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

Advisory Committee on Immunization Practices
February 21-22, 2007
Atlanta, Georgia

Record of the Proceedings

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ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
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February 21, 2007

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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) [proposed] convened a meeting of the Advisory Committee on Immunization Practices (ACIP). The meeting was held on February 21-22, 2007 at CDC's Global Communications Center, Building 19, in Atlanta, Georgia. The list of participants is appended to the minutes as Attachment 1. [Note: the list of participants only includes persons who introduced themselves for the record, presented, made public comments, or registered prior to the meeting.]

INTRODUCTION

At 8:11, Dr. Abramson welcomed everyone to the February 2007 ACIP meeting. Dr. Pickering introduced several international visitors, including Dr. Eibhlin Connolly and Dr. Jim Kiely from the Department of Health and Children in Dublin, Ireland, as well as Dr. Keiko Taya, Infectious Diseases Surveillance Center in Wakayama City, Japan, and Dr. Takehiro Togashi from Sapporo City University, Japan. He also introduced new representatives of ACIP liaison organizations. Dr. Tamara Lewis, American Health Insurance Plans replaces Dr. Andrea Gelzer. Dr. Stanley Grogg represents a new liaison organization: the American Osteopathic Association. Dr. Vesta Richardson from the National Immunization Council of Child Health Program in Mexico replaces Dr. Romeo Rodriquez. Dr. Harry Keyserling represents the Society for Healthcare Epidemiology of America. Dr. Geoff Evans (HRSA) was unable to attend the meeting, so Dr. Jevaji attended on Dr. Evans' behalf. Dr. David Kimberlin from the American Academy of Pediatrics was also unable to attend. Dr. Patricia Whitley-Williams from the National Medical Association also sent her regrets.

Dr. Pickering noted that slide presentations would be posted on the ACIP Web site one to two weeks after the meeting. The ACIP home page is located at www.cdc.gov/nip/acip and is updated at frequent intervals to include meeting agendas, meeting minutes and presentations, ACIP recommendations, and other information related to immunization and ACIP activity.

Dr. Pickering confirmed that there was a quorum of ACIP members present and explained that the ACIP charter gives the Executive Secretary or his or her designee the authority to temporarily designate the *ex officio* members as voting members if necessary. This would occur in the event that there are fewer than eight ACIP members available or who cannot vote because of conflicts of interest. The *ex officio* members will be formally requested to vote when necessary. If this occurs, they will be asked to express and disclose any potential

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conflicts of interest. 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. The conflict of interest provisions state that members agree to forego participation in certain activities related to vaccines during their tenure on the committee. CDC has issued limited conflict of interest waivers for certain other interests that potentially enhance a member's expertise while serving on the committee. Members who conduct vaccine clinical trials or serve on data safety 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 vaccines. Regarding other vaccines of an affected company, a member may participate in all discussions with the proviso that he or she abstains on all votes related to the vaccines of that company. All ACIP members must state their conflicts when they vote for a VFC resolution. ACIP members who may have a potential financial conflict of interest should make it known by disclosing all of their vaccine-related financial interests and work.

Dr. Abramson asked ACIP members to state any conflicts of interest. Dr. Carol Baker stated she had a conflict with Novartis Vaccines. Dr. Janet Gilsdorf stated she was an independent safety monitor on an NIH-sponsored influenza trial, for which she receives no compensation. Dr. John Treanor said his group was involved in clinical trails of influenza or pneumococcal vaccines for sanofi, Protein Sciences, Wyeth, Novartis and Merck. Dr. Lieberman stated that he was involved in clinical trials with Merck and MedImmune. Dr. Abramson stated that he served on a Data Safety Monitoring Board for an NIH-sponsored study of the use of oseltamivir in infants, and he received no compensation for this study.

HEPATITIS A POSTEXPOSURE PROPHYLAXIS

Dr. Beth Bell, National Center for HIV, Hepatitis, STD and TB Prevention (NCHHSTP), CDC
Dr. John Victor, PhD., Department of Epidemiology, School of Public Health, University of Michigan

Dr. Bell explained the current ACIP recommendation with respect to hepatitis A post-exposure prophylaxis calls for a single dose of IG as soon as possible but within two weeks of exposure; if hepatitis A vaccine also is recommended, it can be administered simultaneously with IG. The statement does address the question of the use of hepatitis A vaccine alone, saying results of an appropriately designed clinical trial comparing the post-exposure efficacy of vaccine with that of IG are needed to determine if hepatitis A vaccine without IG can be recommended. With this question in mind, about five years ago a trial was funded to compare the efficacy of hepatitis A vaccine to IG after exposure to hepatitis A virus, through a cooperative agreement with the University of Michigan's School of Public Health.

