revised statement on the use of combination vaccines for review and approval of the ACIP. The last statement was written in 1999. The long-term goal is to review issues surrounding the availability and use of combination vaccines. However, an important and immediate short-term goal was to review an upcoming vaccine known as Pentacel®, a DTaP-IPV-Hib combination vaccine, in anticipation of discussion at a future ACIP meeting, pending the FDA approval.

Sanofi pasteur submitted the BLA for a four-dose primary series in children for the two-month, four-month, six-month, and 15- to 18-month part of the schedule. The FDA requested additional information from sanofi, which resulted in an extension of the review clock for this BLA. Pentacel® was approved in Canada in 1996 and in all the jurisdictions by '97, '98. Canada has had an excellent experience with this vaccine, and any future detailed presentation will include the Canadian experience.

Beginning in April, the WG met weekly by conference call. The WG conducted an overview based on the VRBPAC presentation and looked at the immunogenicity of the vaccine's components. The Canadians presented their experience with Pentacel®, which is now used exclusively there.

The WG talked with the Committee on Infectious Disease about harmonization and the future recommendations in agreement with what is already published in the Red Book. There was also discussion about implementation for special risk populations, such as

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American-Indian and Alaskan-native children, and some of the nuances that will have to be considered for Pentacel® in the childhood immunization schedule.

Future topics for the WG, pending FDA licensure of the vaccine, will be a detailed presentation at the October ACIP meeting on Pentacel-related topics. Work will continue on the draft of the *MMWR* notice to readers, to be presented for discussion most likely at the February 2008 meeting. Then, pending FDA licensure and ACIP recommendation, there would be an ACIP vote on inclusion of Pentacel in the VFC program.

Other future topics would be to review and prepare communications regarding combination vaccines new to the market. For example, GSK recently indicated that the FDA has accepted the BLA for their DTaP-IPV, which is a pediatric booster vaccine for immunizations against diphtheria, tetanus, pertussis, and polio at the four- to six-age group.

The WG will continue work on updating the *MMWR* statement on combination vaccines that was written in 1999. Issues will be reviewed surrounding the availability and use of combination vaccines in the current U.S. market, after which the statement will be revised and there will be a discussion about whether to incorporate the combination vaccine's topic into the general recommendations document. Ms. Stinchfield invited members to offer other agenda items.

Discussion

Dr. Decker explained that Pentacel® was delayed because the manufacturer moved its global pertussis laboratory testing facilities into the United States. In association with that, FDA CBER wanted to review all the comparability data with the existing files for all of the pertussis products, so licensure of Pentacel® has been held up until they finish reviewing the lab validation data.

UPDATE: MENINGOCOCCAL CONJUGATE VACCINE (MCV4)

Dr. Carol Baker, ACIP WG Chair
Dr. Amanda Cohn, CDC/NCIRD/ISD
Dr. Ismael Ortega-Sanchez, CDC/NCIRD/DVH
Dr. Phil Hosbach, sanofi pasteur
Dr. Gregory Wallace, CDC/NCIRD/ISD
Dr. John Iskander, CDC/ISO

Dr. Baker explained that the ACIP MCV4 recommendations were first published in May of 2005, recommending vaccination of the following groups: persons aged 11 to 12 years, adolescents at high-school entry, and other persons at increased risk of invasive meningococcal disease, including college freshmen living in dormitories. This three-cohort list was based on supply and risk considerations. The peak of disease in adolescents begins around entry to high school, and there are strong data on college freshmen living in dormitories, but there was a desire to start immunizing the 11-to-12 cohort as well. This was the first vaccine to go forward, quickly followed by Tdap and HPV, the major tenets of the adolescent platform.

Then there was a supply-demand issue, so an *MMWR* notice in May 2006 deferred the 11- to 12-year-olds because they were at baseline level of risk. When supply became abundant again, an October *MMWR* notice told people to resume the 11- to 12-year-old recommendation, but this was not well implemented. There is currently an excess supply.

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Epidemiology

Dr. Cohn provided an overview of the current epidemiology of meningococcal disease in the United States, including recent trends and the burden in adolescents and young adults. The national passive surveillance system, known as NETSS, receives case reports from all 50 states and provides the numbers seen in the *MMWR*. ABC is an active laboratory and population-based surveillance system composed of ten sites in the U.S. Their data are important for serogroup and additional clinical information on cases.

Data on the incidence of meningococcal disease in the United States from 1970 to 2005 show a cyclical waxing and waning pattern with peaks every eight to ten years. The case-fatality rate decreased in the 1970s but has remained between 5 and 10 percent since the 1980s. Since 1996 incidence of meningococcal disease has been on a downward cycle. Serogroups B, C, and Y each cause approximately one-third of meningococcal disease in the United States. Since 2002 Serogroup B has caused the highest disease incidence, but there is currently no vaccine available in the U.S. that protects against that disease.

Rates of meningococcal disease are highest in infants under one year and remain high in one- to four-year-olds, age groups for which there is currently no effective vaccine. Seventy-five percent of vaccine-preventable cases are in persons 11 years and older.

The 2005 MCV4 recommendations were made to impact the second peak in adolescents, who have the greatest burden of disease among the age groups for which MCV4 is currently licensed. Disease incidence increases through adolescence, peaking in 18-year-olds. Although the duration of protection from MCV4 was unknown, it was anticipated that when given to 11- and 12-year-olds, the vaccine would remain effective through late adolescence. The vaccine was also recommended at high-school entry to correspond to the rising risk.

Most cases of meningococcal disease occur in previously healthy children and young adults. Case-fatality rates among adolescents and young adults are higher than among children less than ten years old and above the overall case-fatality rate of 12 percent. Achieving high coverage with MCV4 could prevent up to 75 percent of cases in 11-19 year olds. Among children four years old and under, around 50 percent of cases would be vaccine preventable if a quadrivalent or CY conjugate vaccine were available. The majority of cases in infants are caused by Serogroup B.

In conclusion, meningococcal disease incidence is currently at the nadir of its normal cyclical disease pattern. Despite implementation of the MCV4 recommendations in 2005, the CDC does not believe the vaccine has impacted current disease trends. Meningococcal disease continues to be a significant cause of morbidity and mortality among adolescents in the United States. Serogroup B vaccines and safe, effective vaccines for infants will be needed to achieve meningococcal disease control in the United States. Vaccinating all persons aged 11 to 18 years with MCV4 would have a substantial impact on disease in this age group. CDC is conducting vaccine effectiveness and carriage studies and will continue to use active surveillance to monitor the impact of MCV4 recommendations and the duration of protection.

The Economics of Adolescent Meningococcal Vaccination in the U.S.: Direct and Indirect Protection

Dr. Ortega-Sanchez talked about the economics of expanding the adolescent

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meningococcal vaccination in the U.S. using the four-serogroup conjugated vaccine. The objective of the study was to see whether vaccinating most adolescents could significantly and immediately generate herd-immunity benefits. Therefore, Dr. Ortega-Sanchez's analysis was focused not only on the direct impact on adolescent vaccines, but also on the potential herd immunity impact in the rest of the U.S. population (the indirect impact)

A Monte Carlo simulation analysis model was constructed, using a one million 11- to 17-year-old sample representative of a 10 million population cohort. The vaccination strategy was a one-time mass vaccination of children ages 11 to 17 years followed by routine vaccination of each new 11-year-old cohort. The timeframe (or time of the interventions) is ten years, but the health benefits and costs are measured over the age-specific life expectancy. The discount rate used for health costs outcomes was three percent.

As an illustration of the model the population was stratified into three age groups: less than 11 years, 11 to 17 years, and 18 years and older. Direct protection can be achieved for adolescents with vaccination. Vaccination also offers indirect protection and a safety net for other age groups who are not vaccinated or for those whom the vaccine fails to protect. In a ten-year period, approximately 16 of the cohorts will be vaccinated: seven cohorts in the mass campaign and nine cohorts of 11-year-olds routinely vaccinated in the subsequent nine years.

Epidemiology data included age, year, and serogroup-specific rates, and the average age- and serogroup-specific case-fatality ratios. The proportion of survivors with sequelae was also estimated using data from the literature. Initial vaccine efficacy data were taken from the U.K. experience with the conjugate Serogroup C vaccination program, which is in line with the studies of the four-serogroups meningococcal conjugate vaccine. The study assumed that duration of vaccine efficacy was ten years, and that vaccine coverage in adolescents was 70 percent, also in line with the U.K. experience.

Age-specific incidence data were used for estimating the number of cases in the population and deaths were calculated using the age- and sequelae-specific case-fatality ratios. Cases with long-term sequelae were then calculated using the proportion of meningococcal survivors with specific sequelae.

Two studies in the U.K. reported age-specific reductions in cases among the unvaccinated from vaccination campaigns with the conjugate Serogroup C vaccine with an average of 57 to 67 percent reductions (Ramsey et al. and Balmer et al.). These age-specific rates were used to calculate the number of cases indirectly prevented in the U.S. study.

Previously published estimates of direct costs were updated to 2006 by using the gross domestic product (GDP) deflator. It was also assumed that each active meningococcal case would be hospitalized. Indirect costs associated with meningococcal disease were used to estimate the cost of illness per case in each age group. Costs were broken down into those associated with the acute infectious phase of the disease and those from long-term complications of permanent sequelae or premature death.

A base-case cost of $83 (range $50 to $110) per vaccinee with a single dose was assumed. Vaccination program costs comprised vaccine, vaccine administration, and 10 percent vaccine wastage. Costs of adverse events were included, but time lost by vaccinees or vaccines' caregivers to get the vaccine was not included.

Without the vaccination program, an average of 1600 meningococcal cases attributable to the C, Y, W135 serogroups would have been expected. The reduction in cases after mass vaccination in 11- to 17-year-olds in Year 1 and the routine vaccination of 11-year-olds in the following years is represented by two extreme scenarios. The first scenario is the

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direct-protection-only scenario, with an average of 156 cases per year, representing approximately a 9 percent reduction. The second scenario is the direct protection plus the full herd-immunity protection, using the proportions observed in the U.K. with the meningococcal Serogroup C vaccine. This would avert approximately 835 cases per year in adolescents, which represents a 48 percent reduction. As seen by these estimates, almost four-fifths of all prevented cases are attributable to the herd immunity.

Over a ten -year period, the mass and routine vaccination program will prevent approximately 8,251 cases, representing approximately 1700 complications and 700 deaths prevented. These reductions will result in approximately 30,000 life-years saved (15,000 when discounted) or 69,000 QALYs saved (27,000 when discounted).

A ten-year cost projection to the whole U.S. population found that meningococcal disease due to the vaccine-containing serogroups will cost approximately $1 billion in direct costs and $1.7 billion in indirect costs, both after discounting. Before including vaccination program costs, mass vaccination followed by routine immunization in subsequent years will save approximately $1.4 billion over ten years. At $83 per vaccinee, the mass and routine vaccination program will cost approximately $3.2 billion over ten years, which translates to about $223,000 per case averted or $2.6 million per death prevented. In assessing the cost-effectiveness of a mass vaccination campaign followed by the routine vaccination program, the cost to society will be approximately $127,000 per life-year saved and $88,000 per QALY saved.

A previous study reported that it was more cost-effective to continue vaccinating adolescents than toddlers and infants. The Shepard study published in *Pediatrics* in 2005 did not include herd-immunity impact, and the vaccine efficacy was assumed to last 20 years. When this study was updated, with an assumption of a ten-year duration of vaccine efficacy, the routine vaccination program was less cost-effective than mass vaccination plus routine vaccination for adolescents. If the most recent data on the reduction in attack rates, those reported in Ramsay's study for the U.K., are used, the societal cost drops to $116,000 per life-year saved or $81,000 per QALY saved.

Regarding indirect protection, mass vaccination followed by routine program had a net societal cost of $414,000 per life-year saved, assuming achievement of only 20 percent herd immunity as reported for the U.K. If the U.S. can reach the same reductions in attack rates as the U.K., the cost per life-year saved here will be $127,000.

Two recent studies of vaccination in adolescents have also considered herd immunity, one on pertussis and the other on human papillomavirus. These studies have shown a lower cost to society per life-year or QALY saved, which means that they are more cost-effective than mass and routine immunization with meningococcal conjugate vaccine in adolescents.

Two other studies reported cost per life-year saved with a vaccine, but neither included herd-immunity assumptions. The first looked at the cost-effectiveness of vaccinating first-year college students in dorms with the meningococcal polysaccharide vaccine and found that mass vaccination followed by routine vaccination would be approximately two times more cost-effective than vaccinating college students living in dormitories with meningococcal polysaccharide vaccine. The other study estimated that if the pneumococcal conjugate vaccine were used only to prevent meningitis in infants, the cost per life-year saved would be more than $300,000 (in 2006 U.S. dollars); namely, it would be much less cost-effective than the mass vaccination program followed by the routine vaccination.

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The current study has some strengths and limitations. One strength is the use of complex modeling, which includes direct and indirect effects of vaccination. It also explicitly used surveillance data for specific ages and serogroups containing the vaccine. A limitation is that data on vaccine efficacy and herd immunity are from the U.K. and are not specific to the U.S. vaccine. In addition, quality of life during the acute disease was not assessed, and the QALY scores used to assess the long-term complications are not meningococcal disease-specific.

In conclusion, the one-time mass vaccination of healthy adolescents followed by a routine program of 11- to 12-year-olds could have substantial impact on the burden of disease. Up to 48 percent reduction of cases could be expected, and 80 percent of these reductions could be due to herd-immunity impact. However, it would have a net societal cost. For the same duration of vaccine efficacy, the one-time mass vaccination followed by routine vaccination could be half as expensive per life-year saved and QALY saved as routine vaccination of 11- to 12-year-olds only.

Discussion

Dr. Neuzil asked whether it was reasonable to assume that the U.S. herd-immunity effects would be the same as the U.K., based on a mass-vaccination campaign of adolescents followed by routine vaccination. Dr. Messonnier replied that the U.K. vaccinated everybody under age 20. It is not clear that the U.S. would see the same impact, even for 11- to 17-year olds. However, that is probably where much of the transmission is coming from, which is why an optimistic scenario was presented.

Dr. Morse was curious why 11 to 17 was used rather than 11 to 18, and whether that would make a difference in the cost estimates. Dr. Ortega-Sanchez responded that 11 to 17 was used for simplicity because there were approximately one million 11- to 17-year-olds in the 10 million population sample. This does not preclude the possibility that there will be 16 cohorts vaccinated in a ten-year period, which will also create herd-immunity impact.

Dr. Treanor noted that the calculation of cost per QALY saved was first based on a policy that does not induce herd immunity (routine vaccination) and then based on mass vaccination, which does induce herd immunity. He asked whether one would save money by doing a mass-vaccination campaign. Dr. Ortega-Sanchez answered that when this study was compared with the Shepard study, assuming ten years duration of vaccine efficacy and costs in 2006 dollars, the cost per life-year saved for the mass and routine vaccination program was less than the cost per life-year saved for the routine vaccination only. Dr. Treanor further asked about the cost of mass vaccination plus routine vaccination per QALY saved in the absence of herd immunity. Dr. Ortega-Sanchez replied that it was more than $414,000 per life-year saved.

Dr. Lieu said she had the impression that mass vaccination actually meant catch-up vaccination for the children who did not fall in those two age bands for whom it is currently recommended. Even assuming zero herd immunity and that the cost per life-year saved is $700,000, she wondered why that was so much higher than what was seen in the original Shepard analysis, which assumed zero herd immunity and found something in the range of $200,000 per life-year saved. Dr. Messonnier explained that by vaccinating at age 11, the benefits are reaped for the next ten years, whereas vaccinating a 17-year-old has fewer benefits because the rates of disease decrease greatly after age 18. Dr. Ortega-Sanchez added that because most vaccination costs in the model happened in the first year and that costs

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close in time usually have bigger weight than cost in the long run when discounted, the mass vaccination program costs have a bigger influence than in a routine programs, which are usually distributed over time.

Dr. Schaffner noted that much of the motivation for the initial recommendations came out of the epidemiology of meningococcal disease on college campuses and wondered if there were any efforts to track the occurrence of meningococcal disease in college campuses subsequently. Dr. Turner, American College Health, replied that there was no comprehensive effort to collect data, but that the number of press reports about individual cases has dropped over the last four or five years. He added that he had been struck by the data showing that Serogroup B now is more common than C and Y. This started around 1999 or 2000 when vaccination of these cohorts began, which seemed to imply that immunizing this group had not had much impact. Dr. Abramson asked what happened to B in England after mass vaccination in C. Dr. Messonnier replied that when they began vaccinating, 60 percent of their disease was B and 40 percent was C. There is currently an increase in B disease, so the dramatic decline in C was not related to B.

Vaccine Supply and Demand

Dr. Hosbach of sanofi pasteur, said that after the recommendation was made in May 2005, there was a very enthusiastic response in uptake of Menactra, as shown by claims filed by physicians in the private sector. Although the recommendations were targeted for three cohorts, there was a large response in all ages from 11 to 18, with some peaks at 14 and 18. This put pressure on the supply, so the CDC, ACIP and medical societies decided to temporarily defer 11- to 12-year-olds, after which the claims shifted to the older age categories.

With demand held down, the manufacturer was able to stock up on vaccine without exhausting supply. In fact, at the end of 2006, there were approximately 2 million doses in the warehouse and there will be twice the amount of vaccine available this season compared to last year. This information gave stakeholders and the working group the confidence to restore the recommendation to include the 11- to 12-year-olds in late 2006. From January through April of 2007, more children were immunized with Menactra in the private sector than at any other time period. So people are responding to the revised recommendations and getting immunized. Tdap was just being introduced during that time, and there was good uptake of the vaccine in 11- to 12-year-olds, but there was still a gap between Tdap claims and Menactra claims, which could be a hang-over effect from the deferral of 11- to 12-year-olds.

In 2006 sanofi pasteur sold and/or distributed 4.3 million doses and had a surplus of nearly 2 million doses, which was carried into this year. Projections, based upon the three-cohort demand, are for an uptake of around 6.3 million doses, which would have meant a surplus of about 3 million doses. Over 9 million doses will be available in 2007, and in 2008 more than 11 million doses will be available.

Marketing looked at low-, medium-, and high-uptake scenarios if there was an 11- to 18-year-recommendation and everyone received one dose of vaccine. They assumed that the 85 percent or 70 percent immunization rate would not be achieved for adolescents overnight. Actually, tripling or doubling the current rate in one year would be quite substantial. But as a cohort gets immunized over time, it shrinks. Starting with immunizing the 30 million adolescent cohort in 2006, by 2007 there are only 27 million to immunize if immunization

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rates are achieved. By 2008, there would be 21.7 million people to immunize. Even with an additional demand for a million-plus doses this year, above the 6.3 million projected, there would still be a surplus for next year. In fact, the number of doses required for adolescent immunization will probably peak at around 7 to 7.5 million doses annually in the next year or two. Supply for January and September is on track and will exceed 6 million doses. With the surplus, there will be more than 9 million doses available.

Beyond 2007, supply is expected to continue to increase each year, but as immunization rates increase, the total number of eligible adolescents will decline. The market peak is not expected to exceed more than 7 or 7.5 million doses over the next three years. However, by that time there could be a recommendation or an indication for two- to ten-year-olds and this committee can consider what to do with the surplus doses.

Vaccine Supply in the Public Sector

Dr. Wallace covered supply and demand in the public sector. After implementation of the recommendation, CDC provided allocations to the states and grantees based on their VFC populations. There already was an 18-year-old demand from the previous polysaccharide recommendation. The real demand for a new vaccine is unpredictable in the public sector. There was a lag in 317 and state funding, and the gap seen with all vaccines. Through the 2005 contract, CDC purchased 1.4 million doses of MCV4 out of a total national sales of 3.1 million doses, or 46 percent. This was lower than the 53 or 54 percent seen for all the pediatric and adolescent vaccines, partly due to the 11-to-12 deferral.

It is difficult to reach public sector adolescents beyond the age of 11 to 12. Grantees loose assess to some at-risk children as they go into their teenage years and the public sector is not the majority provider for 18-year-olds, where demand is highest. Due to that drop in doses used, there was actually a risk of expiration of vaccine already on the shelf. Even when restrictions on the 11- to 12-year-olds were removed, there was no increase in the demand for the vaccine off the CDC contracts. In summary, the number of doses available to the public sector is increasing but use is not, resulting in a risk of expiration of vaccine and missed opportunities for protection.

Update: Vaccine Safety

Dr. Iskander presented a summary of post-licensure safety data for Menactra, as well as data on Guillain-Barré syndrome, or GBS, following Menactra, based mostly on VAERS data, Vaccine Safety Datalink uptake data, and planned and ongoing studies. Dose-distribution data were obtained from the manufacturer.

Through November 2006, a little more than 1,000 adverse event reports have been received for Menactra. Just over 10 percent of those met the criteria for serious adverse events. During the same time period, 7.5 million doses of vaccine were distributed. There is no routine ongoing reporting of numbers of doses administered overall or broken out by age group, but published data on usage of Menactra can be obtained by looking at proportionate use by age group and focusing on the transition from the previous polysaccharide vaccine to the conjugate vaccine. The overall dose-adjusted reporting rates for Menactra are 14 per 100,000 doses and serious adverse events are just over 1 per 100,000 doses distributed.