Dr. John Victor presented the results of that study. As background, he showed post-exposure efficacy estimates for IG from the published literature. Most of the studies were done before the advent of serologic tests. For the most part, these efficacy estimates were quite high and support the notion that IG is at least 85 percent effective for post-exposure prophylaxis.

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Unlike most pre-exposure trials, in a post-exposure study potential participants must be ascertained within a relatively short time period after exposure, which is logistically difficult. Identification of cases and their contacts for potential post-exposure prophylaxis requires a site with relatively high endemicity and high rates of hepatitis A.

The trial was conducted from October 2002 to April 2005 in Almaty, Kazakhstan, a very densely populated city of about 1.4 million people. Major hepatitis A outbreaks occur during the fall and winter periods and typically involve large numbers of young children. Over 95 percent of recognized cases of hepatitis A are hospitalized.

The study objective was to compare the efficacies of hepatitis A vaccine and IG in the prevention of laboratory-confirmed, symptomatic hepatitis A, when given within 14 days of exposure to a symptomatic index case. Eligible participants were household and day-care contacts of index cases identified from surveillance, ranging from 2 to 40 years of age. They had to be exposed to an index case within two weeks after index-case symptom onset, with no reported history of hepatitis A in the past and no receipt of hepatitis A vaccine or IG within the previous six months. Also, they had no reported medical diagnosis of chronic liver disease and no contraindications to either of the study interventions. The study interventions were hepatitis A vaccine, VAQTA, at the age-appropriate, licensed dose for pre-exposure protection and U.S.-manufactured IG at the standard post-exposure dust. Both interventions were administered intramuscularly in the deltoid in a scheme that maximized participant blinding.

Within households and day-care groups, contacts were randomized at a 1-to-1 ratio to receive either intervention. Contacts were blinded to the intervention, but physicians administering the interventions obviously could not be blinded because of the different sorts of dosing. Therefore, physicians who had not administered the intervention, conducted the follow up and they were blinded.

Susceptible contacts were followed weekly for eight weeks. At four and eight weeks post exposure, visits were made to interview contacts about hepatitis A-related symptoms and to collect further blood samples for testing. These visits coincided with the average and the end of the incubation period for hepatitis A. If there was serologic or biochemical evidence of infection or if a contact reported illness, a separate illness visit was triggered. Primary endpoints included illnesses occurring 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 one or more of the listed signs or symptoms of hepatitis A.

Because the purpose of the study was to determine if hepatitis A vaccine is at least equivalent to IG, a noninferiority hypothesis was tested, stated as follows: Among those initially seronegative contacts who receive each intervention within 14 days of exposure to an index case of hepatitis A, the proportions of laboratory-confirmed symptomatic hepatitis A with onset between 15 and 56 days post exposure will be similar in the two intervention groups.

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Similarity was defined as follows: assuming equivalence, one would expect to find a relative risk of 1.0, but one cannot test a statistical hypothesis and prove the null in the traditional sense. Instead, the statistical hypotheses were restated in terms of confidence-interval bounds around the point estimate. A null hypothesis that defined vaccine as substantially worse than IG was specified and rejection of the null would mean the two interventions were equivalent. "Substantially worse" was defined as a one-sided 95 percent confidence interval upper bound of the relative risk of 3.0. In order to reject the null and conclude similarity, the confidence interval bound on the observed relative risk was required to be less than 3.0. This 3.0 margin was selected in a pretrial meeting of experts in the clinical, epidemiological, and laboratory aspects of hepatitis A and in statistics and vaccine field-trial design, based on what was felt to be both clinically relevant and statistically valid. Assuming that IG efficacy would be 90 percent, the confidence interval upper bound of 3.0 translates into a vaccine efficacy of at least 70 percent, so the vaccine efficacy estimate lower bound would be 70 percent. Although this confidence-interval bound defines the minimum vaccine efficacy, the point estimate of vaccine efficacy in this circumstance is greater than 84 percent.

In exploratory secondary analyses, probable hepatitis A was examined, defined as any symptom plus serologic evidence of infection and biochemical or virologic evidence of infection, through PCR testing. The subset of cases that were icteric was examined, as well as subclinical illnesses that were confirmed by serology and by biochemical or virologic criteria but were asymptomatic.