Most of the reports concern the ages between 11 and 12, gender distribution is relatively equal, and the majority of reports involve Menactra given as a single vaccine. The most frequently reported symptoms involve pain. Other frequently reported adverse

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events include headache, fever, myalgia, vomiting, and diarrhea. As is common with reports to VAERS, there was a very close temporal proximity to vaccination in the majority of reported adverse events. There have been 19 reports of unintentional injury related to vasovagal syncope. Two of the more significant injuries involved loss of consciousness following syncope. In addition, there were two instances of individuals who apparently experienced syncope while driving, although neither was reported to be injured. There have also been vaccine-administration errors, but data published in the September 2006 *MMWR* showed no effect on immunogenicity.

Serious adverse events are those that involve hospitalization, deaths, disability, or life-threatening injury with no causality inferred or implied. Three-quarters of those reports involved Menactra given as a single vaccine. Clinical reviewers at the FDA and CDC categorized them according to the primary type of event and/or organ system. Most were neurological in nature, with smaller numbers in a variety of other organ systems.

There have been two reports of death following receipt of Menactra. An 18-year-old male died four days after Menactra with cause of death listed as presumed cardiac arrhythmia. An 11-year-old developed a headache, vomiting, and abdominal pain nine days after receiving Menactra and subsequently became encephalopathic. His autopsy revealed acute hemorrhagic leukoencephalitis, a rare form of acute demyelinating encephalomyelitis.

As of 30 April 2007, a total of 19 confirmed Guillain-Barré syndrome cases within six weeks of Menactra administration had been reported to VAERS. All but two were among 11- to 19-year-olds with onset 2 to 33 days following vaccination. Six had received concomitant vaccines. Reports peaked during the summer months of the past two years. All recovered or are recovering at this time.

Comparing observed confirmed cases from VAERS within six weeks of vaccination stratified by age to the background rates obtained from the Vaccine Safety Datalink and controlling for the seasonality within the VSD, there appears to be a slightly increased risk among 15- to 19-year-olds. Data analyzed to date indicate that, among more than 140,000 doses administered, zero cases of GBS have been observed within six weeks of vaccination. The number of expected cases, based on the background rate observed within the VSD for such a population, would range between zero and one. Within the VSD, 94 percent of Menactra recipients are within that 11- to 19-year-old age group, which also comprises the majority of the GBS reports.

Harvard Pilgrim Healthcare is undertaking a manufacturer-sponsored controlled study of GBS following Menactra. They propose to include a population of approximately 10 million 11- to 18-year-olds, which would have sufficient power to detect an elevated risk ratio; the Vaccine Safety Datalink is not large enough to undertake such a study. The Clinical Immunization Safety Assessment network also continues to conduct detailed case reviews and focused laboratory evaluation with an eye toward studies of hosts, such as genetic risk factors.

For 11- to 19-year-olds overall, there is no statistically significant evidence of an increased risk of GBS after Menactra vaccination, but there does appear to be an increased risk within the 15- to 19-year-old age category. However, this has to be put in the context of the inherent limitations of VAERS and the uncertainty regarding the background rate within the VSD. The timing of neurologic symptoms, which has been consistently within one to five weeks following vaccination among reported cases, remains of concern.

In summary, both the overall and serious adverse event reporting rates are within the average ranges for the VAERS system as a whole. Most reported events are non-serious and

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represent local and systemic reactions, consistent with the pre-licensure safety monitoring. Potentially preventable events, specifically post-vaccination syncope and vaccine administration errors, have been detected for Menactra, as they have been for other newly licensed adolescent vaccines. The small increased risk for GBS following Menactra in the 15- to 19-year-old age group persists across several analyses, but these findings do not represent a definitive study. Among the other serious adverse events reported following Menactra, both neurological and non-neurological diagnoses have been reported in relatively small numbers. Because of the inherent limitations of VAERS, the causal relationship of any individual event of vaccination is uncertain.

Discussion

Dr. Lett asked whether sanofi pasteur had plans for more manufacturing capacity, since there would be an increased number of doses available in 2008 due to accumulated inventory. Mr. Hosbach replied that the company was continuing to expand and increase efficiency in the existing facility, while the new facility would be brought online over time.

Dr. Morse noted that there appeared to be sufficient supply to cover the year, but that the peak occurs in July and August, just before college begins. He asked if there would be a surge then and whether there was enough in the pipeline to meet that increased demand. Mr. Hosbach replied that the company had been carrying somewhere between 1 and 2 million doses in inventory, which could comfortably handle any summertime surge.

Dr. Allos reminded everyone that the most common trigger of Guillain-Barré is Campylobacter infection and that those infections are frequently asymptomatic and almost always undiagnosed. The surge in demand for the vaccine occurs at the same time that there is a natural peaking in the incidence of Campylobacter infection. Of the 19 reported cases of Guillain-Barré, almost all occurred during that time. When intensive surveillance was done for Guillain-Barré among children vaccinated between January and April, there were no cases. The data suggest that there is no relationship between this vaccine and Guillain-Barré, but that Campylobacter-associated Guillain-Barré happens to mirror the timing of when this vaccination is used. Dr. Iskander responded that there is not a great deal of testing for etiologic agents, so broader epidemiologic links of these cases to known outbreaks or known peaks of Campylobacter have not been found. This does not mean there is no possibility of links. CISA is in fact looking at algorithms to promote more standard evaluation of GBS, seeking etiologic agents.

Dr. Keyserling noted that, given the anticipated approval for the 2-to-10-year indication by the end of this year, there could be a significant shortfall if there is uptake in that new age group. Dr. Baker responded that the ACIP does not consider vaccines that are not approved but the 2-to-10 group is at lower risk than the 11- to 19-year-olds.

Dr. Lieu pointed out that there can be a lot of confounding in the rate ratio of 2.5 among 15- to 19-year-olds, but it remains significant after controlling for seasonality. Dr. Baker noted that a significant proportion of the cases had received other vaccines at the same time as Menactra.

Presentation of New Recommendations

Dr. Cohn stated that the meningococcal working group proposed recommending MCV4 for all persons 11 to 18 years old. A change to the MCV4 recommendation would be published as an *MMWR* notice to readers, which would have four sections: a review of the

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May 2005 MCV4 recommendation, the revised MCV4 recommendation, a discussion on the implementation of the revised recommendation, and a recommendation addressing persons with a history of GBS.

The current ACIP recommendation for MCV4 includes routine vaccination of persons aged 11 to 12 years; adolescents at high-school entry; and other persons at increased risk of meningococcal disease, including college freshmen living in dorms. Recommending routine vaccination of 11- to 12-year-olds emphasizes the ACIP-recommended routine healthcare visit for 11- to 12-year-olds. Vaccination at high-school entry was intended to target an additional cohort of adolescents, as risk of disease increases later in adolescence, but implementation of adolescent recommendations for MCV4 might be affected by short-term supply limitations.

The following explains the rationale for changing the MCV4 recommendation at this time: "*Simplified recommendations for use of MCV4 could improve coverage, and current and future MCV4 supply is expected to be sufficient to meet increased vaccine uptake resulting from simplified recommendations.”*

The revised ACIP MCV4 recommendation would be as follows: *"ACIP recommends vaccination with one dose of MCV4 of all 11- to 18-year-olds. Persons 11 to 12 years old should be routinely vaccinated at the ACIP-recommended 11- to 12-year-old healthcare visit."* Routine vaccination is also recommended for persons who are at increased risk for meningococcal disease, including college freshmen living in dorms.

The implementation section of the notice to readers will address the following issues related to improving uptake of MCV4: emphasis on the 11- to 12-year-old recommended healthcare visit; implementation of the recommendation for college freshmen living in dorms; and timing of vaccination, including trying to get adolescents vaccinated throughout the year instead of just during the summer months. The following wording emphasizes the importance of establishing the 11- to 12-year implementation visit. "*ACIP and partner organizations, including the American Academy of Pediatrics, American Academy of Family Physicians, American Medical Association, and the Society for Adolescent Medicine recommend a healthcare visit for 11- and 12-year-olds to receive appropriate immunizations and other evidence-based preventive services.*

"A recommendation for MCV4 vaccination among persons 11 to 12 years old could strengthen the role of this preventive-care visit and have a positive effect on vaccine coverage of all recommended adolescent vaccines.”

To address vaccination of college freshmen, *“College freshmen living in dormitories are at increased risk of meningococcal disease and should be vaccinated with MCV4 before college entry, if not previously. Because of these ability restraints in targeting freshmen in dormitories, colleges may elect to target their vaccination campaigns to all matriculating freshmen."*

The following section encourages providers to vaccinate at any healthcare visit throughout the year. *“Because the incidence of meningococcal disease increases during adolescence, healthcare providers should take the opportunity to vaccinate previously unvaccinated 11- to 18-year-olds with MCV4 at the earliest possible healthcare visit. ACIP encourages healthcare providers to vaccinate with MCV4 throughout the year to minimize seasonal increases in demand associated with back-to-school months. Providers may want to consider that VFC eligibility lapses after 18 years old when making decisions about vaccination.”*

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A draft notice to readers addresses CDC guidance for persons with a history of GBS. *"Because of the reported association of Guillain-Barré syndrome after receipt of MCV4, persons with a history of GBS may be at increased risk and should discuss the risk of meningococcal disease with their healthcare provider when deciding whether or not to be vaccinated."*

This change to the MCV4 recommendation would parallel Tdap and HPV recommendations in the proposed 2008 adolescent immunization schedule. The language in the current MCV4-VFC resolution covers qualified adolescents 11 to 18 years old and would not need to be changed. In conclusion, the meningococcal ACIP working group anticipates that these recommendations would simplify provider decisions to vaccinate and improve adolescent coverage with meningococcal conjugate vaccine.

Discussion

Dr. Hull referred to information from Dr. Ortega-Sanchez about uptake over three to five years, which would blunt the herd immunity as well as the individual protection provided, and wondered what effect that would have on cost-effectiveness estimates. Dr. Schuchat commented that herd immunity does not necessarily require a mass-vaccination campaign. There are many unknowns with meningococcal conjugate quadrivalent vaccine because nobody has evaluated herd immunity yet. However, there was tremendous herd immunity with the pneumococcal conjugate vaccine in infants, without an effective effort at catch-up. The same was true for the Hib vaccine. So using the healthcare visits to vaccinate anybody in that age group, one could realistically expect some herd immunity with this opportunistic vaccination. Dr. Ortega-Sanchez responded that the analysis was based on using a comparator in the no-vaccination scenario. Some vaccination is already happening, but there many places where the uptake has been very slow. He was not sure whether changing the baseline scenario of no vaccination to some vaccination would change the cost per life-year saved or reduce cost-effectiveness numbers.

Dr. Lett asked whether the recommendation referred to a mass-vaccination campaign or routine catch-up over a period of years. Dr. Abramson replied that it was catching up. Dr. Cohn added that it was about opportunistic vaccination as soon as possible.

Dr. Lieu supported the proposed recommendation because the economic analysis and the Guillain-Barré syndrome analysis make clear that it would be better to deliver this vaccination at the 11- to 12-year-old age range or earlier in adolescence rather than later. On the basis of consistency and common sense, providers would clearly vaccinate a 17-year-old about to enter college, even though it is less cost effective.

Dr. Neuzil asked whether there was any evidence or biological plausibility to say someone who has had GBS would be more at risk for it from a different antigen. Dr. Allos did not believe there was any biological basis, but noted that there has been a statement about Guillain-Barré in all the new vaccines. Dr. Iskander added that in the vast majority of all cases, specific etiology is unknown, but once someone has had it, subsequent risk is increased globally. It is important to avoid or disentangle coincidental cases. One of the initial five sentinel cases was someone who had a third post-vaccination recurrent case with a common antigen. Dr. Abramson reminded everyone that people with a previous episode of Guillain-Barré were advised not to get an influenza vaccination.

Dr. Gilsdorf felt there had to be a balance between the fact that the magnitude of GBS goes up with use of the vaccine and the fact that the disease is quite rare. Dr. Abramson

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added that the incidence of GBS goes up in the 15-17 age group.

Dr. Schuchat recalled that at the February meeting there was a decision analysis that looked at a ten-year framework in terms of estimated prevention of cases and deaths caused by meningococcal disease, as well as episodes and possibly deaths from Guillain-Barré syndrome, and the numbers were very much skewed towards the benefits of vaccination.

Dr. Pickering pointed out that death due to mening is clearly worse than Guillain-Barré, but the long-term effects in adults with CNS problems from Guillain-Barré are quite significant. He asked whether the ISO had any plans to utilize CISA units to look at long-term CNS problems or even the genomics of this disease in the people who develop it. Dr. Iskander responded that there were several research protocols moving forward. The idea is to look at rare but instructive issues, such as recurrent GBS or recurrent post-vaccination GBS. The ISO also sponsors some animal model studies to get to underlying pathophysiologic mechanisms. Some of the most compelling cases in the literature suggest an underlying genetic or host-factor basis. The CISA network has identified this clinical entity as a priority.

Dr. Baker noted that if one included the entire 11- to 18-year-old cohort, the risk of invasive meningococcal disease was 0 .5; in college freshmen living in dormitories, it was 3 to 4 per 100,000, with a conservative 10 percent death rate and another 20 percent with long-term sequelae. She thought the increased risk of Guillain-Barré in MCV4 recipients was a little more than one per million. Dr. Iskander agreed but pointed out that this was not the analysis from which one would want to extrapolate attributable risk or etiologic fraction. Depending on when the analysis is done seasonally, it is between one to three attributable cases per million doses.

Dr. Baker asked about the outcomes of reported cases in adolescence. Dr. Iskander replied that there had been no deaths and one or two individuals may still be undergoing rehabilitation. The more difficult question is the one of long-term sequelae and neurologic conditions in general.

Dr. Turner, American College Health., recalled that for every million doses of Menactra administered, it was predicted that about 60 cases would be prevented among 17- and 18-year-olds, with 1.25 additional cases of GBS. So the risks must be weighed against the benefits.

Dr. Treanor felt the recommendation made good sense, but since children make relatively few visits after the 11- to 12-year-old visit, he wondered what the practical consequences of giving vaccines as the opportunity presented itself would be in terms of vaccination rates. Dr. Middleman from the Society of Adolescent Medicine reported that about 34 percent of adolescents make a preventive-healthcare visit, but 80 and 90 percent can identify a primary healthcare provider and about 70 to 80 percent have some contact with either an ED or a physician for another reason. So there are multiple missed opportunities. She added that from a practical perspective, the new recommendation makes it simpler to protect more adolescents. Dr. Temte from the AAFP noted that data for Wisconsin show no difference between the number of visits for children zero to ten and the number for those ages 10 to 20. However most of the zero-to-ten visits are preventive, whereas the others are episodic acute-care visits. Ms. Stinchfield added that most clinicians were already giving the vaccine because they fear the disease so much. Dr. Baker emphasized the need for more education to expand opportunities.

Dr. Abramson asked whether the preference for simultaneous administration of Tdap and meningococcal vaccine needed to be repeated. Dr. Messonnier said that could be added

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to the notice to readers.

Vote

Dr. Baker moved that the committee approve the recommendations as reviewed. Dr. Allos seconded the motion.

Dr. Allos: yes.
Dr. Baker: yes.
Mr. Beck: yes.
Dr. Gilsdorf: yes.
Dr. Hull: yes.
Dr. Lett : no.
Dr. Lieu : yes.
Dr. Morita: yes.
Dr. Neuzil: yes.
Ms. Stinchfield: yes.
Dr. Treanor: abstain.
Dr. Morse: yes.
Dr. Abramson: yes.

Dr. Lett stated that it seemed a little premature to change the recommendation. Providers have been confused and changing so quickly may be disruptive. She felt it would be better to wait another season.

PROPOSED APPROACH TO ECONOMIC ANALYSIS OF VACCINES AND IMMUNIZATION STRATEGIES UNDER CONSIDERATION BY THE ACIP
Dr. Tracy Lieu, ACIP
Dr. Mark Messonnier, CDC, NCIRD/ISD
Dr. Martin Meltzer, CDC/NCIRD/OD

Dr. Lieu explained that ACIP's charter recommends that committee deliberations should include consideration of population-based studies, such as efficacy, cost-benefit, and risk-benefit analysis. Since October 2004, there have been economic presentations on meningococcal vaccine, pertussis for adolescents, adults and healthcare workers, Varicella's second dose, Hepatitis A, HPV, rotavirus, zoster, and rabies post-exposure prophylaxis. These cost-effectiveness studies typically use decision-analysis or computerized models, and are based on assumptions about vaccine effectiveness, disease epidemiology, vaccine cost, and duration of immunity. Those assumptions are not based on empirical studies, so economic analyses are particularly easy to bias. They are also hard to understand because there are so many numbers and each presenter uses a slightly different format to present the data. Therefore, the ACIP formed a working group to look at standardization of methods used to offer information to the committee. Recommendations were drafted based on existing standards set up by the U.S. Preventive Health Service. The gist of those recommendations is that every economic study should be carefully reviewed by CDC economists before being presented to ACIP or its working groups in order to ensure that the best information available is given to the committee or working groups as decisions are being made.

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Dr. Messonnier talked about what needed to be included in a study and how it should be presented. Around 11 years ago, the *British Medical Journal,* developed a checklist for editors and reviewers to judge whether a submitted study was sufficient for publication. *Vaccine* followed suit. Many professional economic organizations require papers to be submitted in advance of their annual meetings as well. The working group has been working on a set of standards, which is almost complete. Basically they require submission of a manuscript comparable to a journal article, with less detail on introduction and discussion, and more detail on methods and results. There will be no word limit so as to get the fullest explanation possible. A set of presentation slides will also be required in advance. A suggested template is available, though not required.

The material should be submitted to the working group chair and a CDC liaison eight weeks before the general meeting in order to find a reviewer. This includes internal CDC studies as well. Extraordinary exceptions will be allowed, but not failure to plan.

There will be an internal anonymous peer review, coordinated by the NCIRD's lead economist. That reviewer can consult with subject-matter experts at CDC, but the completed review should be back to the working group chair and the CDC liaison at least four weeks before the general meeting to allow time for discussion, review, revision and a decision about whether to present it. The author must provide affiliations and statements about potential conflicts of interest.

Details on methods are contained in the text document, but there are a few main points. First the study question must be clearly and adequately stated and the perspective must be societal because this is a public policy decision-making body. Other perspectives--payer, healthcare system, patient -- are invited but not essential.

The intervention strategies must be clearly specified and described, as well as the time frame and analytic horizon, and the type of economic modeling done, whether it is cost utility, cost-effectiveness, or cost-benefit analysis.

Technical equations can be included, but preferably in a technical appendix. The equations and the economic model should be written out in sentence form. The health outcomes need to be specified, along with any underlying epidemiologic models. The inputs used and cost values must be stated, whether they are assumed or measured, together with any citations from the literature or justifications for those assumptions.

The discount rate used needs to be specified and applied to costs and outcomes. Discounting has nothing to do with inflation, rather with observations made of people's preference for consumption over time. Undiscounted-form results can also be presented, but the discounting needs to be applied to all the costs and outcomes.

There must be a multivariate sensitivity analysis, since changing one variable is unlikely to leave all other variables completely unchanged. Sensitivity analyses need to be presented in a clearly defined section with all the relevant tables and graphs, identifying the most influential variables. Independent replication is very important—not exact numbers but somewhere in the ballpark.

The results section of the manuscript has to answer the study question. Results must be clearly identified and in one place. Summary measures have to be clearly presented and match the perspective. Supplementary results may be presented, preferably in some sort of technical appendix.

Tables and graphs should stand alone. They should add value to the manuscript and

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not detract from it. Supplementary tables can be included in an appendix as well. (Tufte is a good source on the guidelines for presentation of graphical data.)

Discussion should be limited to study limitations, the study's relation to other relevant studies, or how the results might change if some assumptions change. Policy implications are not necessary since it is the ACIP's prerogative to think about the policy implications of the decisions it is about to make.

Discussion

Dr. Decker of sanofi pasteur said he felt the guidelines were reasonable, but was concerned about meeting ACIP and working group deadlines. Economic societies do require manuscripts, as mentioned, but they are less concerned about getting studies published rapidly. Some of the data may not be available to make a decision about costs and benefits if there was not enough time to get a manuscript written. Dr. Pickering clarified that what was needed was a descriptive paper that will allow CDC economists to say this is a scientifically valid study and be understood by non-economists

Dr. Decker than asked what would happen if, for example, something was about to be licensed and there was an economist who was able to brief the committee but had not written anything. Dr. Schuchat responded that the ACIP is a volunteer, deliberative body that is making important decisions for the country, including inclusion of vaccines in the Vaccines for Children program, which has a huge economic impact. This committee is asked to understand, digest, deliberate and vote based on cost-effectiveness data. She felt it was reasonable to expect members to receive complete, well-documented data, with adequate time for an independent economist to review and weigh in on them. The working group is just requesting a complete, interpretable analysis, with documented methods and assumptions, and results in a standard format.