The results of the trial were as follows. During 29 months of enrollment, there were 4,524 enrolled household and day-care contacts of 920 index cases of hepatitis A; 2,272 were randomized to vaccine and 2,252 received IG. Because about two-thirds were immune to hepatitis A from previous exposure in their lifetime, this left 740 susceptible persons who received vaccine and 674 who received IG. In this modified intent-to-treat data set, a little over half of contacts were female and about 85 percent were household contacts. Since over 95 percent of primary endpoints and 98 percent of secondary endpoints observed in the study were among household contacts, there was actually very little day-care transmission. Both the index cases of contacts and the contacts themselves were on average relatively young, in early adolescence. Most contacts were immunized late in the two-week window of post-exposure prophylaxis. Over 86 percent received one of the study interventions in the second week post exposure.

During follow up, 29 vaccine and 22 IG recipients were found with an illness confirmed by serology and ALT elevation. The independent data monitoring committee determined that 26 vaccine and 18 IG cases actually met the criteria for primary endpoints. Most outcomes occurred during the second week of the post-exposure period. Illnesses occurred on average a few days earlier than the reported average incubation period for hepatitis A of 28 days, on days 24 and 25. There seemed to be a truncation of the incubation period since the latest case seen was at day 33 post exposure. The average age of cases among those who received vaccine was a bit lower than among IG recipients, though not statistically significant in the crude analysis. The peak ALT elevations measured at the time of illness among vaccine recipients were a bit higher than among IG recipients. Rates of PCR positivity, icteric illness, and frequency of gastrointestinal symptoms were similar in both groups.

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In order to assure maximum robustness, the primary endpoint analysis was done on a per-protocol basis; for a non-inferiority study, it is important to remove all possible misclassification, since that biases toward the null. So 172 vaccine and 150 IG recipients were eliminated, leaving 568 vaccine recipients and 522 IG recipients. In the per-protocol data set, contacts had characteristics similar to those in the intent-to-treat analysis.

For the primary endpoint, 25 cases of laboratory-confirmed hepatitis A occurred among vaccine recipients and 17 occurred among IG recipients, yielding a relative risk among vaccine versus IG of 1.35. That is the point estimate for the relative risk; the one-sided 95 percent confidence interval upper bound of the relative risk was 2.4, which was well within the pre-specified margin of 3.0. The difference of the observed risks for the two groups was only 1.1 percent. So although vaccine might appear to perform slightly less well than IG, even though it met the criteria, the results show only a miniscule difference in the risk of hepatitis A in the two groups, especially compared to not treating at all.

For the secondary endpoint of icteric illness, a similar point estimate was found for the relative risk; even though the confidence interval upper bound is slightly higher, there were fewer cases that were icteric. Looking at all clinical and subclinical infections together, both the confidence interval and the point estimate are less than a relative risk of 2.0. Most cases were among children in the study, so that is where most of the inference was made. However, no major differences appear in estimates for adults.

Dr. Victor then put the relative-risk results in context and described implications for vaccine efficacy. The assumption of 90 percent IG efficacy implied an underlying secondary attack rate of 33 percent in the study population. If this assumption was correct, the study results would translate into a point estimate of vaccine efficacy of 86 percent and the lower bound of the 95 percent confidence interval would have been 76 percent. Therefore one can be quite confident that vaccine efficacy is high in this situation. Using a slightly lower secondary attack rate, the estimate of vaccine efficacy is still very good.

In summary, the efficacy of vaccine post exposure appears quite high and similar to that of IG. The risk of hepatitis A for vaccine recipients was never more than 1.5 percent greater than the risk for IG recipients for any of the endpoints looked at. There is some evidence that IG may be attenuating clinical illness based on the characteristics of the cases seen. There was no evidence that vaccine given in the second week after exposure resulted in lower clinical protection. Finally, contacts in households experienced the highest transmission rates in the study.

Dr. Bell provided some additional data and talked about potential implications. The question before the committee has to do with using hepatitis A vaccine alone post exposure. There are a number of potential benefits of being able to use vaccine, including long-term protection, ease of administration, acceptability, and availability. In addition, there is currently only one U.S. supplier of immune globulin and the cost has risen considerably over the last five or ten years, making it similar to that of hepatitis A vaccine. A single adult dose of IG now is about $20, a pediatric vaccine dose under government contract is about $12, and an adult dose is

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about $19. Another benefit of being able use hepatitis A vaccine is that it brings U.S. practice in line with many other countries that recommend vaccine as post-exposure prophylaxis.