Mr. Beck commented that when he joined ACIP, he was absolutely amazed at the quality of the economic data presented. It would never have been permitted in the corporate world. He felt there needed to be a system and a level playing field, and welcomed the new guidelines.

Dr. Treanor noted that listening to presentations that he could not understand was actually counterproductive in terms of making a decision. Dr. Feinberg agreed that it was in everyone's best interest to make sure the data used to make recommendations were as outstanding, rigorous, and thoroughly vetted as possible. He wondered whether any thought had been given to seeking external reviewers and what would happen if there was a difference of opinion between reviewers. Dr. Pickering responded that the CDC planned to put together a list of CDC economists as well as outside reviewers who could be contacted for special expertise. There also needs to be a time line, since implementation of the new guidelines will be gradual. Regarding Dr. Feinberg’s second question, Dr. Messonnier responded that criticisms had to be valid and reasonable before there would be rejection of a manuscript. A provision will be made for comments from the reviewing economist to be aired as well.

Dr. Markson from Merck asked how the committee would handle multiple models, developed by several groups. Dr. Messonnier replied that it would be up to the working group to decide whether to hear two or three different estimations on cost-effectiveness or cost benefits.

VACCINE SUPPLY AND IMPLEMENTATION

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Dr. Greg Wallace, CDC/NCIRD/ISD

Dr. Wallace first gave the committee a brief update on varicella zoster virus bulk-based vaccines, which include varicella vaccine (Varivax); MMRV(ProQuad); and the zoster vaccine (Zostavax). When Merck temporarily suspended production to work out yield issues, the ad-hoc supply work group recommended no change in the varicella vaccine vaccination policy, which meant the two-dose schedule should still be implemented. Merck was prioritizing production of Varivax and Zostavax and expected MMRV (ProQuad) to be depleted in the third or fourth quarter of 2007. After announcing the production issues, Merck experienced record sales of ProQuad, and supply was exhausted by June 15th. Any current orders through the CDC contract may not be filled until July or August. However, there is no change in the recommendation for vaccination to protect against varicella disease; Varivax supply is adequate to meet these needs and Varivax and MMR would be given as separate doses. Mixing the two together to try and make ProQuad will not work.

Dr. Wallace then reviewed implementation of adolescent vaccines, particularly in the public sector. Overall, the CDC contract accounts for around 50 percent of the national total for pediatric and adolescent vaccines.

Regarding public sector demand, CDC started off with around 46 percent of the Menactra market in 2005. This dropped to 40% in 2006, but there was a modest increase in the number of doses purchased. Through the first half of 2007, no increase has been seen, but decisions made earlier in the meeting may have some impact. Tdap started slowly (24% of market in 2005), but the contract happened relatively late in the season and probably missed some of the pre-school vaccination in the public sector the first year. The market share increased to 41% in the second year of implementation, but appears to have dropped off in the first half of 2007. The CDC contract was two months after the licensure for HPV in 2006, but caught up pretty quickly and has increased the number of doses purchased.

Another way to look at adolescent implementation status is as follows: CDC purchased approximately two cohorts worth of Tdap vaccine in 2006, but that appears to be falling off in 2007. For HPV, about one cohort of a three-dose series has been purchased to date and CDC is a bigger proportion of that market than for other adolescent vaccines. For Menactra, grantees purchased doses for less than half of a cohort for each of the last two and a half years, so there is certainly room for improvement there.

With the CDC contracts and new vaccines, there tends to be a lot of enthusiasm for the vaccine early on, but reaching adolescents is still a big challenge. The adolescent platform is not the same as the pediatric; the 11- and 12-year-old visit does not have the same coverage as the four- to six-year-old visit and may involve different providers. Also, activity in the adolescent arena tends to be disease specific. Grantees have gotten some pushback by groups with specific vested interests instead of looking at the big picture. New access strategies need to be developed and grantees need guidance from others who have learned what works.

Discussion

Dr. Stanley Plotkin asked whether any thought had been given to repairing the school-based immunization system. Dr. Schuchat announced that there would be a supplement to *Pediatrics* focusing on adolescent immunization, which will pull together results from a workshop about a year and half ago. It is an area of major importance to CDC and many of the liaison groups, and will require a lot of creativity. School-based immunization has been

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successful in many areas and allows for quite a bit of public/private collaboration. She also mentioned the September workshop on school-aged recommendations for influenza, which will include thought about the school venue. Dr. Abramson added that NVAC also had an adolescent work group thinking about this issue.

UPDATE: PNEUMOCOCCAL WORKING GROUP

Dr. Julie Morita, ACIP Working Group Chair

Dr. Morita explained that the working group's charge was to review the need and optimal timing for updated statements on the use of the conjugate vaccine and the polysaccharide vaccines and to develop a revised statement on the use of the pneumococcal vaccines for ACIP review and for approval. The polysaccharide vaccine statement was issued in 1997 and the conjugate vaccine recommendations were issued in 2000. The group's agenda included any changes to the current recommendations based on existing data, for example, direct and indirect population effects from the conjugate vaccine, non-vaccine serotype replacement, or trends in antimicrobial resistance. In addition, the group reviewed the conjugate use and effects in special populations, specifically Alaskan-native and American-Indian children, and alternative vaccine schedules with reduced number of vaccine doses.

A number of presentations were made to the working group. Matt Moore described trends in invasive pneumococcal disease in the U.S. before and after the conjugate vaccine. Marie Griffin from Vanderbilt reviewed the population impact of the conjugate vaccine on pneumonia, hospitalizations, and otitis media visits. Tom Hennessy and Ros Singleton from Arctic Investigations Program reviewed an increase in invasive pneumococcal disease in Alaskan-native children due to serotypes not in the conjugate vaccine and Kate O'Brien reviewed the impact of nine years of conjugate vaccine use on invasive pneumococcal disease among Navajo children. Wyeth Vaccines reviewed the comparative immunogenicity of conjugate vaccine using a two-plus-one alternative dosing schedule. Tammy Pilishvili from CDC also reviewed the post-licensure effectiveness of conjugate vaccine against invasive pneumococcal disease in the U.S. Pekka Nuorti reviewed the uptake of conjugate vaccine among children in the United States, and David Goldblatt reviewed the experience with reduced conjugate dose schedules in the U.K. Lastly, Philippe DeWals from Canada reviewed the impact of the three-dose conjugate vaccine program in the province of Québec.

Key issues regarding the pneumococcal polysaccharide vaccine include contradictory data regarding vaccine effectiveness, and limitations of the polysaccharide vaccine in elderly persons and high-risk groups. It will also review the duration of protection, safety, and immunogenicity of revaccination and optimal timing and frequency of revaccination. The goal is to look at the overall achievable public health impact.

Lisa Jackson reviewed contemporary studies of the polysaccharide vaccine efficacy and effectiveness. Outcomes included invasive disease, pneumonia, and mortality. Those study designs included clinical trials, observational studies, and ecological studies. Considerations regarding revaccination with polysaccharide vaccine include the duration of protection, safety, immunogenicity, and effectiveness of first revaccination; safety of multiple revaccinations; and the optimal timing and frequency of revaccination.

Before the October meeting, the group hopes to look at possible new polysaccharide target groups based on available data regarding newly identified risk groups; the

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polysaccharide programmatic and implementation issues; some updated polysaccharide and conjugate economic studies; and the manufacturer's review of potential time lines for new pneumococcal vaccines in the pipeline.

Discussion

Dr. Abramson asked whether the workgroup would look at the use of a combination of PCV7 and pneumococcal 23 in the same patient, for example a sickle-cell patient. Dr. Whitney responded that the group still needed to go over all those high-risk groups and new data that may have become available since the last recommendation.

Dr. Bruce Gellin noted that there needed to be more clarity about the use of pneumococcal vaccine as part of pandemic preparedness. Advice from the committee would be welcomed regarding whether people should be vaccinated now, should there be a stockpile, is there a role for conjugate vaccine, etc. Dr. Morita replied that this issue was in the original work plan.

UPDATE FROM THE PREGNANCY AND BREAST-FEEDING WORK GROUP

Dr. Kathy Neuzil, ACIP WG Chair
Dr. Stephanie Schrag and Dr. Tami Skoff, CDC, NCIRD/DBD

Dr. Neuzil introduced the new ACIP working group on vaccines during pregnancy and breast-feeding. The main motivation behind forming this working group was the recognition that pregnant women and newborns are at risk for vaccine-preventable diseases, and yet attention toward vaccine coverage in these groups and vaccine recommendations in these groups is not always optimal. Recent discussions around new vaccines like HPV and Tdap highlighted these issues. For HPV, during the catch-up period women up to age 26 will be vaccinated; for Tdap there has been concern about harmonization with other professional societies for pregnancy-specific recommendations.

Dr. Schrag explained that the new working group initially spent time thinking about terms of reference and identified three main tasks. The first was to review existing recommendations for use of vaccines during pregnancy and breast-feeding. The second will be to develop guiding principles to inform development of ACIP recommendations for pregnant and breast-feeding women as new vaccines are licensed and existing recommendations are routinely updated. Finally, the group wants to help resolve inconsistencies within ACIP recommendations and facilitate harmonization of ACIP recommendations with those of other professional organizations.

In addition to three ACIP voting members, the working group has liaison representatives from AAFP, ACOG, and AAP, as well as from FDA and the NIH group in charge of maternal vaccine research. There are also many subject-matter experts representing current vaccines indicated for adolescents or adults and relevant subject areas, for example, immunology and health law.

The work-group membership was identified in January and the first in-person meeting was held in February at the last ACIP meeting, where it focused mainly on terms of reference. Since then, the focus has been on reviewing existing recommendations by conference call.

Dr. Skoff briefly summarized some of the general themes uncovered thus far. The

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ACIP stated in an *MMWR* that the risk to a developing fetus from vaccination of the mother during pregnancy is primarily theoretical, based on the fact that, to date, no evidence exists to support a risk from vaccinating pregnant women with inactivated virus, bacterial vaccines, or toxoids. That *MMWR* also stated that the benefits of vaccinating pregnant women usually outweigh potential risks, when the likelihood of disease exposure is high, when infection would pose a risk to the mother or fetus, and when vaccine is unlikely to cause harm.

As a starting point, the working group tried to categorize existing ACIP recommendations and found variation both in the recommendations themselves and the language of the recommendations. But it did come up with four general groupings of vaccines. The first group is recommended for all pregnant women; to date, the only vaccine that falls in this category is inactivated influenza vaccine. The second is those vaccines that follow routine adult immunization recommendations regardless of a woman's pregnancy status. The third and largest group is vaccines recommended for pregnant women only under special circumstances, such as when exposure risk is high, and the last group includes vaccines that are not recommended for pregnant women.

Many of the ACIP recommendations are challenging to interpret. In fact, it is not uncommon for similar recommendations to use very different language. Second, there seems to be an inconsistent message about the role of limited safety and/or efficacy data for some of these vaccines. For some products, limited data are used to support vaccination of pregnant women, whereas for others, lack of sufficient data is a reason against vaccination. When grouping the vaccines based on their recommendations, it was found that the majority of the vaccines are recommended for pregnant women when the benefits of vaccination outweigh the risks to the individual. This type of language places a large burden on healthcare providers and pregnant women to make responsible decisions about vaccination during pregnancy. Finally, the ACIP does address the issue of breast-feeding and makes an overall general statement supporting vaccination in breast-feeding women, the notable exception being smallpox vaccine.

The second work-group call focused on a review of the FDA process for making indications for the use of vaccines during pregnancy and breast-feeding. As part of that process, all vaccines must be classified under one of five pregnancy categories, which are based on the risk of reproductive and developmental adverse effects and, for certain categories, on the basis of such risk weighed against potential benefit. Of the currently licensed vaccines, all but two fall under Category C, which includes products that lack human data, but for which animal studies have shown an adverse effect on the fetus or animal studies have not been done.

These pregnancy categories are often confusing because they convey the false impression that there is a gradation of risk among categories and the same level of risk within any given category. The FDA is improving pregnancy labeling and considering either changing or creating alternatives to the current pregnancy categories.

The group discussed the fact that vaccine companies write the vaccine labeling and that it is the responsibility of the FDA to review and approve the label language. The content is constrained by federal regulations. No implied claims of product use may be made if there is inadequate evidence of safety or lack of product effectiveness, which limits what can be printed on the labeling. In general, the language on the labeling tends to be much more conservative than the language of the ACIP recommendations, not only for vaccination during pregnancy, but also during breast-feeding.

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The most recent conference call focused on the recommendations of AAFP, ACOG, and AAP, which are generally harmonized with ACIP's recommendations, although interpretation may vary. Translation of the recommendations by the organizations to a more user-friendly and easy-to-understand language can be challenging and may actually result in altered content of the original recommendations. The biggest difference in recommendations was observed for Tdap, which is recommended for pregnant women by AAP and is under consideration for a similar recommendation by ACOG.

The next step is to start discussions on the development of guiding principles for recommendations for vaccines during pregnancy and breast-feeding.

Discussion

Dr. Schaffner expressed surprise that Td did not fit into the universal pregnancy immunization category. It was his impression that before the ACIP made its recommendation regarding influenza vaccine, the vaccine was universally recommended. Dr. Neuzil responded that this confusion was related to inconsistencies in the way recommendations were worded. Td is recommended for pregnant women if they are unvaccinated, or due for a booster. Dr. Houn of the FDA added that Category C actually has two meanings, which is confusing. One is that there is an absence of animal data as well as an absence of human data, which is probably the case for Td. The second is that the animal data show adverse effects but there is absent human data.

Dr. Baker clarified that the FDA was consistent about Td, so it belongs in Category C, as does influenza. Both are recommended on the basis of public health issues. HPV did pass into Category B. To obtain category B, the vaccine manufacturers must request that category and then provide the data, and the minimal data are animal data. She felt the FDA rules were very straightforward and that the disconcerting thing was that Category B is considered okay and D is bad.

Dr. Iskander suggested that the work group could also provide clarity and education on pregnancy registries, why they exist and what lessons have been learned from them. It might even be possible to frame some recommendations about preferential reporting to registries rather than to other passive surveillance systems. Dr. Whitley-Williams noted that the Department of Defense has a wonderful registry, which showed that some pregnant women were inadvertently immunized. Some of the data on congenital rubella syndrome also come from that database.

Dr. Peter noted that there was a lot of research going on regarding immunizing pregnant women to protect the newborn, which should give the working group considerable work in the future. Dr. Neuzil added that the group was looking at burden of illness both in the pregnant women and in the newborn.

Dr. Plotkin emphasized that if the group could come up with general conclusions, it would be very helpful in trying to convince manufacturers to develop vaccines that would be used in pregnancy and would provide some protection in legal matters. He also commented that assessing the risk of disease in the pregnant woman was inherently difficult, and favored taking that aspect out. For example, risk is a very difficult way of evaluating whether to give a vaccine to a woman who is traveling.

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Day Two June 28, 2007

INFLUENZA VACCINES
Dr. Ban Mishu Allos, WG Chair
Dr. Anthony Fiore, CDC/NCIRD/ID
Dr. Angela Calugar, CDC/NCIRD, ISD
Dr. Karen Broder, CDC/ISO
Dr. Gina Mootrey, CDC/NCIRD/ISD

Dr. Fiore thanked the departing influenza work-group members who are also members of the ACIP and noted that during their tenure vaccination was expanded to include children aged 23 to 59 months old and their household contacts, and a framework and a time line were laid out for expanding the recommendations to additional ages and groups.

Influenza Activity in the US during 2006-2007

Dr. Fiore presented data from laboratory surveillance conducted by the U.S., the World Health Organization and the National Respiratory and Enteric Virus Surveillance System through June 5th, 2007. Since October 1st, about 173,000 specimens have been tested for flu viruses, of which 13 percent were positive. Among the 22,000 positives, 79 percent were influenza A and 21 percent were influenza B. About a third of the influenza A viruses have been subtyped: 64 percent were influenza A-H1 viruses and the rest were H3 viruses. The season peaked in mid to late February. The intensity and peak time were similar to the previous two seasons. Deaths attributed to pneumonia and influenza did not exceed the epidemic threshold during the season, based on information from the 122-city mortality reporting system.

Laboratory-confirmed influenza-associated pediatric hospitalization is tracked in several population-based surveillance networks. Rates for this past season were similar to the rates of the past two seasons, for children aged 4 and under and for children 5-17 years old, and were considerably below the rates observed during the 2003-2004 season. As of June 22nd, CDC had received 67 reports of influenza-associated pediatric deaths this season, compared to 45 and 46 deaths, respectively, in the last two seasons, and about 153 in the 2003-2004 season when reporting began.

Compared to the previous two seasons, there has been an increase in the mean age of reported influenza deaths to seven years from four to five years in 2004 to 2006. There has also been an increase in the proportion reported to have the invasive MRSA-associated co-infections along with influenza, from less than 5 percent in the previous two years to 27 percent this past year. CDC and the state health departments are planning additional investigations and increased surveillance for these MRSA-influenza co-infections among children.

Dr. Fiore shifted attention to the time frame for considering expansion of the recommendations, which may include school-aged children by 2008, followed by household contacts and caregivers of those school-aged children and then, by 2012-2013, discussion of implementation of universal vaccination for all age groups. Expanding the recommendations to include routine vaccination of school-aged children has been a major topic in the work-group discussions over the past year. A CDC/CSTE-sponsored consultation to consider the

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scientific and implementation issues raised by the proposed expansion will be held September 10th and 11th in Atlanta. Approximately 75 consultants have been invited, including influenza researchers and epidemiologists, representatives from public health and professional and medical organizations, community vaccinators, safety experts, and people who have implemented vaccination programs in school-aged children. The agenda will include a review of the evidence base supporting expansion of the recommendations, including the burden of disease in this age group; vaccine effectiveness and safety; cost analyses; the potential direct and indirect impact in communities; and experiences and pilot projects from around the country and in other countries. Key evidence gaps will be identified. The second day will largely focus on implementation challenges and the potential solutions, which would include sustainability, infrastructure and resource needs, the feasibility of delivering the vaccine in nonmedical and medical settings, priority communication messages, and how to assess impact over time. The outcomes of this meeting will be presented at the October 2007 ACIP meeting.

Dr. Fiore briefly mentioned the strain selections for the upcoming season, which were made at the VRBPAC meeting and FDA on February 28th. One strain has been changed out. The A/Solomon Islands/3/2006 strain will represent the H1N1 antigens. The other two strains are the same as last season -- the A/Wisconsin/67/2005 (H3N2) and B/Malaysia/2506/2004.

Dr. Fiore introduced a discussion of the FluMist licensure. FluMist was first licensed in June 2003. The frozen formulation was licensed for use in healthy persons aged 5 to 49 years. In January 2007, a liquid formulation was licensed, which allows the product to be shipped and stored in a refrigerated state. Commercial use was anticipated during this upcoming flu season. Around the same time, MedImmune submitted a BLA application to FDA for use of liquid FluMist in children aged 12 to 59 months of age without a history of wheezing and asthma. The analyses were presented on May 16th to VRBPAC. The primary data source was the pivotal trial CP-111, published by Belshe, et al, in the *New England Journal of Medicine* in 2007 and also presented here to ACIP, both in October 2006 and in February 2007, with the later presentation focusing largely on safety issues. This was a randomized, double-blind active control with TIV multi-center study, with pre-specified analyses for 6- to 23-month-olds and 24- to 59-month-olds.

The FDA concluded that the data indicated that FluMist was safe and effective in subjects 24 months of age and older. However, among subjects less than 24 months of age, there were some safety concerns, including the fact that participants who received FluMist had increased all-cause hospitalizations, severity of wheezing, and severity of respiratory events, compared to the TIV-receiving group. FDA also noted that a history of wheezing was poorly predictive of wheezing post vaccination among FluMist recipients. Persons with a history of severe asthma were excluded, but about 20 percent of participants did have a history of wheezing.

All of the adverse events were uncommon, mostly among the children 6 to 11 months old. However, the FDA noted that the post hoc analyses conducted among the 6- to 11-month-olds should be interpreted with caution, recalling that the pre-specified age-group analyses were for 6- to 23-month-olds and 24- to 59-month-olds.

After hearing the evidence, the committee members concluded that FluMist efficacy was not inferior to TIV. For the safety vote, the committee was asked whether the data demonstrated that the benefits would exceed the risk of FluMist in three groups. For children 12 to 59 months of age without a history of wheezing and asthma, the vote was nine yeses and six no's. For 6- to 23-month-olds, regardless of wheezing history, the voting was three yeses

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and 12 no's, and for children 24- to 59-months, regardless of wheezing history, the vote was 15 yeses and zero no's.

The FDA decision on licensure is currently on hold pending resolution of issues identified during manufacturing plant inspections, but this is not expected to significantly affect availability of FluMist for the 2007-2008 influenza season. MedImmune can continue to manufacture its products while taking corrective action, however this makes it difficult to come to a decision on the age-indication change, so the committee vote as well as the VFC vote will be delayed.

The influenza working group members agreed that the data indicated that FluMist efficacy was not inferior to TIV for all the age groups in the study. In fact, FluMist provided significantly increased efficacy compared to TIV in the flu year studied. The data also indicated no safety signal among children 24 months and older with no history of wheezing. However, there was concern that additional information was needed, particularly for children 6 to 11 months old, with regard to wheezing outcomes and all-cause hospitalization rates compared with TIV; additional information on safety was also needed for children 24 months of age or older with a history of asthma or wheezing.

The working group will review the FDA-approved age and medical indications once they become available. Clinicians and immunization programs must be able to screen for conditions that are a contraindication to LAIV use, such as a history of asthma or recurrent wheezing. The working group will also continue discussions on the advantages and disadvantages of recommending LAIV over TIV for healthy young children, based on the interesting but limited data showing that LAIV has better efficacy in preventing lab-confirmed influenza among young children. Finally, safety monitoring will be critical, including updates from the Vaccine Adverse Events Reporting System, the Vaccine Safety Datalink, and the other planned postlicensure safety studies.

Discussion

Dr. Neuzil asked whether Dr. Fiore could provide an update on antiviral resistance from this past year and if there were any plans for a case-controlled study to get more definitive data on the efficacy of influenza vaccine in preventing death in children. Dr. Fiore responded that resistance to the adamantanes continues to be quite high: 80 percent or more and even 100 percent in some parts of the world. So for this coming year, CDC advises not using the adamantanes for treatment or chemoprophylaxis of influenza. Resistance to the neuraminidase inhibitors remains well below 1 percent. For the upcoming season, a health advisory network letter was sent out to stimulate reporting of severe illness with MRSA co-infection and not just deaths, with the hope of capturing larger numbers to expand the study size. CDC is looking for both influenza virus isolates and MRSA isolates, since it does not have MRSA isolates from the dozen or so children previously reported. From the influenza-virus testing, no particular strain appears to be associated with these co-infections. As cases are accumulated, an epidemiologic investigation will be carried out using population-based surveillance systems and then the case-control study will be resumed if an increase in these co-infections is identified.

Dr. Morse pointed out that there is a two-year gap in considerations for the flu vaccine and suggested that this gap could be decreased since the vaccine supply seems to be increasing steadily. Also, for pandemic flu preparations, it is probably better to have a larger vaccine supply available sooner. He wondered whether the timetable could be moved up.

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Dr. Allos explained that the working group's goal was universal protection and that it may not be necessary to vaccinate everybody to achieve full protection. The reason for the gap is that once all school children up to the age of 18 have been vaccinated, there needs to be a period of time when surveillance data can be collected to assess the decline in flu rates in the elderly populations, based on expanded vaccination.

Dr. Poland argued that such a study would be fine in a static population, but given the number of people who travel each year, questions about the real impact of the new policy could not be answered. He also noted that there are many adults not covered by existing recommendations and the number of deaths among this population was much greater than those among school-aged children. In addition, millions of doses of influenza vaccine are thrown away each year, while more manufacturers are coming into the market, so previous fears about supply not keeping up with demand were unfounded. Given that there is a vaccine informed by six decades of efficacy and safety data and annual epidemics kill tens of thousands of Americans, he recommended moving quickly to universal vaccination, with an emphasis on specific high-risk target groups.

Dr. Baker reminded the audience that there was already a recommendation to immunize all children 6 to 59 months of age, but less than 20 percent of that group was actually getting immunized. Physicians and the general public continue to believe that the vaccine has to be given before November and young children have to have two doses at least four weeks apart. However, for the past ten years, 60 percent of the flu seasons have peaked in February, so vaccination needs to continue through December and even into January. Everyone was shocked at the Prevnar efficacy in the un-immunized older population. Young children have higher titers of flu, and they shed almost twice as many days as do adults. Thus there is good reason to a better job with pediatric immunization, followed by surveillance.

Dr. Baker noted that the National Foundation for Infectious Disease has a new initiative called the Childhood Influenza Immunization Coalition, whose goal is to protect children against influenza by communicating with one strong voice the importance of making influenza immunization a national health priority. The coalition is led by the Surgeon General and co-chaired by Dr. Baker. On May 23rd, over 20 of the nation's leading public health, medical, and parent organizations met to discuss the objectives of the coalition and outline ways to improve immunization rates. The coalition will educate healthcare professionals and parents on the importance of vaccinating children throughout the influenza season and then measure the outcome of their campaign.

Dr. Poland pointed out that with pertussis the policy is not to immunize adults to protect children, even though adults are a reservoir for pertussis. Because all adults cannot be immunized, children are immunized against pertussis. Similarly, because all children have not been immunized against influenza, and because of the dynamicity of the adult population, adults need to be immunized. However, he applauded the initiation of a new coalition that would push for influenza immunization.

Dr. Schuchat asked what kinds of studies were being done on vaccine effectiveness for direct protection in children. Dr. Fiore responded that vaccine efficacy studies were going on in several different sites, including the Marshfield group and the EIP sites, as well as in the new vaccine surveillance network sites. The aim is to do more rapid efficacy estimates that would be available shortly after the end of the season. The past couple of flu seasons have been very mild and the few cases that were available to study were actually the same circulating strains in the vaccine. Influenza epidemiology makes it difficult to design studies

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that reliably have the power to measure efficacy.

Dr. Abramson asked whether the timetable would be part of the September meeting's deliberations. Dr. Allos indicated that it would not. Dr. Schuchat pointed out that the focus of the September meeting would be on the first point on the timetable, based on information about effectiveness, safety, feasibility, and logistics. The rest of the timetable will depend on what happens with the first point.

Dr. Treanor observed that because of the extreme variability from season to season, it may not be possible to gather useful data over a short time period. A drop in pediatric deaths over a couple of years could be the result of a vaccination campaign but could also represent epidemiologic variability.

Dr. Hosbach of sanofi pasteur asked whether manufacturers would be invited to the September meeting. Dr. Fiore replied that vaccine supply was not considered a limiting factor. Dr. Hosbach noted that vaccine manufacturers were also interested in increasing immunization rates and that the logistics of immunization was part of their planning for each flu season. Dr. Lewin of the Biotechnology Industry Organization added that manufacturers are not just suppliers. They can also provide guidance on products that are in development and indications, as well as their experience in distribution and ideas that might help implement these recommendations smoothly.

Dr. Tan of the American Medical Association and also representing the National Influenza Vaccine Summit, advised that physician groups prefer a simpler recommendation for vaccination and would support moving toward universal recommendations.

Dr. Duchin of Seattle, Washington expressed concern about the two-year observation period after the recommendation to expand to all school-aged children, particularly in the context of looking at any effect on older adults. He felt it was a very short time frame and encouraged the committee to consider ways to facilitate uptake, particularly in the school setting.

Ms. Stinchfield requested that there be a phone conference if the FDA FluMist decision were to come through during the next few weeks. The issue is time sensitive and there will also have to be public notice. Dr. Abramson added that the label will probably be for age two and older, which makes the consideration somewhat easier, but the committee is getting five new members who must be caught up before there is a vote.

Update on FluMist Safety Monitoring

Dr. Broder reminded the committee that the general approach to safety monitoring of new vaccines or new indications is to review prelicensure safety data to identify potential risk from Phase III prelicensure trials, recognizing that rare adverse events may not be apparent until wider use. Post marketing data are reviewed and then a Vaccine Adverse Event Reporting System monitoring plan is developed, as well as a Vaccine Safety Datalink project plan, where risk is assessed through near real-time or planned studies. Next the need to create key case definitions is identified, along with candidate protocols and special studies that might involve collaboration with other partners.

The main study supporting the FluMist age change under consideration was a multi-center randomized trial. About 50 percent of the subjects were in the U.S. and the age group was 6 to 59 months. The study group received FluMist and an intramuscular placebo saline, while the active control group received TIV plus an intranasal placebo of saline. Each group enrolled about 4,000 children. Subjects were excluded if they had a history of severe asthma

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or medically diagnosed or treated wheezing within 42 days before enrollment, but they were not excluded for more mild forms of wheezing. In fact, recurrent wheezing was a criterion for stratification in the study.

There were two pre-specified safety outcomes. The primary one was medically significant wheeze (MSW), and the secondary one was any wheeze. MSW was the presence of wheezing on physical exam and at least one of the following: signs of respiratory distress, hypoxemia, or a new prescription for a daily bronchodilator that was not prescribed on an as-needed basis.

The key safety finding was an increased risk for MSW in children age 6 to 23 months after FluMist, compared with TIV. This risk was not observed in the 24- to 59-month group. Although the breakdown of 6 to 11 months and 12 to 23 months was not an original pre-specified age group, that risk persists when the data are analyzed that way.

Compared with TIV recipients, FluMist recipients had more frequent reports of runny nose, nasal congestion and low-grade fever after Dose 1. But they had a similar rate of serious adverse events (about 3 percent in both arms), which were rare throughout the study's six-month period. The vast majority of these SAEs were hospitalizations. FluMist recipients in the age group 6 to 11 months (not a pre-specified age group) did have an increased risk for all-cause hospitalizations during that six-month monitoring period for SAEs. In the FluMist group, 6.1 percent of the recipients were hospitalized versus 2.6 in the TIV group. The rates persisted when looking at respiratory hospitalization versus all-cause hospitalization, but no supporting biologic mechanism was apparent.

Dr. Broder then shared some data from VAERS for the current indication, which is 5 to 49 years in persons without a history of wheezing or asthma. From licensure through the end of February 2007, VAERS received 744 reports after FluMist. About 6 percent of the reports overall were serious, and only 15 reports were received among children less than five. This was an off-label indication, and none had serious adverse events. When serious adverse events are linked to age, they are all less than 10 percent, which is lower than expected for VAERS reports.

The most common reported condition overall was respiratory events. In the pediatric age group, 6 percent of the reports were asthma-wheezing. Of the 16 reports, 7 had a history of asthma or wheeze, which indicates off-label use. This raises the question of whether it might be more likely to occur in a younger group where wheezing is common and screening might be harder.

Three questions seem critical. First, when the screening criteria are established, particularly for exclusion related to wheezing, will the screening for history of wheezing appropriately identify children who should or should not receive vaccination? Second, is the safety profile of FluMist within about six weeks or possibly a little longer after vaccination comparable to TIV in children less than five years? It will be important to look at the risk for medically attended wheeze and for all-cause hospitalization, as well as potential unexpected safety signals. Finally, if there is some off-label use or if there is a permission for use in certain wheezing populations, are children with a history of wheezing in fact at increased risk for wheezing or hospitalization or other adverse events after FluMist compared with those who do not have such a history?

VAERS will be the cornerstone of initial monitoring, particularly if uptake is low. CDC and FDA scientists will review daily alerts of serious adverse event reports and other medically important conditions, including medically important wheezing after FluMist. The

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second avenue will be the Vaccine Safety Datalink. The main limitation of VSD is limited power to assess risk for rare adverse events, particularly if uptake is low. VSD will examine the clinically important outcomes in children, especially medically attended wheezing and all-cause hospitalizations. But the FDA licensure and ACIP recommendation decisions and the uptake patterns in the VSD will affect specific aims and methods of the VSD study.

The Brighton Collaboration is developing standardized case definitions for wheezing and asthma outcomes, which will be important to communicate risk information and screening guidance. A primary vehicle will be the vaccine information statement. Finally, a Phase IV study is under way among 60,000 FluMist recipients aged 5 to 49 in the Kaiser Permanente system. This manufacturer-sponsored study has no CDC involvement. Results are anticipated in 2011.

Discussion

Dr. Schaffner asked whether children with a previous history of asthma and wheezing had more serious cases of influenza and whether hospitalization was increased. He wondered whether that information was needed to contrast what is happening after either vaccine. Dr. Abramson replied that flu was a well-known inducer, however it is not clear that the virus has to get into the lung to induce asthma. Dr. Iskander commented that a corollary question was, what is known about the inactivated influenza vaccine and wheezing? Several VSD studies revealed that the initial signal of wheezing following inactivated influenza vaccine was ultimately found to be an artifact of low vaccine coverage and the fact that children with more severe asthma disease were more likely to get the vaccine in the first place.

Dr. Whitley-Williams was concerned about the use of historical screening for asthma, especially in the 6- to 11-month-old age group. Wheezing is often associated with upper respiratory tract infections, which have viral etiology, yet parents may not be aware that the child has asthma reactive airway disease.

Since asthma is significantly on the rise in some minority and urban populations, Dr. Whitley-Williams asked if there was any information about whether postvaccination wheezing occurred more in any particular group. Dr. Broder replied that VAERS does not routinely collect that information. Dr. Walker from MedImmune talked about CP-111, a multinational study in North America, Europe, and Asia, where about 80 percent of the children were Caucasian. In that study, there were no appreciable ethnicity differences in terms of asthma rates, although the Asian population was only about 5 percent. The study did find that rates were more common in males than females, across the board for both FluMist and TIV recipients. Dr. Malinoski added that MedImmune had made three post-marketing commitments with the FDA pending approval, one of which was a large study in children less than five. It will obviously be possible to collect ethnicity data within that analysis. MedImmune has two additional studies that will look at the effectiveness of the label in excluding children less than 24 months of age and excluding children and adults with asthma and recurrent wheezing as a surrogate for asthma. Those studies can be shared with the working group or members of the safety group at CDC.

Dr. Malinoski informed the group that the current proposed label was for children 24 months and above, with warnings and precautions for anyone with asthma and children less than five with recurrent wheezing as a surrogate for asthma, so that the label consistently excludes anyone from 2 to 49 years of age with asthma. Discussions with the FDA office of compliance are moving forward relative to resolving manufacturing practices. Both the

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agency and MedImmune are confident that 7 million doses will be available this summer.

2007 National Influenza Vaccine Summit

Dr. Mootrey provided an overview of this year's National Influenza Vaccine Summit, which took place on April 19 and 20. It has become an annual meeting co-sponsored by the American Medical Association and the CDC to discuss influenza vaccine issues with a broad stakeholder base. There were 190 attendees representing 74 organizations. The manufacturers estimated that, barring any unforeseen glitches in the system, up to 132 million doses of vaccine could be expected this year. Carol Baker described NFID's Childhood Influenza Coalition, the American Lung Association discussed its flu clinic locator and Tony Fiore presented a summary of the ACIP recommendations. Key issues discussed were the vaccine composition, the pediatric second dose, recommended groups, the remaining age groups, the potential time frame for modifying influenza vaccine recommendations, considerations for expanding those recommendations, and some future challenges as the recommendations were expanded. There was quite a bit of discussion of the fact that ACIP now recommends vaccination for persons, including school-aged children, who want to reduce the likelihood of becoming ill with influenza or transmitting influenza to others, should they become infected.

There was an emphasis on supply and distribution issues, including the rationale for post-season shortages, supply challenges, and providers' misperceptions regarding the prioritization of vaccine delivery. The CDC presented some data from the secure data network indicating that private providers had received proportionately equitable supplies throughout the 2006-2007 season.

One very active session had to do with legislation. Some legislative initiatives may present barriers to achieving coverage, for example, those that prohibit the use of thimerosal in vaccines. Others may complicate equitable distribution. Several proposals suggest prioritizing distribution to certain provider groups. There will be an effort to provide much needed education and information to lawmakers and community leaders.

Another session focused on increasing demand for vaccination through a variety of partnerships. Awards were given for immunization excellence in three different categories. For extending the season, the getaflushot.com organization received the award, and they partnered with an unusual group of food banks. The Virginia Mason Medical Center got the award for the healthcare worker partnership. Through their mandatory vaccination program, they have achieved 98 percent vaccination of all of their staff for the past two years. The seasonal activities award went to a Maryland elementary school influenza vaccination project; in some schools, more than 40 percent of the children were vaccinated using two different models and over 114,000 doses of vaccine were distributed.

As far as increasing vaccination coverage, there was a presentation showing how to measure vaccine use, followed by a discussion about the length of the season and how to expand it. Dates for the National Influenza Vaccination Week were presented for the first time. Throughout the meeting, there was discussion about the need for more timely and consistent messaging. Other items for discussion included how to better balance supply and demand; how to track discarded doses and possible ways to redistribute doses; ideal settings for vaccination; and ways to expedite and smooth out the vaccine approval, testing, and delivery process.

The executive committee of the Summit will continue to work on improving coverage

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of healthcare workers and is also encouraging the formation of an informal legislative task force, whose primary intent would be educational. Another objective is to develop a simple, consistent statement on when and who to vaccinate. The current statement is, *"The National Influenza Vaccine Summit encourages that every year influenza vaccine be administered to all people, including school-aged children, who want to reduce their likelihood of becoming ill of influenza or transmitting influenza to others as soon as the year's vaccine becomes available. Influenza immunization should continue throughout the influenza season through the winter months and beyond as long as vaccine is available."* Suggestions are welcome.

Discussion

Dr. Abramson noted that there had been a healthcare summit five years ago and not much progress had been made. Dr. Schaffner responded that the National Foundation for Infectious Diseases continues to promote healthcare worker immunization. However, with rare exceptions where institutions have been extraordinarily forceful and innovative in providing influenza vaccine and obliging all healthcare workers to participate, coverage remains at just about 50 percent. Nurses in particular are very reluctant to be vaccinated, based on an embedded myth that one can get flu from the vaccine. In addition, many prominent physicians remain skeptical about the efficacy of influenza vaccine. So any suggestions on how to move ahead are welcome.

Ms. Stinchfield reported that rates had increased by 10 percent in Minnesota using the declination form. They are also working on real time IT solutions to track who has come in, who needs follow up and who has filled out a declination form. The challenge is that the myths are very strong, very old, and mostly unfounded. The message that all vaccines are 100 percent effective is not correct, but this in fact underscores the need to get everybody in so there will be a better immunized population. A simple message works best: Everybody needs flu vaccine. It is needed throughout the season. It will help healthcare workers as well as all the other high-risk populations.

Dr. Tan of the American Medical Association pointed out that the Summit executive committee was collaborating with some other organizations to provide a best-practices package, highlighting three to five facilities across the country that have successfully increased healthcare worker immunization rates, starting with the Virginia Mason program. Some of the techniques were very innovative but also very aggressive. The idea is to offer a variety of models that work. The Summit Web site -- www.preventinfluenza.org -- has a specific healthcare worker site with all the necessary resources, including a sample declination form that can be downloaded. It also has guidance from organizations such as the National Foundation for Infectious Diseases, the HICPAC-ACIP statement and the joint commission standard.

Dr. Poland noted that it has been shown that if it is mandated, healthcare workers get immunized. Out of 5,000 employees, Virginia Mason had only six leave over the policy. It would be unconscionable to allow a rubella-naïve nurse to work in a maternity ward because he or she had misconceptions about rubella vaccine, and this thinking should extend to influenza vaccine. It has also been shown that informed declination helps. Finally, trial attorneys now understand that multiple professional organizations have listed this as the standard of care. Unfortunately it may take a few well-publicized lawsuits to get everyone on board in terms of quality and patient safety.

Dr. Lett wondered if there were any activities to educate legislators about influenza

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vaccine, and in particular whether there was going to be an organized national effort. Dr. Tan replied that the Summit had already formed an informal task force, which had met twice regarding legislative issues across the country. An educational fact sheet on the challenges of influenza vaccine organization will be produced, including administration, supply, and distribution. Obviously, thimerosal will be another focus.

Dr. Iskander noted that if healthcare workers are concerned they may get the flu from the vaccine, then perhaps it is time to study that issue in more depth rather just a lot of hand wringing. Dr. Abramson responded that the question of whether this was a safety issue had been raised with OSHA and their answer was, "We did not have proof that patients did not give the flu to healthcare workers."

Dr. Sumaya said that if the healthcare system only relies on individuals to implement immunization schedules, coverage would always remain at 50 to 70 percent. Although it sounds militaristic, it might be necessary to make immunization more obligatory. Healthcare workers are familiar with the safety and quality issues, so it may be one place where there can be stronger urging, such as making immunization coverage part of hospital accreditation or part of individual performance evaluations. There would always have to be a mechanism for opting out, but the issue is something the ACIP could tackle.

Dr. Turner of American College Health thought there had already been an effort to consolidate messages and make them consistent. He asked whether last year's vaccine production goals had been met, whether the messaging had resulted in an increased uptake and whether there had been an appraisal or assessment of last year's efforts. Dr. Wallace replied that manufacturers produced around 120 millions doses and that 102.5 million were distributed. He did not know how many doses were administered.

Dr. Decker suggested that NIOSH could take an active role in the influenza-among-healthcare-workers issue and provide some science to guide OSHA. Dr. Landry of GSK added that this could be viewed as a quality-improvement measure for hospitals and that NCQA should be approached as well.

Dr. Abramson thanked Dr. Allos for her work on the influenza working group.