Only one other clinical trial used hepatitis A vaccine post exposure and that was conducted in Italy in 1997. This study enrolled 212 household contacts, aged 1 to 40 years, of hospitalized hepatitis A cases. Contacts were randomized to receive either the GSK vaccine within eight days of symptom onset of the index case or no intervention. The outcome was IgM positivity as measured either at Day 14 or Day 45 post vaccination or post no intervention. The trial was stopped when the study results reached statistical significance. The estimated vaccine efficacy was 79 percent, with a very wide confidence interval. The outcomes identified included two in the vaccinated group, ages 10 and 11 years, both of whom were asymptomatic with normal ALTs. Since vaccination can induce IgM, it is possible that these two so-called vaccine failures, in fact, did not have hepatitis A. In the no-intervention group, there were 12 outcomes, aged 3 to 25 years, the majority with symptomatic hepatitis A and elevated ALTs. This study was of limited usefulness in the U.S., where there was already an efficacious intervention in IG, but it did provide good evidence that the vaccine did a reasonable job of preventing hepatitis A.

Unfortunately, results of the current study and previous information cannot answer all questions about how hepatitis A vaccine performs post exposure. Eligibility was restricted to age 40 and under in the Kazakhstan study. Most cases and study participants were fairly young, which is not surprising, given that essentially all adults older than 40 are immune to hepatitis A, as are many younger adults. Patients who reported a diagnosis of chronic liver disease were excluded, based on concern about the increased severity of hepatitis A in those people. People with other medical conditions were not explicitly excluded, but in general, the study population was young and healthy.

Only one of the two U.S.-licensed vaccines was used, so there is the question of the generalizability of the findings to both licensed vaccines. There is also the question of time since exposure. Going into the study, many might have thought that vaccine would not perform as well in the second week after exposure. Any recommendation the committee might make about the ability to use vaccine would represent off-label use because the manufacturers do not intend to apply to FDA for this as an indication. Finally, it is likely that currently available data are all that will be available. Additional studies addressing these areas with limited data are logistically unfeasible.

Dr. Bell shared some technical information about the antibody to hepatitis A virus. The minimum protective antibody concentration is unknown, and in fact, it may be below the assay-detection limit. For example, after IG administration, it is known that protection continues after antibody is no longer detectable. In vaccine immunogenicity studies, protection has been defined as the lower limit of detection of whatever assay was being used. This can vary from 10 to 33 mIU per ml, which complicates the precision with which one can look at the available pre-exposure immunogenicity data.

With that caveat, Dr. Bell presented a summary of data available from the pre-exposure studies about seroconversion after one dose of hepatitis A vaccine, which seem to be most

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relevant to how hepatitis A vaccine might perform post exposure. Ninety-five percent or more of children seroconvert by four weeks after the first dose. However, many of these studies were conducted using old formulations of the vaccine, which was a three-dose series, with the first dose being half of the currently licensed dose. That makes it very difficult to study response after one dose of what is used now. Thus there are no published data among children that report seroconversion at two weeks. The GSK package insert reports that 92 to 96 percent of children have seroconverted at two weeks, citing unpublished data.

Essentially all adults (over 18 years old) seroconvert by four weeks. Using the currently licensed formulations, one or two published studies and information in the package inserts quote anywhere from 70 percent to 100 percent seroconversion at two weeks after one dose. Only one published study was found that directly compares the response after a single dose of vaccine in younger versus older adults, and that study used the currently licensed formulation of the GSK vaccine. At Day 15, the study reported 90 percent seroconversion among younger adults versus 77 percent among older adults, and by one month, 97 percent were seropositive in both groups.

Data from the National Health and Nutrition Examination Survey conducted in 1988 to 1994 address the likelihood of adults and older adults in the United States being susceptible to hepatitis A. About 50 percent of 40- to 49-year-olds are immune, rising to 60 to 65 percent in older adults and reaching over 70 percent in adults age 70 or older. It is reasonable to conclude that the majority of adults remain susceptible to hepatitis A in the U.S.

The next issue addressed was the response to hepatitis A vaccine among people with medical conditions and immunocompromised people. The data are fairly limited with respect to response after one dose of vaccine and there are no data regarding response at two weeks; all the data are at four weeks. Among HIV-infected patients, the three relevant studies report a wide range of seroconversion after one dose, ranging from 10 to 78 percent. The percent positive is higher with a higher CD4 cell count, but in several studies a much lower than the usual 95 percent of adults seroconvert after one dose. 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, the percent positive at four weeks ranges from 63 to 93 percent. In the one study that used a control group, the percent positive was lower than controls. It appears that the response rate is lowest in patients with decompensated cirrhosis. Finally, a few studies in liver and kidney transplantation patients show a much lower percent positive at four weeks.