USE OF VACCINES IN PERSONS WITH HIV/AIDS

Dr. Jane Seward, CDC/NCIRD/DVD
Dr. Gina Mootrey, CDC/NCIRD/ISD

Children and Adolescents

Dr. Seward focused on changes made in the immunization schedule for HIV-exposed and infected children and adolescents. The term 'exposed' is used because infants cannot be called 'infected' until definitive testing has been done. New guidelines are being developed for prevention and treatment of opportunistic infections in this population, as a collaboration among CDC, NIH, and IDSA. The new guidelines will be divided into 2 documents, one for children and the other for adults. Accompanying the guidelines for children will be vaccine schedules for zero-to-six and 7- to 18-year-olds. Another group is developing the document for adults which will include the vaccine schedule for adults (≥ 18 years). Publication of both documents as *MMWR*s is expected sometime in the fall, but they will be updated on the Web as new data related to prevention and treatment of opportunistic infections become available and ACIP recommendations are passed.

The published 2007 immunization schedule for all children in the three different age

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groups was modified with specific HIV language, taken from published ACIP recommendations. The footnote language was clarified in discussion with CDC subject-matter experts. The colors of the bars on the immunization schedule were also changed, based on recommendations for HIV-status. Draft schedules were shared with CDC, NIH, and the IDSA working groups. The zero-to-six and 7-to-18 schedules were presented to the harmonized working group and they suggested that the ACIP vote on the schedules specifically because of the rotavirus language. There are no plans to harmonize the schedule with AAP and AAFP because of the small number of children involved. They suggested just staying with the ACIP recommendations.

The rotavirus language is as follows: *"No safety or efficacy data are available for the administration of rotavirus vaccine to infants who are potentially immunocompromised, including infants with HIV.*" (That language is right now in the footnote.) *"Data are insufficient from the clinical trials to support administration of rotavirus vaccine to infants with indeterminate HIV status who are born to mothers with HIV/AIDS. Practitioners should consider the potential risks and benefits of administering rotavirus vaccine to infants with known or suspected altered immunocompetence."* (That language includes HIV-infected infants.)

The existing language already provided the option for physicians to vaccinate after weighing the risks and benefits, but the "*however*" language supports vaccination of HIV-infected infants.

There are 6,000 to 7,000 HIV-exposed infants born each year in the United States. HIV status is not definitively known by six weeks, but most will be presumptively negative until they have been tested. They cannot be definitively negative until four months of age according to current guidelines. Only 100 or 200 will eventually test positive and those are basically infants of mothers who did not get any prenatal care and did not receive HIV prophylaxis during pregnancy.

Rotavirus is a ubiquitous infection in childhood. Virtually every child in this country and other countries will become infected by five years of age. So if these children are not vaccinated, they will certainly come down with wild rotavirus disease. RotaTeq is the only vaccine licensed in this country currently and that strain is considerably attenuated with a very low incidence of fever, other constitutional symptoms, or viral shedding. Available data suggest that rotavirus disease is not more severe in HIV-infected infants, which propelled the commencement of trials in HIV-infected children in Africa.

The same studies that showed no difference in disease severity did show higher all-cause mortality in HIV-infected children during four weeks of follow-up after rotavirus illness, but the significance of that is unknown because it was not directly related to the rotavirus illness.

Most of the studies comparing rotavirus disease severity between HIV-infected and non-infected infants were done in infants, and more data are needed on disease severity in older, immunosuppressed HIV-infected children. It may be that in countries without good HIV treatment, there are differences as children become more immunocompromised.

Oral polio vaccine replicates much more robustly in the intestinal tract with a much higher viral-shedding risk than RotaTeq, and it is considered to be safe and is immunogenic in HIV-infected children, according to two published studies.

No trials with rotavirus vaccine are planned for the U.S. in HIV-infected infants, mainly because there are not enough infants to do a study. In developing countries, where the

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numbers of HIV-infected children are higher, co-morbidities are also higher, especially malnutrition, and the rotavirus disease mortality and burden are significantly higher. Trials with both the GSK and Merck rotavirus vaccines are under way or planned. It is not known when those data will become available, but presumably not anytime soon.

The fact that no safety or efficacy data are available is in the ACIP statement already. However, the following considerations support vaccination of HIV-infected infants. One, the HIV diagnosis may not be established before the age of the first rotavirus vaccine dose. Only 1.5 to 3 percent of HIV-exposed infants in the U.S. will eventually test HIV positive. Two, natural rotavirus infection does not appear to be more severe in HIV-infected infants. And three, RotaTeq vaccine is considerably attenuated.

When these data were presented to the NIH, CDC, IDSA group, there was considerable discussion about the safety of giving the vaccine to HIV-infected infants. Use of RotaTeq vaccine in HIV-exposed or infected children was discussed when vaccine policy recommendations were made by the ACIP. It was considered to be the intent of the ACIP to administer the vaccine to those infants, but the statement did not state that intent strongly. After the meeting, the group expressed discomfort with giving the vaccine to HIV-infected infants because of lack of safety and efficacy data. Another suggestion was to change the title of this schedule to “HIV-exposed and infected infants”.

The schedule for children age zero to six years follows the same order as the regular schedule with the following changes to some of the bar colors. For influenza, HIV status is considered one of the high-risk groups so this vaccine is recommended annually for HIV-infected children and the bar color is changed accordingly from purple (high-risk groups) to yellow (routine recommendation). For MMR and varicella, there is red language saying: "Do not administer to severely immunosuppressed children." For hep A and mening polysaccharide vaccine, these children are not in the high-risk group, but they could be if they had additional areas of residence or conditions, so the bar is left purple. They are potentially high-risk but not by virtue of their HIV status, so they should get PPV. The footnote language is absolutely word for word out of approved statements, except for rotavirus, which is a little different.

The vote is whether to approve the immunization schedules for both age groups and, as new ACIP recommendations are made, to incorporate them into the schedule after publication of provisional or final ACIP recommendations. The options for rotavirus vaccine language are to adopt the new language presented above, use exact language from the ACIP statement, which says to weigh the risk and benefits but it can be given, or recommend that the vaccine not be administered until safety and immunogenicity efficacy data are available.

Discussion

Dr. Baker thought the comment about exposed and infected children was a good one, since the rotavirus schedule is to be completed by 32 weeks of age, before it can be established whether children are infected. In addition, the first 32 weeks are when CD4 counts are very good. She favored the implicit recommendation from the rotavirus schedule; it is a benefit to children in general and why should HIV-infected children get less benefit than regular children under these circumstances?

Dr. Gilsdorf brought up her suggestion from the previous day about the use of the word "recommended" in the title because it suggests that all of the bars represent recommendations from the ACIP. She felt that there was a difference between a

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recommendation and support. Dr. Schuchat clarified that the previous discussion had focused on adults and that the committee was staying away from recommendations on certain of the adult vaccines for the HIV-infected population because data were forthcoming, for example for zoster and HPV. That language is much more critical for the adults where there is a large HIV-infected population that is looking for guidance and there are more data available. Dr. Gilsdorf also noted that the wording for HPV should indicate females only.

Dr. Treanor pointed out that when the original rotavirus recommendation was made, the vaccine had not been used extensively; now that there has been extensive use of the vaccine without problems, people are more comfortable. However, regarding the fact that rotavirus disease is not more severe in HIV-infected children, there is the possibility that people will conclude that there is no special reason to vaccinate. His recommendation for the wording would be to just leave out No. 2. Dr. Baker affirmed that suggestion.

Dr. Morse asked about the footnote that says only TIV should be used for HIV-infected persons. Dr. Seward clarified that it was strongly recommended that their contacts get vaccinated, and they can get LAIV. Dr. Morse thought that was confusing. His second question was whether revaccination for PPV should be offered or recommended. Dr. Seward affirmed that 'offered' was the exact language. The data on safety and immunogenicity of PCV for children aged 2 to 18 years will be presented in the fall and if it is voted on, it could change the PCV recommendation.

Dr. Sumaya asked whether natural rotavirus infections appear to produce similar levels of severity in HIV-infected as in non-infected HIV infants and, if so, that needs to be more clearly stated. Dr. Baker responded that there are actually not strong enough data to say anything.

Dr. Offit from Children's Hospital of Philadelphia emphasized that rotavirus vaccine is a very highly attenuated strain and a pentavalent vaccine. It is 1.6 times 10 to the sixth platform units per strain and there are five strains, so 8 million infectious particles are given by mouth. However, less than 10 percent of children shed and they shed for, at most, a day or two and in very limited quantities. Oral polio vaccine or RotaShield shed to a greater extent. This is now the only live attenuated viral vaccine given routinely to young infants. Typically, severe combined immunodeficiency disease is not a diagnosis made until about eight months of age. Since children with SCIDs are clearly getting this vaccine, it would be interesting to see whether they have increased or prolonged shedding associated with symptoms.

Dr. Halsey from Johns Hopkins said he was surprised to hear the discussion about whether these were recommendations. The public needs clear recommendations and it would be more efficient than having to revise other statements.

Dr. Pickering said the transcript of the rotavirus meeting indicates a preference that rotavirus vaccine be given to children who are born to mothers who are HIV exposed. Dr. Parashar added that a number of studies had looked at viral shedding and immunologic response in HIV-infected and noninfected children, and the disease severity by a variety of parameters was identical in both groups. Both mounted equally good immune responses to natural infection--about three-fourths of infants in each group. Shedding was slightly longer in HIV-infected kids, but most of it was asymptomatic. So they concluded there really was no difference in the natural history of rotavirus infection in HIV versus non-HIV kids.

Dr. Rathore of Jacksonville, Florida suggested that many practitioners, particularly for HIV-exposed children, may already be using rotavirus vaccine in these children because his practice had not seen an infected child in ten years.

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Vote

Dr. Baker made a motion to accept Dr. Seward's recommendation with the edits that had been discussed. Ms. Stinchfield seconded the motion. Dr. Gilsdorf asked whether this motion addressed the concerns about the difference between a full recommendation and support of use. Dr. Schuchat responded that the distinction was not critical for pediatric cases, but it was important for adults. Dr. Seward thought that with live viral vaccines more data might be needed, but not with inactivated vaccines. An unidentified speaker suggested using a different color, indicating that the recommendations is being made without data. Dr. Pickering suggested referring the question back to the respective work groups for consideration of the wording change in the title.

Dr. Seward summarized the motion, which was that ACIP approve the immunization schedule for HIV-infected children -- exposed and infected children zero to six years and 7 to 18 years, with the changes in the footnote as suggested for rotavirus and for influenza and that new ACIP recommendations will be incorporated into the schedule after publication of provisional recommendations. Edits include using "exposed or infected" and specifying females for HPV.

Dr. Morse: yes.
Dr. Treanor: abstain.
Dr. Sumaya: yes.
Ms. Stinchfield: yes.
Dr. Neuzil: abstain.
Dr. Morita: yes.
Dr. Lieu: yes.
Dr. Lett: yes.
Dr. Hull: yes.
Dr. Gilsdorf: yes.
Mr. Beck: yes.
Dr. Baker: yes.
Dr. Allos: yes.
Dr. Abramson: yes.

Adults

Dr. Mootrey then showed the recommended schedule for HIV-infected adults. One difference between the children and adults was that there was already a schedule for children, which just had to be modified. The adult schedule is a new addition to the guidelines and it has not been brought to the ACIP adult immunization work group yet. There should be an updated draft for the opportunistic infections adult work group by the end of the summer.

Dr. Morse commented that there should be consistency across the tables for the "Do not administer" recommendation.

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UPDATE ON ROTAVIRUS VACCINES

Dr. John Treanor, ACIP, Working Group Chair
Dr. Umesh Parashar, CDC/NCIRD/DVH
Dr. Penina Haber, CDC/ISO
Dr. Manish Patel, CDC/NCIRD/ISD
Dr. Hector Izurieta, FDA/CBER

Dr. Treanor announced that he would be rotating off ACIP and wished his successor luck in chairing the rotavirus working group.

Safety Monitoring Update

Dr. Haber provided a summary of RotaTeq vaccine adverse events reported to VAERS, followed by updates on the Vaccine Safety Datalink and Merck Phase IV study. From March 2006 up to June 14, 2007, about 6.2 million doses of RotaTeq were distributed. During the same time period, VAERS received a total of 1,251 reports of adverse events following RotaTeq vaccination. Of those, 573 (46%) were from RotaTeq given alone, and 609 (47%) were after the first dose. The most frequently reported outcomes were diarrhea, vomiting, fever, and hematochezia.

Of all the reports, 9.4 percent or 117 were confirmed intussusception reports. Thirty-eight were within 1 to 21 days after vaccination and of those, 23 were within one to seven days. No intussusception deaths were reported.

Dr. Haber described 116 cases in a graph, which showed a couple of peaks but no major pattern. When intussusception reports are analyzed by dose distribution of intussusception and by onset interval in days, there again is no major pattern. After the FDA notice on February 13th, 2007 and following the *MMWR* publication in March, reports to VAERS of events occurring over 21 days increased, which indicated higher reporting efficiency to VAERS.

Overall, the mean age at symptom onset symptom was 23 weeks, the range 9 to 45 days. There was equal distribution between male and female. Fifty-seven or 49 percent had contrast enema, 32 percent (37) had surgical reduction, and 16 percent (19) had surgical resection. Two experienced spontaneous resolution, and for two reports there was no information.

Dr. Haber then provided an update on the Vaccine Safety Datalink. From May 21, 2006 up to June 17, 2007, 68,858 vaccinations were given and there was no report of intussusception within 30 days post vaccination. An analysis of distribution by age and dose by age shows that almost 50 percent of vaccinations were Dose 1, and about 30 percent were Dose 2.

Dr. Haber gave an update on the Merck RotaTeq post licensure safety study. This is a prospective observational active surveillance. The study population is a large insured U.S. population with annual birth cohort of about 100,000, and the planned final study size is about 44,000 vaccinated children. The study plan is to monitor rates of intussusception and overall vaccine safety, comparing the rates of several control groups 30 days post vaccination for each dose.

So far, there have been 7,196 RotaTeq recipients through the third quarter of 2006. As of December 31st, 2006, there were no cases of intussusception in RotaTeq recipients, but there were three cases in controls. The next review will include about 18,000 RotaTeq

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recipients vaccinated from February 2006 to December 2006.

Data Interpretation

Dr. Patel focused on whether the observed number of cases exceeded what would be expected to occur by chance alone. Intussusception rates vary in the first six months of life when the vaccine is being administered, so age stratification must be taken into account for the calculations.

Dr. Patel first talked about the calculations for the 1- to 21-day window. VAERS received reports of 38 cases of intussusception occurring within 1 to 28 days of vaccination, whereas approximately 99 cases would be expected to occur by chance alone, after adjusting for age. The reporting rate ratio is 0.37, with the upper 95 percent confidence limit being less than one. Data assumptions are 100 percent reporting completeness and 100 percent administration of the doses distributed. In each of the three age groups, the observed numbers did not exceed the expected.

For the one- to seven-day window, VAERS has received reports of 23 cases of intussusception, whereas approximately 33 cases would be expected after adjusting for age. The reporting rate ratio for the one- to seven-day window was 0.67, which is higher than for the 21-day window. However, the upper 95 percent confidence limit was 1.08. Within each of the three age strata, observed numbers did not exceed the expected, but for the 6- to 14-week age group, the number of observed cases was the same as the expected number.

Most of the RotaShield action occurred during the first week of vaccination with Dose 1. For Dose 1 of RotaTeq, in total, there were 12 cases observed in VAERS after Dose 1 and one would expect approximately 12 background cases within seven days of vaccination using the same 100 percent assumptions. With RotaTeq, it appears that Dose 1 is generally being administered according to the ACIP recommendations, at 6 to 12 weeks of age. The VSD data show that 93 percent of the doses were administered in the 6- to 14-week age group and the majority of the Dose 1 cases were also in that age group (10 of the 12 cases). Only two cases occurred in the second age group (15- to 23-weeks).

The RotaShield Dose 1 experience was quite different: 80 percent of the reported VAERS cases for RotaShield were after Dose 1, suggesting a clustering effect after Dose 1, as opposed to RotaTeq, where only 34 percent occurred after Dose 1. Eighty percent of the RotaShield Dose 1 was administered to children older than 90 days or 12 weeks of age, whereas only 7 percent of the RotaTeq in VSD has gone to children over 90 days old.

The nationwide case-control study for RotaShield revealed a 37-fold risk for Dose 1 within three to seven days of vaccination, whereas no similar signal has been seen with RotaTeq yet.

An important question is, of all the cases that are actually occurring within 1 to 21 days of vaccination, how many are being reported to VAERS? Looking at all intussusception cases reported to VAERS by onset month, two-thirds were outside the 1- to 21-day window, which is when vaccine is unlikely to be biologically linked to intussusception. The FDA notification in February did stimulate reporting, but most of the reports in the two months since the FDA notification were also outside that 1- to 21-day risk window, which suggests that reporting efficiency is high for the first 21 days of vaccination.

A second data assumption has to do with vaccine administration, and the question is, what proportion of the doses that are distributed is actually being administered? RotaTeq has been on the market for approximately 16 months and two factors suggest favorable vaccine

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uptake. One is that the manufacturer has been distributing 400,000 to 600,000 doses of vaccine per month for the past eight months and the other is that the VFC contract now has been in place for about a year. The National Immunization Survey after RotaShield showed that 66 percent of the vaccine doses distributed were actually administered during the nine months it was on the market.

In order to do the sensitivity analysis, the assumption was that reporting completeness was around 75 percent and that 75 percent of the doses distributed were actually administered. With these assumptions, the reporting rate ratio is 0.7 for the 1- to 21-day window, and slightly above 1 for the 1- to 7-day window. But neither of these is statistically significant. If the reporting completeness was 50 percent and vaccine administration was 50 percent of the doses distributed, one would begin to see a signal. For the 1- to 21-day window, the reporting rate would be 1.47, and for the 1- to 7-day window, the reporting rate would be 2.6. Despite these assumptions, the reporting rates are still rather small.

Looking at all intussusception cases by onset interval in days, more cases have been reported during Week 1 compared to Weeks 2 and 3. There are several possible explanations for this clustering effect. One is the well-known effect of passive surveillance of adverse events, where reporting tends to be better closer to the exposure. Another possibility is that this clustering could represent a two- to three-fold risk in Week 1 compared to Week 3. Week 1 clustering could be also a random event. However, since the number of cases is small by week, one should be cautious in over-interpreting those data.

In summary, no intussusception signal has been identified with post-licensure monitoring for RotaTeq in the U.S. To date, the combined safety data include the 105,000 doses for the REST clinical trial; about 70,000 doses for the VSD; 7,000 Merck postlicensure doses; and 16 months of VAERS data, none of which has identified a signal. However, one must be cautious and continue monitoring because the current data cannot exclude smaller magnitudes of risk, which would require large sample sizes. If one wanted to exclude a five-fold risk in the first week of vaccination, for example, one would need follow-up data on nearly 130,000 vaccinees. However, to exclude a two- or three-fold risk, follow up data for one week on 400,000 to 1.3 million vaccinees would be needed. Even a case-control study would be fairly cumbersome to rule out such a magnitude.

To place this risk in perspective, if there was a two- to three-fold risk after Dose 1 and the entire U.S. birth cohort of 4 million were to receive that dose, one would see approximately 25 to 50 additional cases per year. In contrast, approximately 50,000 to 70,000 rotavirus hospitalizations would be prevented and possibly 20 to 60 deaths from rotavirus.

To reiterate the conclusions from the previous ACIP meeting in February and the most recent *MMWR*, the observed reporting rates of intussusception do not appear to be greater than what would be expected to occur by chance alone. Nonetheless, these data must be interpreted with the limitations of the passive surveillance system in mind. Ongoing monitoring will be crucial, particularly for Week 1 after vaccination, where there may be a clustering effect. Finally, it will be important to continue to follow VSD and Merck post-licensure cohorts, because a larger cohort would be needed to exclude smaller risks.

RotaTeq and Kawasaki Disease: Pre- and Post-Licensure Experience

Dr. Izurieta presented data from a study done by a number of investigators and groups, including the CDC, the Vaccine Safety Datalink group and the FDA. As background, he explained that the original FDA-approved label did not include Kawasaki disease cases. In

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the original license application were three cases in the vaccine group, and zero in the placebo group. In the four-month safety update, there were five in the vaccine group, and zero in the placebo group. Following an inquiry from the Swiss regulatory agency, an FDA review of Kawasaki disease showed a total of five cases in the vaccine group, and one in the placebo group. The placebo was from Finland, and the vaccine cases were all from the same center in the U.S. None were of Asian descent. All cases were between 12 and 22 weeks of age and all, except for the placebo, had received other concomitant childhood vaccinations. All but the placebo case completed the series of three doses of vaccine.

When the label revision was made in 2007, Kawasaki disease was reported among the serious adverse events. For each dose in the Phase III clinical trial, infants were followed for up to 42 days. Kawasaki disease was reported in 5 of 36,000 vaccine recipients and 1 of 35,000 placebo recipients. The difference was not statistically significant.

Regarding the post-marketing experience, there were reports of Kawasaki disease, but this does not mean there is or is not an association. No changes were made in the indications, warnings or precautions regarding the use of this vaccine.

In the U.S., Kawasaki disease is the leading cause of acquired heart disease in children, with over 4,000 cases every year. Almost 80 percent of these children are under five years of age. The incidence in children under five, as reported by Dr. Belay in a 2000 *Pediatric Infectious Disease Journal* article, was between 9 and 19 per 100,000 per year. Recent unpublished data from the Kids Inpatient Database for 2003 showed an incidence of 21 per 100,000 for all children under one year of age and 11 per 100,000 per year for children under six months of age. Data are missing from 20 percent of the children for specific age in months, so the 11 per 100,000 for children under six months of age could be underestimated.

The disease has not been reported in association with vaccinations, but in 1983 Japanese investigators reported finding rotavirus particles or capsomers in 29 of 39 (74%) stool specimens obtained within a few days of admission for Kawasaki disease to a Tokyo hospital. These patients did not necessarily have gastrointestinal symptoms. In the control group, which did not have Kawasaki, the rates of finding rotavirus particles were much lower. There are no confirmatory studies in the literature.

Again with regard to the postmarketing experience, there were four reports to VAERS following RotaTeq vaccination as of June 19, 2007. Three were received before the FDA notification and one after notification.

Approximately 6 million RotaTeq doses had been distributed in the U.S. of June 6, 2007, therefore the reported rates from the passive surveillance system are, in fact, lower than what would have been expected. This is subject to the limitations of any passive surveillance system, including VAERS. In addition, providers may not associate Kawasaki disease with vaccines and will not necessarily report them.

Of the four suspected Kawasaki disease cases identified in VAERS, one was a female of Korean descent, who was almost three months old at first dose. She had some symptoms, but not enough to be considered classic Kawasaki disease. The patient was treated by a well-known Kawasaki expert from Hawaii.

The second case was a black Hispanic from Texas, almost three months old as well. For the first dose, there was a three-day interval between vaccine and onset of symptoms. This patient had all the classic symptoms for Kawasaki except adenopathy, and also had coronary ectasia. The patient was treated by intravenous immunoglobulin.

The third case was from North Carolina, a six-and-a half-month old, with some classic

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symptoms after the third dose. But the conjunctival injection was yellowish, and the patient was diagnosed originally as having a bad rash. It is not known whether this case will be considered confirmed or not.

Information on Case No. 4 is incomplete. The report is for a male from California, five months of age, with onset 14 days after vaccination. The medical chart has not been received. All four cases described received other childhood vaccines as well.

There has been an ongoing review of all suspected Kawasaki disease reports to VAERS since it started in 1990. Out of 81 suspected Kawasaki cases after all vaccines, 44 were from the U.S. Of those 44, 19 were among children less than a year old, and 13 were under 16 months of age. Again, this does not mean they are confirmed Kawasaki disease or that they are causally associated with vaccination.

The CDC's Vaccine Safety Datalink study data come from six of the VSD sites. There was one unconfirmed Kawasaki disease case, meaning no chart review was made, out of over 68,000 doses of vaccine. This was within the expected rate, which would have been around two cases. VSD has agreed to incorporate Kawasaki disease into the ongoing Rapid Cycle Analysis of RotaTeq adverse events, as they have done with intussusception.

Merck has provided preliminary data from their observational Phase IV study. As an agreement for licensure, They agreed to an approximately 44,000 study population, and Kawasaki is incorporated. So far, for the primary analysis window of 30 days after vaccination, no Kawasaki disease or vasculitis cases have been found in the 7,000 RotaTeq vaccinees or in the 14,000 concurrent controls.

In summary, the signal from the pre-licensure clinical trials is now captured in the label. The Kawasaki reports in VAERS are within what would have been expected, but risk cannot be excluded. The ongoing observational studies from the VSD and the Phase IV show reassuring data, but they are limited because of insufficient power. One will have to wait until these studies progress to be able to reach conclusive results. At this time, there is no cause-and-effect relationship established between Kawasaki disease and RotaTeq or any other vaccine. FDA, CDC, and Merck will continue to monitor the safety of RotaTeq vaccine using VAERS, VSD, and the Merck Phase IV data.

Discussion

Dr. Baker asked whether fever was part of the criteria for reporting the second case. Dr. Izurieta replied that the patient had fever for five days. Dr. Baker then asked whether all four patients had cardiac echoes and when. Dr. Izurieta replied that the Texas case did. Dr. Baker noted that coronary ectasia was one of those things that may resolve. Dr. Izurieta replied that sometimes there is no evidence of ectasia or the evidence comes later and then resolves if the patient is treated early.

Dr. Baker then asked if other etiologies were excluded in the chart reviews. Dr. Izurieta replied there was not enough information on all the VAERS cases. The case from North Carolina had an alternative diagnosis and the case from Hawaii also had otitis. Only the Texas case was really classic. Dr. Baker said that it was very difficult to distinguish Kawasaki from certain viral etiologies, especially in children under six months of age. Even classic cases may have an alternative infectious disease diagnosis. On the other hand, those are the patients more likely to have an atypical presentation of Kawasaki disease where the physician may not make the diagnosis. This is a very complex association, so it is good that the rapid cycle safety analysis will be performed.

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Dr. Abramson confirmed that children less than six months of age more often than not have atypical Kawasaki and those who really have Kawasaki disease also have a higher incidence of coronary aneurism. He felt it was imperative to look for those children with the atypical Kawasaki, even though it might require outside expertise.

Dr. Gentsch emphasized the importance of standardizing case definitions for adverse events because, unlike efficacy, safety cannot be measured directly. It can only be inferred indirectly from measuring multiple, different adverse events. Without standardization, there is a lot of heterogeneity and lost data. He added that pre-licensure safety processes can be improved or standardized using lessons learned from RotaShield, where there was a similarly small number of events--about five in the vaccinated and one or two in the unvaccinated placebo group. They did a simple 2-by-2 chi square, and the P value was not significant. But some of those five cases were clustered around the same time. So a person-time analysis, while not statistically significant, would have been closer to significance. If a person-time analysis was not taken into account in the pre-licensure data, it should be in the future.

Dr. Pickering asked whether the three cases for which data were available were already symptomatic when immunized. Dr. Izurieta replied that one had what appeared to be a bad rash, onset date unknown, but all of the other symptoms appeared after vaccination, from a few hours up to Day 14 in Case No. 4.

Dr. Iskander clarified that VAERS specifies onset as the first symptom, whereas the standard criteria for Kawasaki define it as the onset of fever. Dr. Slade added that one child had an onset of fever at 12 hours after vaccination, but none were symptomatic at the time of vaccination.

Dr. Gellin asked what it takes to get something included in the label initially. He also wondered how robust the Kids' Inpatient Database (KID) was. Dr. Houn replied that the adverse reaction section of the label was governed by 21 C.F.R. 201.57(c)(7), which says that adverse reactions identified for clinical trials, especially those with significant clinical implications, must be supplemented with additional details, such as frequency or nature.

Dr. Iskander said KID more typically uses either the VSD or the HCUP (Healthcare Utilization Program) databases, but they are happy to work with any and all databases that provide reasonable background rates.

Dr. Abramson asked whether there would be a study design to compare those who get every immunization but rotavirus with those who get every immunization including rotavirus. Dr. Gargiullo replied that Ermias Belay was planning to look at all cases of Kawasaki syndrome going back to 1992 and one of the hypotheses would be live vaccine versus inactivated.

UPDATE: HPV VACCINES

Dr. Janet Gilsdorf, Chair, HPV Working Group
Dr. Gary Dubin, GlaxoSmithKline
Dr. John Iskander, CDC/ISO
Dr. Lauri Markowitz, CDC

Dr. Gilsdorf reviewed the activities of the working group to date. In June 2006, the ACIP voted on the recommendations for the quadrivalent HPV vaccine. These provisional recommendations were available on the Web in July 2006, and the HPV vaccine official statement was published in the *MMWR* in March 2007. The recommendations have since been

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adopted by a number of other collaborating organizations.

The working group has continued to meet monthly to review the bivalent HPV vaccine for safety, immunogenicity, and primary and secondary endpoints. The GSK bivalent vaccine BLA has been submitted to the FDA, so the working group has also considered future recommendations to be addressed with the predicted licensure of the bivalent vaccine.

Post Licensure Vaccine Safety Data

Dr. Iskander provided an overview of postlicensure safety surveillance for Gardasil, the first U.S. vaccine licensed for human papillomavirus, and summarized available data from the Vaccine Adverse Event Reporting System and the Vaccine Safety Datalink.

Gardasil is an inactivated vaccine, which was licensed by the FDA in June 2006 with an age indication of 9 to 26 years old and was subsequently recommended by the ACIP for routine use among 11- to 12-year-old females. General safety data were collected from almost 12,000 vaccine recipients in pre-licensure trials, and more detailed safety data were obtained from a subset of over 5,000 girls and women. Adverse reactions noted more commonly among vaccine recipients compared to placebo were injection-site pain, swelling, and erythema. Serious adverse events were rarely reported during pre-licensure trials. Among the ten deaths that occurred among Gardasil recipients, cause of death varied and did not appear plausibly related to vaccination. A total of four thromboembolic events were reported among vaccine recipients and six among placebo recipients. There was one fatality in each study group. Both involved oral contraceptive use, a known risk factor for thromboembolism.

Post-licensure safety data primarily focused on VAERS reports of commonly reported as well as serious adverse events, as defined in the Code of Federal Regulations. Reports involving population subgroups of special interest were analyzed separately. The data presented encompassed the first 11 months of the U.S. experience with Gardasil. Distribution data were obtained from the vaccine's manufacturer, Merck.

The vast majority of VAERS reports involved females and 70 percent covered the indicated age range of 9 to 26 years. Nearly 90 percent of reported events concerned Gardasil used as a single vaccine. Most reported adverse events that specified dose number followed the first dose in the series, however a substantial minority did not indicate the dose number. Reports to manufacturers, which typically originate from healthcare providers, make up the majority of reports to VAERS. Following a pattern typically seen within VAERS, a substantial proportion of reported adverse events begin on the day of or within a few days following vaccination. The most commonly reported events following Gardasil were fever, dizziness and loss of consciousness, also coded as syncope. Reports typically involved more than one adverse event, but only 5 percent of all reports were classified as serious.

Dr. Iskander then presented clinical details of four deaths following Gardasil. Case No. 1 was originally reported as being due to influenza A virus infection. Case No. 2 involved preliminary embolism in an oral contraceptive user. For Case No. 3, no additional medical records or clinical information were provided to VAERS, despite multiple attempts at follow-up. Case No. 4 involved laboratory-confirmed influenza B virus infection along with MRSA infection and has been reported to the national surveillance system for pediatric influenza-associated deaths.

Among 13 Guillain-Barre syndrome reports, nearly half have involved co-administration of meningococcal conjugate vaccine (Menactra®). Only two GBS reports that

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meet the Brighton Collaboration case definition have followed Gardasil given as a single vaccine with symptom onset within six weeks following vaccination.

Eleven serious reports have involved syncope, all occurring within ten minutes of vaccination. There have been two documented instances of intracranial hemorrhage and three non-serious reports of confirmed nasal fractures. (ACIP recommends a 15-minute waiting period following all vaccines. Also, syncope is a common condition with a variety of triggers among young adults.)

Two additional reports involved thromboembolism. Case No. 2 involved multiple risk factors for thromboembolism, including a medical one of OCP use, an environmental one of air travel, and multiple documented genetic risk factors. Incidence of thromboembolism in OCP users varies across studies. Risk increases with age and smoking and is also higher during initiation of medication use, regardless of age.

VAERS reports among preadolescents involved commonly reported local and systemic non-serious events. The one report of Stevens-Johnson syndrome was poorly documented.

Through the end of March 2007, more than 5 million doses of vaccine have been distributed in the U.S. Age-specific dose-distribution data are not available. Within the Vaccine Safety Datalink, three-quarters of vaccine use has occurred among females under age 18. Safety endpoints being monitored through rapid-cycle analysis include a range of events identified through prelicensure study and/or events that commonly occur among the target age group for this vaccine. The quadrivalent HPV vaccine is now covered under the Vaccine Injury Compensation Program.

The vaccine safety data presented should be considered as one of a variety of sources of post-licensure surveillance for this vaccine. VAERS data may be available more rapidly, but is subject to data quality and other concerns. CDC will continue to collaborate with FDA, the World Health Organization, and other public and private entities on post-licensure surveillance and communication activities.

Efficacy and Safety Data – Bivalent HPV Vaccine

Dr. Dubin presented the results from an interim analysis of GSK's largest single efficacy study, referred to as HPV-008. The GSK cervical cancer candidate vaccine contains HPV 16 and 18 virus-like particles, 20 micrograms of each VLP type, and is adjuvanted with AS04 adjuvant. The AS04 adjuvant was selected because its use resulted in higher levels of immunogenicity when compared to an aluminum hydroxyl adjuvant.

Based on these early results, GSK initiated a rather large Phase III development program that included immunogenicity and efficacy studies. The immunogenicity studies take data from the efficacy studies been conducted in women between the ages of 15 and 25 years, and then extend that through immunogenicity bridging to younger girls and women over the age of 25 years. The first efficacy study, HPV-001, has been reported on extensively. A second study called HPV-007 has now followed women in a blinded fashion through five and a half years following receipt of the first dose of vaccine.

There are two other efficacy studies. One is being conducted in Costa Rica by the U.S. National Cancer Institute, and that has approximately 7,500 subjects enrolled; the other is the HPV-008 trial, the subject of this presentation. In 2006, GSK started another efficacy study, which has enrolled over 5,700 women over 25 years of age.

Results from previous studies have shown that the GSK candidate vaccine is generally

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well tolerated and is highly efficacious in preventing HPV 16 and 18 endpoints; it was up to 100 percent effective in preventing CIN lesions and persistent infections associated with HPV 16 and 18 in fully vaccinated women and also prevented abnormal cytologies in women in these studies.

The previous efficacy study presented primarily assessed the vaccine in women who were screened and were naïve to oncogenic HPV types at study entry. In the older studies protection or cross-protection has been observed against incident infection with a number of HPV types that are phylogenetically related to HPV 16 and 18, including types 45 and 31, the third and the fourth most common types associated with cervical cancer. Immunobridging studies have also demonstrated good immunogenicity of the vaccine in younger women down to the age of ten and in women over 25 years of age, with titers in the range associated with protection in the long-term follow-up study.

The recently conducted HPV-008 study enrolled 18,644 unscreened women age 15 to 25 in North and South America, Europe, and the Asia-Pacific region, including Australia. The cohort included women with current or prior oncogenic HPV infections. This broad, unscreened population was thought to represent the kind of target population the vaccine ultimately will be used in.

Women were enrolled regardless of baseline cytological abnormalities. Many were infected with oncogenic HPV and many of these were non-vaccine types, although there were some with vaccine types as well. The interim analysis only excluded women found to have high-grade cytology abnormalities at the entry visit. It included all events reported in women who have received at least one dose of vaccine.

Regarding baseline characteristics, 90.5 percent of women had normal cytologies and the rest had abnormal cytologies, the majority of which were low grade. The half a percent of women with high-grade cytology abnormalities were immediately referred for colposcopy. Among women with normal cytologies at entry, about 15 percent had high-risk HPV, but women with low-grade cytology abnormalities or high-grade cytology abnormalities had progressively increased risk of having oncogenic HPV infection at entry; 91 percent of women with high-grade cytologies at entry were found to have high-risk HPV infection.

The women enrolled in this double-blind study were randomized one to one. The control vaccine was an adapted formulation of hepatitis A vaccine given on a three-dose schedule, which visually appeared identical to the active vaccine under investigation. Ten visits were scheduled over a 48-month period of time. The three-dose schedule was administered at zero, one, and six months. Blood samples were collected periodically for serology and cervical samples were collected at six-month intervals. The cervical samples were routinely tested for HPV infection and also used to assess cytologies. Management of women with abnormal cytologies was according to a prespecified algorithm.

The mean follow-up time when the interim analysis was triggered was 15 months following receipt of the first dose of vaccine. This is a relatively early time point in the planned longitudinal follow-up, which will extend through about 48 months.

When the women with high-grade cytology findings and those who were missing cytologies were eliminated, a total of 18,525 women remained for evaluation of efficacy. Immunogenicity was assessed randomly in a pre-specified subset of subjects that was representative for the regions participating in the study.

The primary endpoint of the study was to assess efficacy of the vaccine and the prevention of histopathologically confirmed CIN2+ associated with HPV 16 or 18 in the

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cervical lesion. Diagnosis of CIN2+ was confirmed by a consensus-panel diagnosis, using three independent histopathologists who had been trained to evaluate these lesions. This was separate from the routine panel that assessed the results in a real-time frame to help guide subject management.

The methodology used to detect HPV 16 and 18 DNA in the lesion involved the use of a broad-range consensus primer system, referred to as the SPF-10 system, and detection was done by a line-probe assay. This SPF-10 system actually detects 14 oncogenic HPV types--16 and 18 plus 11 nonvaccine types, which were routinely evaluated in all samples collected. In addition, type-specific PCR was done for HPV 16 and 18 to supplement the broad-consensus primer PCR.

A sample was considered positive if HPV 16 or 18 DNA was detected using either of the two methods. Women who were HPV-DNA negative and sero-negative were assessed at study entry in the primary endpoint analysis. If a woman was HPV 16 DNA positive or seropositive at entry and subsequently developed an HPV CIN2+ lesion, she was not counted in the final efficacy evaluations. However, if she developed an HPV-18-associated CIN2+ lesion, she was counted. The use of broad-spectrum PCR in a population of women that was broadly defined and included many women with prevalent infections with other types at entry allowed the study to fully characterize lesions for vaccine and nonvaccine types.

The interim analysis was event-triggered, defined as whenever 23 HPV 16 or 18 CIN2+ lesions were detected in the total vaccinated cohort. The final analysis will also be event-triggered and will generate additional data on CIN2+ outcomes. GSK intends to continue blinded follow-up for up to four years.

A high rate of prevalent HPV infections was observed at study entry, even in women with normal cytologies. Of the 23 lesions that triggered the interim analysis, 14 or 61 percent showed more than one HPV type detected in association with the lesion by PCR. Fourteen of the 23 lesions were derived from infections detected prior to completion of the three-dose series. The third dose is given at the Month-6 visit, which means the infections were acquired very early in the trial. The high rate of multiple infections in CIN lesions was not expected, based on published natural history literature or vaccination trials, so this was a unique observation, based on evaluating the HPV types across all lesions and all subjects in all cytology samples.

The 23 cases could be described by three patterns of HPV detection in the lesion and also considering HPV types detected in samples collected prior to detection of the lesion. The first pattern was a relatively classic one. These were cases where a single HPV type was found in the CIN2+ lesion and the same type was found in prior samples. Based on the well-established association between persistent infection and development of a high-grade lesion, this pattern of detection seemed very clear-cut. Nine cases fell into this category. An example is a woman who, after the Month-12 visit, had a punch biopsy triggered by an abnormal cytology. The punch biopsy showed HPV 18 in association with a CIN2+ lesion. This subject had prior infection with HPV 18 at the Month-6 and Month-12 visit; this is also a fairly classic case.

The second pattern included cases where multiple HPV types were detected in the CIN2+ lesion with HPV 16 or 18 infection preceding the development of the lesion. An example of that pattern is a subject who had a CIN2+ lesion after the Month-12 visit, with HPV 16 and 51 detected. This subject had a number of HPV types detected at previous time points, but 16 was detected at the Month-6 and the Month-12 visit, so it was counted as a case

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of HPV-16-associated CIN2+. There were 11 similar cases with multiple types in the lesion but a clearer pattern of prior detection of the vaccine type in preceding samples.

The third pattern, which was the least common and the most unusual, included cases with multiple HPV types in the CIN2+ lesion with no prior detection. There were three such cases. The lesions also contained additional non-vaccine types, serotypes that were not considered in the analysis, so the question was, which type was the cause of the lesion?

Dr. Dubin discussed three cases to show how lesions were assessed. One subject had a CIN3 lesion detected by punch biopsy after the Month-12 visit, and HPV 16 and 58 were detected in that lesion. That subject subsequently had a LEEP, which confirmed the diagnosis of CIN3, but only HPV 58 was detected in the LEEP and at Month 0, Month 6, and Month 12. There was no prior detection of HPV 16 in any preceding samples.

The second case was a woman who developed a small CIN2 lesion with HPV 18 and HPV 58 detected in association with the lesion. A subsequent LEEP was normal, so the lesion was removed by the punch biopsy. HPV 58 was detected at entry and at the Month-12 visit; there was no prior detection of HPV 18.

In the third case, the subject had a CIN3 lesion with HPV 16 detected at punch biopsy. She subsequently had a LEEP, which showed multiple lesions, each of which had HPV 16. HPV 18 was found in a single lesion. Looking back at the history of this patient, multiple HPV types were detected, but the only consistent type was HPV 16. There was no prior detection of HPV 18. This case would not count as a case of HPV-16-associated CIN2+ in the efficacy evaluation because there was prior infection, but it would count as a case of HPV-18-associated CIN2+.

Another analysis was done to evaluate the efficacy of the vaccine against lesions considered to be causally associated with HPV 16 or 18. It considered not only the HPV type detected in the lesion, but any HPV types found in preceding cytology samples. The use of this algorithm was based on the well-established association between persistent oncogenic infections and development of CIN2+ lesions.

Of the 23 cases detected in the broad analysis, two were in the vaccine group and 21 were in the control arm, giving a point estimate of vaccine efficacy of 90.4 percent, which was highly significant. The majority of these lesions were derived from infections that began prior to completion of the three-dose series.

In the three cases where the lesions were not believed to be caused by the types detected just in the lesions, two were in the vaccine group and one was in the control arm. This left 20 cases: zero in the vaccine group and 20 in the control arm. So in this evaluation, vaccine efficacy was 100 percent, which is highly statistically significant.

In another analysis, the restriction for subjects to be seronegative for the type ultimately found in the lesions was removed. This analysis now considers a broader group of individuals, including those who might have been seropositive for HPV 16 to 18 prior to vaccination. In the pre-specified analysis, vaccine efficacy was over 90 percent. In the analysis that considered not only the DNA detected in the lesion but the prior samples as well, the analysis that best reflects lesions likely to be causally associated with HPV 16 and 18, vaccine efficacy was 100 percent. Results from an additional analysis, which included women who were seropositive for HPV 16/18 prior to vaccination, suggest that vaccine efficacy is not likely to be impacted by serostatus prior to vaccination.

Dr. Dubin then described some efficacy results that looked beyond HPV 16 and 18, based on persistent infection endpoints included in the interim analysis. Persistent oncogenic

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infection is well established as a necessary precursor for the development of cervical cancer. When multiple types are detected in the lesion, causality must be assessed related to individual types. This is likely to be a bigger issue with lesions caused by less frequent types, such as 45 and 31, where co-infections are quite common. Persistent infection was used because causal association is not an issue when looking at the virus itself and it avoids possible confounding effects of multiple types in lesions.

Given the timing of the interim analysis, most of the persistent infections detected began prior to completion of the three-dose series. To assess a 12-month persistent infection, a woman would have to be positive at Month 6, Month 12, and Month 18 or Month 12, Month 18, and Month 24. Very few women had completed the Month-24 visit at the time the interim analysis was triggered. Over 90 percent of the 12-month persistent infections were first detected at the Month-6 visit, which means they began sometime between Month 0 and Month 6. Over 70 percent of the six-month infections began prior to completion of the three-dose series.

In the Phase II program, there was evidence of cross-protection using an incident infection endpoint, and this cross-protection was against types 45 and 31, two types closely related to 16 and 18. The interim analysis of the Phase III trial confirmed this effect using a more robust endpoint, six-month persistent infection instead of incident infection. So for types 35 and 41, statistical significance was achieved using the six-month definition of persistent infection. These two types are responsible for about 10 percent of cervical cancers. Type 45 is the third most common globally, and 31 is the fourth most common, followed by 33 and 52. Statistically significant protection was also observed against six-month persistent infection with type 52 and it was close for type 33, though not achieved.

Another analysis looked at 12-month persistent infections, but because of the lower frequency of this endpoint, no assessment could be made on an individual type-specific basis. For the 12 oncogenic HPV types, other than 16 and 18, that can be detected with the SPF-10 system, a point estimate of vaccine efficacy of about 27 percent was observed and was statistically significant.

Results showing immunogenicity of the vaccine over a five-and-a-half year follow-up period have been presented previously. The interim analysis assessed immunogenicity over a 12-month follow-up period, and found that the vaccine was highly immunogenic for the HPV 16 and 18 components. Vaccine and immune response were also assessed in subjects who were initially seronegative and seropositive for the vaccine types being evaluated. There was no real difference in immunogenicity. In fact, when looking at earlier Phase II studies, the only difference was that seropositives achieve a higher immune response earlier, but the plateau is essentially the same regardless of serostatus.

Lastly, Dr. Dubin covered some of the safety evaluations. There was a very high level of compliance with completion of study visits and it was comparable between the two groups. There were very few dropouts related to adverse events, and this was also well balanced between the treatment groups. There was no difference in the number of events that led to dropout, and there were many other reasons for subjects dropping out of the study, mostly migration from the study area.

Adverse events reported during a 30-day period following each dose of vaccine were categorized as local injection-site symptoms, general symptoms, and combined symptoms. The vaccine induced a somewhat higher rate of local injection-site symptoms -- pain, redness, and swelling -- compared to the control used. General symptoms were more comparable

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between the two groups, with slightly higher rates in the HPV group compared to the control. There was no increase in local or general symptoms with subsequent doses, and the majority of these reports were low-grade and transient events.

The reactogenicity profile of the vaccine did not result in any differential compliance with receipt of the second and the third dose, which indicates that the vaccine is well tolerated from the perspective of the subject. All events following each dose of vaccine were stratified by initial serostatus or DNA status and no differences were seen in the reactogenicity pattern, depending on whether subjects were naïve to the vaccine types, seropositive, or DNA positive to one or both of the vaccine types. The safety profile appeared to be quite comparable.

Another analysis considered less frequent events. Data on symptoms were solicited very proactively for the 30-day period following each of the three doses. Medically significant events, defined as conditions that prompted an emergency room visit or a physician intervention, new onset of chronic diseases and new onset of autoimmune diseases, were actively solicited throughout the entire duration of the trial. There was no difference in the proportion of subjects reporting any of these events. Serious adverse events were reported over the duration of the trial without any time restriction; both the proportion of subjects reporting serious adverse events and the number of serious adverse events reported were quite similar in the two groups.

Pregnancy outcomes were assessed as one of the important safety measures, even though there were contraindications to pregnancy in the vaccination phase of the protocol. The rate of specific pregnancy outcomes was well balanced between the two groups.

This is the largest vaccine study conducted to date and it has helped to characterize the natural history of HPV in association with multiple types detected in lesions. With the methodology that will be used to look at lesions that develop in vaccinated women in a post-licensure setting, this will be important in trying to better understand causal association with vaccine and non-vaccine types.

This study has confirmed a high level of protection against HPV 16 and 18 CIN2+ lesions in a broadly defined cohort of women. The vaccine efficacy estimate is 90 percent considering any CIN2+ lesions with HPV 16 or 18 detected and 100 percent against lesions where HPV 16 and 18 were likely to be causally associated with the lesion. There was a high level of vaccine efficacy regardless of initial HPV 16/18 serostatus, which will be important as use of the vaccine is considered for non-naïve women. The majority of endpoints were derived from infections detected prior to completion of the three-dose series, which suggests that the onset of vaccine effect may actually begin prior to completion of the full three-dose series.

The HPV-008 study extends some previous preliminary evidence of cross-protection. There is evidence of efficacy against HPV 45, 31, and 52, using a six-month persistent infection endpoint. Efficacy is also seen against 12-month persistent infection in an analysis that considers a combination of 12 non-vaccine types. Persistent infection is an important endpoint in assessing these other types because the analysis is not confounded by the potential for multiple types detected in biopsies. Finally, the study confirmed that the vaccine is highly immunogenic and generally well tolerated.

HPV Vaccines: Future Recommendation Considerations

Dr. Markowitz provided information on distribution, post-licensure monitoring, and state legislative action, as well as the next issues for the ACIP consideration related to HPV

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vaccine. The ACIP made its recommendations a year ago, followed by a VFC vote, recommendations on the Web in July and the VFC contract in October. The vaccine was included in the National Injury Compensation Program in February, and the ACIP statement was published in March. Through March of 2007, about 5 million doses have been distributed, 49 percent of that through the CDC contract and 51 percent non-CDC. By April 2007, all states had purchased vaccine for the public sector.

Monitoring includes post-licensure safety monitoring, vaccine coverage, and disease impact. Merck has an extensive post-licensure safety program as part of their agreement. They will be doing a post-marketing study in a managed-care organization. They also have a vaccine pregnancy registry in which about 300 women have been enrolled. That annual report will be analyzed and could be presented to ACIP at a later date. A variety of safety studies are ongoing through the Nordic cancer registry and those could also be presented.

Regarding coverage, a variety of data will be available. Some are in the traditional vaccine coverage surveys, but information on HPV vaccine has also been included in other national surveys and those data will become available. The teen module of the National Immunization Survey was conducted in the fourth quarter of 2006 and will be repeated in the fourth quarter of 2007. This is a random-digit dialing telephone survey of parents, with provider check for verification of immunizations. Funding was just received to expand this in 2008 to provide state-specific estimates. The adult module is being conducted now (May through August), and the first data will be available in the fourth quarter of 2007. That is also a telephone interview, but with no provider check for verification of immunization status. The National Survey of Children's Health, which is ongoing, will provide national as well as state-based estimates. There are about 92,000 children in that sample and data are based on parental recall only.

There has been substantial media attention around HPV vaccine legislation. As of June 2007, legislation has been introduced in 41 states, and in 11 states bills have been signed into law. The vast majority of these laws are about education related to HPV and HPV vaccine; some are related to funding and insurance to cover HPV vaccine. Twenty-four states have introduced legislation specifically to mandate HPV vaccine for school entry. In Texas, there was an executive order for a middle-school vaccination requirement, which was overridden by the legislature. In Virginia a mandate did pass that requires HPV vaccine for girls entering grade six, but there are very broad exemptions. In North Dakota and New Hampshire, legislation has been passed to allocate funds to provide vaccines at no cost to females 11 to 18 years of age.

There are four major upcoming issues for ACIP: considerations regarding the bivalent HPV vaccine; issues related to having two HPV vaccines on the market; additional data from the quadrivalent and bivalent vaccine trials that may impact recommendations in the coming years; and considerations that were not included in the first ACIP statement.

Information about the bivalent vaccine was presented earlier. The BLA submitted to FDA in March of 2007 included data on females 10 to 55 years of age. The FDA decision would be in January 2008 at the earliest. If the vaccine receives an indication for currently recommended age groups, the work group and ACIP will need to review the clinical trial data on efficacy, immunogenicity, and safety, as well as additional information on adjuvants, since this is a new adjuvant. If there are indications for use in older women, the committee will have to consider recommendations for those age groups. Options include permissive, risk-based, no recommendation, or some other recommendation. Data on sexual behavior in the

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U.S. will be reviewed, from national surveys, natural history, and HPV incidence data in older women as well as other information on HPV and cost-effectiveness in this older age group.

With two HPV vaccines on the market, there will be considerations and data needs around the issues of preference and interchangeability. The work group has started examining whether there are differences related to protection against HPV 16 or 18 and cervical cancer between the two vaccines, or differences related to duration of protection, immunogenicity, or cross-protection. There are differences related to protection against HPV 6 and 11 related diseases since these types are included in the quadrivalent vaccine and not in the bivalent vaccine. Another issue will be cost-effectiveness. Any precedent for how ACIP has dealt with the preference when making recommendations for other vaccines will be reviewed. There has been no situation completely analogous to HPV vaccine that ACIP has had to consider.

If there is no preference, there will be issues around interchangeability of doses. At the time of licensure, there will be no data on interchangeability. If someone starts the series with one vaccine, the quadrivalent, for example, can she complete her doses with the bivalent vaccine?

In terms of additional data, both manufacturers are looking at efficacy in females older than 25 or 26; safety and immunogenicity; co-administration with adolescent vaccines; safety and immunogenicity in HIV-positive women and, from Merck, HIV-positive men. Efficacy trials in men are being conducted for the quadrivalent vaccine, and both manufacturers are doing Phase IV and long-term follow-up studies.

On-going studies with the quadrivalent vaccine could impact recommendations. The efficacy trial in women 24 to 45 years of age is looking at prevention of persistent infection and disease in this older age group of women. There are also two studies in men; the earliest data would be available in the third quarter of 2008. If FDA or ACIP require efficacy data instead of immunogenicity data to consider recommendations in older women, 2008 would be the time frame, and for recommendations in males, it would be 2009 or 2010. This depends on when the endpoints occur because these are endpoint-driven analyses.

Some issues have come up about considerations not included in the current statement, such as inadvertent administration of the vaccine by the subcutaneous route or other special situations related to pre-existing disease in women.

Finally, the ACIP work group has talked about ACIP statements for HPV vaccine, including format. The preference was a new ACIP statement with information on both vaccines, rather than a separate statement for the bivalent vaccine. The time line for a new draft statement would probably be February 2008.

Future plans for ACIP meetings include further review of Phase III data, a discussion of the adjuvant, and an update on any new data from the quadrivalent HPV vaccine in October. Epidemiology of HPV and various HPV-related outcomes should be addressed, including genital warts and RRP, followed by discussion of potential recommendations. February would be the earliest there could be a vote. At that time, cost-effectiveness data would be reviewed as well.

Discussion

Dr. Gilsdorf asked about the tissue samples obtained by punch biopsy, cone, or LEEP, and whether the virus was detected by PCR only or also confirmed by tissue probes. Dr. Dubin replied that the protocol was to do microdissection of the lesion and then apply PCR on

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samples derived from the lesion. One of the ways this is being assessed now is to look at assays that allow evaluation of gene expression in these cases. The assay currently being used has type specificity for expression of the E-4 protein. Analyses done with the E-4 protein immunohistochemical assay fully support the causal associations made in the study.

Dr. Gilsdorf asked whether the histochemical data confirmed the PCR data. Dr. Dubin replied that the study specifically looked at lesions where HPV 16 or 18 was detected only in the lesion but not in any prior samples. The available immunohistochemical probes are for HPV 16 and 18, and those were not detected in the lesions. In other lesions where the vaccine type detected in the lesion and in the prior cytology samples were known, the E-4 immunohistochemical signal was consistently detected in the lesions.

Dr. Chen commented that it is challenging to sort through a large number of individual HPV VAERS reports with multiple adverse events when the staff is limited. At one point, a panel of data safety monitoring tools was developed to look for new permutations of new adverse events or new syndromes. He asked whether these tools were being applied to HPV. Dr. Iskander responded that Dr. Chen was referring to advanced signal-detection techniques or data mining, as a way of sorting through very large and complicated databases. A conscious decision was made not to present that type of data to the ACIP without sufficient background, but in fact steps are being taken to use both types of analyses. They are routinely used in joint analyses of VAERS done with FDA and incorporated into publications. Some of those methods will be brought before the committee in the future, first in terms of general background and then incorporated routinely in some of the safety analyses.

Dr. Abramson asked whether there was any plan to look at the effect of the new mandate in Virginia, in terms of increasing immunization and opt-out categories. Dr. Markowitz replied that there was an adolescent work group at CDC and the issue has been discussed with the Immunization Services Division. There is also the interesting case of New Hampshire and other states that have made vaccine available free of charge. CDC is actively discussing how to evaluate those states that have adopted either legislation or other implementation measures.

Dr. Schuchat commented that there was now an opportunity to pitch state-specific estimates for adolescent coverage through a teen module at the NIS. There will be an on-going examination of attitudes about vaccine acceptance in the NIS and also in insurance modules. The plan is also to collect ongoing information about coverage, acceptability or safety concerns, and financial patterns.

UPDATE: VARICELLA

Adriana Lopez, CDC/NCIRD/DVD

Ms. Lopez presented results from an investigation of an outbreak of varicella among two-dose recipients. In the past two years, ACIP has made new recommendations for varicella immunization. In June 2005, a second dose of varicella vaccine was recommended in children for outbreak control, resources permitting. Then in June of 2006, a routine second dose for all children was recommended, with the first dose given to children 12 to 15 months of age, the second dose for children four to six years of age, and catch-up vaccination for all persons over age six.

During the fall of 2006, an outbreak of varicella occurred in southeast Arkansas. When the outbreak came to the attention of the health department, 31 cases had been reported.

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Of these, eight were among two-dose recipients, and all cases were reportedly mild. The outbreak occurred in an elementary school complex that housed three schools. School A included pre-K students, School B included grades K through three, and School C included grades four through six. The same school complex had experienced an outbreak during January and February of 2006. During that outbreak, in accordance with the June 2005 ACIP recommendation, the Arkansas health department set up a vaccination clinic to help with outbreak control. Approximately 400 students were vaccinated at that time, and many received a second dose.

Because cases in this current outbreak included two-dose recipients, CDC was invited to assist with the investigation. The main objectives of the investigation were to confirm varicella in cases that had received two doses and to characterize the vaccine effectiveness among one- and two-dose recipients, if possible.

A case was defined using the Council of State and Territorial Epidemiologists case definition of acute maculopapular vesicular rash without other apparent cause occurring between September 1 and December 18 among students in the school complex. Disease in vaccinated persons is generally mild with fewer than 50 lesions, shorter duration of illness, and atypical appearance with macules and papules and few or no vesicles. Given the large number of insect bites common to this area, a person had to have at least three lesions to be considered a case. Laboratory confirmation of cases was done using PCR to test lesion specimens and environmental samples and IgM for blood and saliva specimens.

Cases among students in the school complex were identified from the health unit, the school nurse, and a survey that was sent to the entire school. The survey included questions about vaccination status and varicella disease history, medical conditions, and screening questions for rash illness to try to identify mild cases. Parents of case-patients were contacted and asked about clinical information, medical conditions that could affect immunity, and medication.

Varicella vaccination status was verified by reviewing the Arkansas immunization registry. Alternate sources included paper records at the local county health department and the parental surveys, if the parent had provided date of vaccination. Children were considered unvaccinated if they had received their first dose less than or equal to 42 days before rash onset. Children receiving their second dose less than or equal to 42 days before rash onset were considered as having indeterminate vaccination status.

The overall response rate from the school-wide survey was 79 percent, with the response from School C being significantly lower than responses from Schools A and B. No differences were identified between responders and non-responders with respect to gender and vaccination status. However, a difference was found for race/ethnicity, where African-American children were less likely to respond compared to white or Hispanic children.

A total of 85 cases were identified during the outbreak, which lasted almost four months. Most cases occurred among one-dose recipients, but two-dose recipient cases occurred throughout the entire outbreak. None of the cases had more than 250 lesions. The two-dose cases tended to be slightly milder than the one-dose cases and those with previous disease, although the difference was not statistically significant. Those with unknown number of lesions were excluded from this analysis. Similarly, no statistically significant differences were seen between the one- and two-dose cases and those with prior disease history with respect to rash description, median duration of rash, and fever. However, two-dose cases and those with prior disease tended to have shorter rash duration than one-dose cases, four and six

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days, respectively.

The mild clinical presentation of cases during this outbreak made diagnosis difficult. Clinical specimens from a lesion and saliva were collected on the day of rash onset. Twenty-five (29 percent) of the cases were among two-dose vaccine recipients, with three of them having either previous or unknown history of disease, for an attack rate of 10.4 percent. A majority (64 percent) of the cases occurred among one-dose vaccine recipients. Seven of these had previous history of disease, for an attack rate of 14.6 percent. Lastly, six cases (7 percent) had no history of vaccination, but all had previous history of disease. Thus, it was not possible to calculate an attack rate or vaccine effectiveness against no vaccination.

The overall vaccination coverage with at least one dose in the school complex was 97 percent, and the two-dose coverage was 41 percent. Twenty-seven cases had specimens collected for laboratory confirmation. Six of those had positive results; five specimens were from lesions and positive by PCR; one from a two-dose recipient, three from one-dose recipients, and one from an unvaccinated person with history of disease. The sixth positive result was from IgM from a one-dose recipient.

Environmental samples collected from the school, and bedding and bedclothes from cases were also tested. A set of pajamas from a case with indeterminate vaccination status was PCR positive. This case also had a positive lesion specimen. A pillowcase from a one-dose recipient was also PCR positive. This case did not have clinical specimens for testing.

Because there were no cases in persons with no vaccination and no disease history, vaccine effectiveness was calculated against clinical varicella using historic attack rates. An attack rate for unvaccinated of 80 percent was used. The vaccine effectiveness among two doses versus unvaccinated for this outbreak was 87 percent, with 95 percent confidence intervals of 80.5 to 91.4. The one-dose versus unvaccinated vaccine effectiveness was 81.8 percent with 95 percent confidence intervals from 75.8 to 86.2 percent. Although the two-dose vaccine effectiveness point estimate was higher than the one-dose estimate, the confidence intervals overlap.

Some limitations to this investigation included that there may not have been sufficient power to detect differences between the one- and two-dose cases. Misclassification of cases could have occurred because of the broad clinical definition used, which could have led to false positives. Similarly, mild disease could have led to false negatives. Lesion-based laboratory diagnostics were only helpful while transient rash was still present; it was not possible to confirm any of the cases reported before CDC's arrival. Misclassification of disease history could have occurred because this was based mainly on parental report. Response rate was significantly lower among students from School C, however since vaccination status was obtained from the state registry, this is unlikely to have affected vaccination coverage and effectiveness estimates.

This was one of the largest varicella outbreaks investigated in recent years, and the first U.S. outbreak reported with a significant number of two-dose vaccine recipients. Challenges with case ascertainment, because of the mild presentation of disease, may preclude the evaluation of two- versus one-dose risk-reduction assessments in outbreak settings. Moderate two-dose coverage of 40 percent was insufficient to prevent this outbreak. Additional vaccine-effectiveness studies for two doses are needed. Lastly, to assess the impact of the routine two-dose varicella vaccination policy, it will be important to monitor the number and size of outbreaks as a key outcome.

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Discussion

Dr. Gilsdorf asked whether the two-dose failures all received their vaccine from the same provider and if so, how about vaccine storage. Ms. Lopez replied that they all received their vaccine at the clinic held in February of 2006. Handling and storage were evaluated and everything looked fine.

Dr. Katz asked why pillowcases and pajamas were cultured. Ms. Lopez replied that they were trying to see if environmental sampling would be a good way to diagnose varicella in outbreaks where CDC comes in after the fact. Dr. Katz asked if there were any data from past environmental sampling of varicella and Ms. Lopez replied that environmental sampling had been done during an outbreak in a West Virginia long-term care facility. The index case was a zoster case, and there were three varicella cases that occurred subsequent to that zoster case. Environmental sampling made it possible to link the cases, which all had a unique strain of varicella.

Dr. Iskander shared a recent observation from VAERS on reports of multiple, small clusters following second doses of varicella vaccine described as “cellulitis”. They do not appear to be clustering and may represent provider unfamiliarity with the normal safety profile of the vaccine. The other possibility is that there may be a biologic difference in the reactogenicity of second dose depending on the age at which it is given. Pictures or any other information are being sought that might shed additional light on this emerging clinical observation.

AGENCY UPDATES

CDC

Dr. Schuchat reported that the reorganization of the Coordinating Center for Infectious Diseases at CDC was approved in March, so the National Center for Immunization and Respiratory Diseases now has official status. There is an annual report and a new web site, including a vaccine component. There is also a new module for adolescent immunization coverage. An adolescent immunization campaign will be launched this summer, targeted to parents of 11- to 12-year-old children.

CMS

Ms. Murphy mentioned the VFC maximum administration rates and the fact that she had been receiving many inquiries. She explained that she is the immunization focal point for Medicaid, but Medicare and Medicaid are not related and do not always share information, so she would appreciate being kept in the loop. She formulates answers to letters that come to her. Because of the publicity that the low VFC administration rates have been getting lately, the stock answer has been, "I can't do a thing about it. It's all in regulation. It's all in statute." If the VFC maximum regional administration rate is to be changed, states must demonstrate that this needs to be done. When the discussion started in 2005, she discovered that only five states were actually paying the maximum rate for Medicaid. Since she has been working with agencies and associations to work with Medicaid and individual states, there are now nine states paying the maximum rate for Medicaid and 12 other states have raised their rates. She urged the committee to continue working with the state Medicaid agencies and immunization program agencies to have rates raised to the maximum. If that can be done, Ms. Murphy can then work with the different associations to ensure that studies are undertaken in order to

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show what is needed to obtain a more equitable rate.

DOD

Dr. Cieslak first addressed the issue of smallpox vaccine and contact *vaccinia* in vaccine recipients. After vaccinating for exactly five years with well over a million recipients, there have been 60 cases, which is an average of one case a month over the life of the DOD's resumption of smallpox vaccination. In March of this year, there were five cases, but that is probably just a statistical aberration. All of the vaccine is coming from the same lot and the five cases were widely dispersed geographically.

The second issue involved the adenovirus vaccine. The DOD is engaged in a study of a new bivalent adenovirus vaccine involving Serotypes 4 and 7, which are historically the types that have caused most severe adenoviral disease amongst military recruits. There is currently an outbreak of severe adenoviral-14 disease among Air Force basic trainees at Lackland Air Force Base in San Antonio. The long-term implications are being studied, i.e., whether this is an aberration or here to stay. The DOD is also interested in whether the bivalent 4/7 vaccine will provide any cross-protection against serotype 14 or whether a type-14 serotype might have to be added to a vaccine construct.

FDA

Dr. Houn reminded the audience that the sanofi pasteur H5N1 influenza virus vaccine was approved in April. In May, the final guidance on development of both seasonal and pandemic influenza virus vaccines was issued. At the May VRBPAC meeting, FluMist was discussed, as well as the Acambis smallpox vaccine, which was voted by the VRBPAC to be the first vaccine to have a recommendation for a medication guide. This is an FDA-approved patient package insert on risks and benefits. It was also recommended to have a risk-minimization action plan to minimize identified risks of that vaccine.

HRSA

Dr. Jevaji reported that the vaccine autism trial started on June 11th and concluded on June 26th. Three special masters heard the evidence on a test case. The test case was determined by the petitioners, and then petitioners and respondents introduced testimony for the general population, as well a specific causation related to the test case.

The inquiries involved a theory that MMR vaccine and thimerosal-containing vaccines can cause the alleged injury. So far, 5100 thimerosal-related autism claims have been filed with the National Vaccine Injury Compensation Program, and of these, 4800 cases are pending. The remaining 300 were either dismissed because of the statute of limitations or they chose to go to the regular program. Since both parties responded and the petitioners consented, the hearing can be accessed online by searching on the web for "autism and court hearing." Future hearings regarding the autism trial will be heard on two theories; designation of the test cases will be determined by the Court and the special masters.

On February 7th, Representative Dave Weldon, a Republican from Florida, and Carolyn Maloney, a Democrat from New York, introduced a bill called the Mercury-Free Vaccines Act of 2007. This bill was introduced to amend the FDA act to eliminate mercury exposure from the vaccines. The bill was referred to the Committee on Energy and Commerce.

On April 20th, the *Federal Register* notice was published announcing the addition of

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the meningococcal and HPV vaccines to the list of vaccines covered by the National Vaccine Injury Program.

The Statute of Repose for influenza vaccine is coming to an end on June 30, 2007. So far, there have been 117 claims, of which 106 represented adults and the rest were children under the age of 18 years. The Statute of Repose is a look-back provision that goes back eight years from the date the vaccine came onto the table.

NIH

Dr. Curlin announced that the *Jordan Report* had finally been delivered, on the last day of the ACIP meeting. It can be downloaded or one can get hard copies by emailing Barbara Mulach at NIH.

NVPO

Dr. Gellin announced that Angela Shen would be returning from maternity leave after Labor Day and that Dan Salmon was returning to NVPO to focus on vaccine safety. The national vaccine plan is in need of an update and more will be said about that in the future. The adolescent working group has a paper in the process of being submitted that highlights the challenges of adolescent vaccination.

Dr. Hinman provided information about the NVAC registries. The immunization coverage subcommittee of NVAC has led the development of a progress report on immunization and information systems or immunization registries. This was approved in February of this year by NVAC and should be posted on the Web in October or November, and we hope that it will be published.

NVAC's target is 95 percent of children less than six years of age having two or more immunizations recorded in an immunization registry by the year 2010. As of the end of 2005, it was at 56 percent and at the end of 2006, it appeared to be about 65 percent.

Registries are the most developed of the public health information systems and, perhaps, the only ones that really cross the public sector/private sector divide. They provide clinical-decision support to providers in states around the country. They are increasingly containing information about adults and the majority of registries accept information on all ages. The majority of pandemic influenza plans incorporate the use of registries to track immunizations given during pandemic response. The next step is linking with electronic health records, which is already being done in a limited number of places. Some of the major barriers have to do with exchanging information across state lines, which currently requires setting up individual memoranda of agreement. Providing long-term financial sustainability for registries continues to be a problem, but progress is being made.

PUBLIC COMMENT

Mr. Scott Lassiter said he believed the CDC had misled the ACIP on thimerosal and that the five oft-quoted epidemiologic studies weren't worth the paper they're written on. At the request of Congress last year, the NIH convened a panel of the top epidemiologists in the country who concluded that the Verstraaten study had several serious flaws and that the other studies were even worse. The panel concluded it was still an open question whether vaccines cause autism.

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According to Mr. Lassiter, internal correspondence obtained by the Freedom of Information Act indicates that the CDC knowingly manipulated data that originally showed a connection between thimerosal and autism. For proof, he suggested reading the web site putchildrenfirst.org, or reviewing the CDC's own e-mails and meeting minutes from that time period. The hard science in lab and animal research from leading universities indicates that thimerosal is a dangerous neurotoxin, twice as potent as methylmercury, and that it causes autism-like behaviors and white-matter changes in the brain. He reminded the committee of its responsibility to put children first and urged members to do their own research.

Karen Beauvais spoke on behalf of the National Autism Association of the greater Atlanta area, consumers of vaccines, and a seven-year-old boy named Joshua Beauvais who received 277 times over the EPA-allowable amount of thimerosal in his infant vaccines. Joshua has undergone four years of very aggressive chelation therapy. He was endoscopied and not found to have the typical autism-measles hyperplasia, which led to extensive industrial testing of urinary porphyrins. Joshua is showing hundreds of times over what he should have for mercury in his body, all of which is believed to have been from his Hib, his DTaP, and his hep-B series.

She read the following from the material data safety sheet for thimerosal, which is still in influenza vaccine and other vaccines: "This substance may be toxic to the kidneys, the liver, the spleen, bone marrow, and the central nervous system. Repeated or prolonged exposure to the substance can produce target organ damage. Repeated exposure to highly toxic material may produce a general deterioration of the health by accumulation in one or many of the organs."

The work of Amy Tsao indicates that children have sustained DNA damage, and the material data safety sheet indicates that new genetic defects are being seen in humans with thimerosal. She implored the committee to make vaccines safe for all: for pregnant women and for little children.

As there was no further public comment, the meeting was adjourned at approximately 1:33 p.m.

I hereby certify that to the best of my knowledge, the foregoing Minutes of the June 27-28, 2007 ACIP Meeting are accurate and complete.

_____

Date

_____

Jon S. Abramson, M.D., Chair,
Advisory Committee on Immunization Practices

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Attachment One: List of committee members and liaison members and other attendees

CHAIR
JON S. ABRAMSON, M.D.
Weston M. Kelsey Professor and Chair, Department of Pediatrics
Wake Forest University School of Medicine, Winston-Salem, North Carolina

EXECUTIVE SECRETARY
LARRY K. PICKERING, M.D.
Senior Advisor to the Director, National Immunization Program
Centers for Disease Control and Prevention, Atlanta, Georgia

ACIP MEMBERS

BAN MISHU ALLOS, M.D.
Assistant Professor, Division of Infectious Diseases
Vanderbilt University School of Medicine, Nashville, Tennessee

CAROL BAKER, M.D.
Professor of Pediatrics, Molecular Virology and Microbiology
Baylor College of Medicine, Houston, Texas

MR. ROB BECK
Palmyra, Virginia

JANET R. GILSDORF, M.D.
Director, Pediatric Infectious Diseases, Department of Pediatrics and Communicable Diseases
University of Michigan, Ann Arbor, Michigan

HARRY HULL, M.D.
State Epidemiologist and Director
Minnesota Department of Health, Minneapolis, Minnesota

SUSAN LETT, M.D., M.P.H.
Medical Director, Massachusetts Department of Public Health
Jamaica Plain, Massachusetts

TRACY LIEU, M.D.
Associate Professor of Ambulatory Care and Prevention
Harvard Pilgrim Healthcare and Harvard Medical School, Boston, Massachusetts

JULIE MORITA, M.D.
Medical Director, Immunization Program
Chicago Department of Health, Chicago, Illinois

DALE L. MORSE, M.D.
Director, Office of Science and Public Health
New York State Department of Health, Albany, New York

KATHLEEN NEUZIL, M.D., M.P.H.
Clinical Associate Professor of Medicine
University of Washington, Seattle, Washington

PATRICIA STINCHFIELD, NP
Director, Pediatric Infectious Disease and Immunology
Children's Hospitals and Clinics of Minnesota, St. Paul, Minnesota

CIRO VINCENT SUMAYA, M.D., M.P.H.
School of Rural Public Health
Texas A&M University System Health Science Center, College Station, Texas

JOHN J. TREANOR, M.D.
Associate Professor of Medicine
University of Rochester, Rochester, New York

***EX OFFICIO* MEMBERS**

NORMAN BAYLOR, Ph.D.
Food and Drug Administration, Rockville, Maryland

JAMES E. CHEEK, M.D.
National Epidemiology Program, Indian Health Program, Albuquerque, New Mexico

GEORGE CURLIN
Medical Director, National Institutes of Health, Bethesda, Maryland

BRUCE GELLIN, M.D.
Director, National Vaccine Program Office, Washington, D.C.

WAYNE HACHEY, DO, M.P.H.
Department of Defense, Falls Church, Virginia

INDIRA JEVAJI, M.D.
Medical Officer, Division of Vaccine Injury Compensation

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HRSA, Bureau of Health Professions, Rockville, Maryland

LINDA MURPHY
Centers for Medicare and Medicaid Services, Baltimore, Maryland

KRISTIN NICHOL, M.D.
Chief of Medicine, VA Medical Center, Minneapolis, Minnesota

LIAISON REPRESENTATIVES

American Academy of Family Physicians
DOUG CAMPOS-OUTCALT, M.D.
University of Arizona, College of Medicine, Phoenix, Arizona

JONATHAN TEMTE, M.D.
Family Practice Residency Program, Madison, Wisconsin

American Academy of Pediatrics
JOSPEH A. BOCCHINI, JR., M.D.
Children's Hospital of LSU, Shreveport, Louisiana

America's Health Insurance Plans
TAMARA LEWIS, M.D., M.P.H.
Medical Director, Intermountain Healthcare, Salt Lake City, Utah

American College Health Association
JAMES C. TURNER, M.D.
Director, Elson Student Health Center
University of Virginia, Charlottesville, Virginia

American College of Physicians
SANDY FRYHOFER

American Medical Association
LITJEN TAN, Ph.D.
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American Osteopathic Association
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American Pharmacists Association
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Association of Teachers of Preventive Medicine
W. PAUL MCKINNEY, M.D.
Professor and Chief, Division of Internal Medicine
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Biotechnology Industry Organization
CLEMENT LEWIN, Ph.D., MBA
Executive Director for Strategic Planning & Intelligence
Chiron Vaccines, Orange, Connecticut

Canadian National Advisory Committee on Immunization
DR. JOANNE LANGLEY, Division of Infectious Diseases, Department of Pediatrics, Canadian Center for Vaccinology, Dalhousie University, Nova Scotia, Canada

Healthcare Infection Control Practices Advisory Committee
STEVE GORDON, M.D.
Cleveland Clinic, Cleveland, Ohio

Infectious Diseases Society of America
SAM KATZ, M.D.
Wilbert C. Davison Professor
Duke University Medical Center, Durham, North Carolina

London Department of Health
DAVID M. SALISBURY, M.D.
Director of Immunization, Department of Health. London, UK

National Association of County and City Health Officials
NANCY BENNETT, M.D.
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JEFFREY DUCHIN, M.D.
Chief, Communicable Disease Control, Seattle, Washington

National Foundation for Infectious Diseases
WILLIAM SCHAFFNER, M.D.
Professor and Chairman, Vanderbilt University School of Medicine
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National Immunization Council and Child Health Program, Mexico
VESTA RICHARDSON, M.D.
General Director, National Center for Health and Infancy and Adolescence
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National Medical Association
WINSTON PRICE, M.D.

National Vaccine Advisory Committee
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Division of General Pediatrics, University of Michigan, Ann Arbor, Michigan

Pharmaceutical Research and Manufacturers of America
DAMIAN A. BRAGA
President, sanofi pasteur - U.S., Swiftwater, Pennsylvania

PETER PARADISO, M.D.
Vice President, Wyeth Vaccines, Collegeville, Pennsylvania

Society for Adolescent Medicine
AMY B. MIDDLEMAN, M.D., M.P.H.
Baylor College of Medicine, Texas Children's Hospital, Houston, Texas

Society for Healthcare Epidemiology of America
HARRY L. KEYSERLING, M.D.
Professor of Pediatrics, Emory University, Atlanta, Georgia

Other Registered Attendees

Peter Alberti, Merck & Co.
Christopher Ambrose, Medimmune, Inc.
Dilek Arman, GAZI University, Turkey
Judith Armoni, sanofi pasteur
Jennifer Armstrong, GlaxoSmithKline
Phyllis Arthur, Merck & Co.
Kevin Ault, Merck Vaccine Division
Mutlu Aydingulu, sanofi pasteur, Turkey
Lynn Bahta, Minnesota Department of Health
Yaela Baine, GSK Biologicals
Allyn Bandell, Medimmune
Robert Bargatze, LigoCyte Pharmaceuticals, Inc.
Eliav Barr, Merck & Co., Inc.
Kenneth Barr, National Vaccine Program Office
Joan Benson, Merck & Co., Inc.
Eugenia Barnard, Parent
Guthrie Birkhead, New York State Department of Health
Andrew Bowser, AB Writing & Editing, Inc.
Lynn Bozof, National Meningitis Association
Kimberly Bradley, Merck & Co., Inc.
Esthel Brakel, GlaxoSmithKline, Belgium
Dennis Brooks, Merck & Co., Inc.
Ariel Buda-Levin, SciMed
Delvin Carmel, Wyeth
Donna Cary, sanofi pasteur
Danielle Castellani, Cooney/Waters Group
Dan Pharm Casto, Merck Vaccine Division
Michael Chaney, GA Chapter, AAP
Richard Clover, University of Louisville
Kathleen Coelingh, Medimmune Vaccines
Chis Colwell, Biotechnology Industry Organization
Edward Conner, Medimmune
Lenore Cooney, Cooney/Waters Group
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Mike Corvaia, Balance Medical Staffing
Margaret Cross, Palo Alto Medical Foundation
Christensen Cuculich, Wyeth Pharmaceuticals
Gerard Cunningham, Merck & Co., Inc.
Stephen Dachowski, Merck Vaccine Division
Donald Dalrymple, Dalrymple & Associates, LLC
Adrian Dana, Merck & Co., Inc.
Ana Dayton, Constella Group
Michael Decker, sanofi pasteur
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Sal Espinosa, Merck & Co., Inc.
Geoffrey Evans, Division of Vaccine Injury Compensation/HRSA
Lievano Fabio, Merck & Co., Inc.
Mark Feinberg, Merck & Co., Inc.
Gerald Ferguson, GlaxoSmithKline
Stephen Ford, Military Vaccine Agency
Vicent Frascatore, Merck & Co., Inc.
Sylvina Frutos, GlaxoSmithKline
Mary Gadek, Novartis
Stanley A. Gall, American College of Obstetricians & Gynecologists
Diana Gaskins, Division of Public Health, Georgia Immunization Program
Richard Gesser, Merck Research Laboratories
Christopher Gilbert, Merck & Co., Inc.

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Ruth Gilmore, Georgia Immunization Program
Karen Goldenthal, Pharmanet Consulting
Michelle Goveia, Merck & Co., Inc.
John Gravenstein, Merck
Jesse Greene, SC Dept of Health and Environmental Control
Sylvester Gregg, Merck & Co., Inc.
Carolyn Griffing, Merck & Co., Inc.
Neal Halsey, Johns Hopkins University
Janice Hashimoto, Novartis
Richard Haupt, Merck & Co. Inc.
Alan Hinman, Task Force for Child Survival and Development
Phillip Hosbach, sanofi pasteur
Florence Houn, FDA
Wan-Ting Huang, CDC, Taiwan
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David Johnson, sanofi pasteur
Eric Jones, sanofi pasteur
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Jason Kemner, GlaskoSmithKline
Glennie Kertes, Dwight D. Eisenhower Army Medical Center
David Kimberlin, AAP Committee on Infectious Diseases
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Denise Kruzikas, GlaxoSmithKline
Barbara Kuter, Merck & Co., Inc.
Fred Lake, Cooney/Waters Group
Sarah Landry, GlaxoSmithKline
Scott Laster, Autism Parent
Jennifer Lastinger, Families Fighting Flu
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Grace Lee, Harvard Medical School
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Jennifer Lichtner, Wyeth
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Mobeen Rathore, University of Florida
Jill Ray, Georgia Chapter – AAP
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Tom Shin, Baxter BioSciences
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Gary Stein, Families Fighting Flu
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Theodore Tsai, Novartis
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Michael Vinluan. CDC-INFO/Constella Group
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Joel Ward, Novartis
James Wassil, Merck & Co., Inc.
Barbara Watson, Philadelphia Department of Public Health
Rita Watson, Epilepsy Therapy Development Project
Deborah Wexler, Immunization Action Coalition
Patricia Whitley-Williams, UMDNJ Robert Wood Johnson Medical School
Matt Whitmann, GlaxoSmithKline
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Marcellette Wise, Wyeth Pharmaceuticals
Eileen Yamanda, California Department of Health Services
Laura Jean York, Wyeth Vaccines
Jennifer Zavolinsky, Every Child by Two

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Attachment Two: Acronyms

AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare and Medicaid Services
DHHS	Department of Health and Human Services
FDA	Food and Drug Administration
HCUP	Healthcare Utilization Project
HRSA	Health Resources and Services Administration
IOM	Institute of Medicine
ISO	Immunization Safety Office
NCHHSTP	National Center for HIV, Hepatitis, STD and TB Prevention
NCIRD	National Center for Immunization and Respiratory Diseases
NIH	National Institutes of Health
NVAC	National Vaccine Advisory Committee
NVPO	National Vaccine Program Office
NVSN	New Vaccine Surveillance Network
VAERS	Vaccine Adverse Event Reporting System
VFC	Vaccines for Children
VSD	Vaccine Safety Datalink

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