Dr. Bell mentioned two other considerations. The first was time since exposure. The Italian study cut off at seven days post exposure. The current study appears to remove theoretical concern about diminished vaccine efficacy with longer time since exposure; there was no difference between the groups in time since exposure, and most interventions were given fairly late in this two-week post-exposure limit. A second question is the comparability of the two U.S.-licensed vaccines. They are considered equivalent for pre-exposure use but there have been very few head-to-head comparisons. Because of problems with the different assays, it is difficult to make precise comparisons but the percent seroconverting appears to be similar.

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Many other industrialized countries that recommend post-exposure prophylaxis have recommendations for using vaccine. In Canada, since 2000 the recommendation has been that vaccine without IG is preferred during the first 7 days after exposure, with a recommendation of IG for infants and immunocompromised persons. Apparently IG is more difficult to get in Canada than in the U.S. In the U.K., since 2001 the recommendation has been to use vaccine if the exposure has been within the previous seven days, based on the Italian study, and to continue to use IG if the exposure has occurred more than seven days previously and for people older than 50 years, cirrhotics, and people with chronic viral hepatitis. During 2000-2003, a survey was conducted of European countries with respect to viral hepatitis. France, Italy, and Belgium all reported using vaccine only for post-exposure prophylaxis. Only Sweden and perhaps Norway reported using only IG for post-exposure prophylaxis. The majority of the other countries used vaccine or vaccine and IG.

Dr. Bell then described the current epidemiology of hepatitis A in the United States. The provisional total number of cases in 2006 was about 3300, compared to 20,000 - 35,000 hepatitis A per year during the past several decades. Although communitywide outbreaks do occur not anymore, vaccine has been recommended in that context for the past decade. The common setting for IG use as post-exposure prophylaxis currently is among household and other close personal contacts. Outbreaks in childcare centers used to often require IG, but now these outbreaks are rare.

It is difficult to quantify exposure from an infected food handler, but surveillance data indicate that 3 to 7 percent of reported hepatitis A cases are food handlers. A study funded a few years ago in a couple of states found that about 5 percent of food handlers worked while they were infectious and were felt to pose a transmission risk. In the context of contact notifications, an average of 350 IG doses per episode were administered. Health departments do not systematically keep track of how much IG has been used such settings, but given the low number of cases these days, it is potentially on the order of tens of thousands of doses and not likely more than 100,000.

In summary, vaccine offers a number of advantages over IG, and the flexibility to use vaccine in some circumstances would be beneficial. The available data suggest that vaccine is efficacious post exposure, but not all populations were studied. The relevance of pre-exposure immunogenicity data is unclear and they do not suggest large differences in responses of children and healthy adults to vaccine. Some adults might not respond as briskly, but the clinical significance of this finding is quite unclear. It does appear that there are suboptimal responses at least in some immunocompromised persons. Since additional data are not likely to be forthcoming, the committee needs to balance the practical public health implementation considerations against the limitations of the available information.

Discussion

Dr. Bell read the two paragraphs the committee was considering: "*Persons who recently have been exposed to HAV and who previously have not received hepatitis A vaccine should be administered a single dose of IG as soon as possible.*" She explained that this was the

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wording of the current statement and the proposal was to add the following: "*Based on limited data showing equivalent efficacy to IG, hepatitis A vaccine at the age-appropriate dose licensed for pre-exposure use can be used instead of IG. The efficacy of IG or vaccine, when administered more than two weeks after exposure has not been established. For persons who receive vaccine the second dose should be administered according to the licensed schedule to complete the series."*

The second paragraph read, *"IG should be used for children less than 12 months old, immunocompromised persons, and persons for whom vaccine is contraindicated. The postexposure efficacy of hepatitis A vaccine in persons younger than two or older than 40 years old and persons with chronic liver disease or other medical conditions has not been studied. Persons who have been administered one dose of hepatitis A vaccine more than two weeks before exposure to HAV do not need IG."*

Dr. Allos asked whether it was correct to say that there was no greater risk of developing one of the endpoints or increased LFTs if either the IG or the vaccine was received later in that two-week interval. Dr. Victor replied that he categorized time of receipt as either within the first week or second week and then also looked at it on a continuous scale. Most of outcomes occurred the second week after exposure and there was no difference between vaccine and IG in that context. Dr. Allos then asked for clarification of the phrase "*it hasn't been studied*" in the recommendation. The presentation suggested there were immunologic data available for people with HIV and liver disease. Dr. Bell explained that the post-exposure efficacy has not been studied, and that the data shown were immunogenicity when the vaccine was given pre-exposure.

Dr. Treanor asked why, if the hepatitis A is a neoantigen in a susceptible person, the response was so rapid to a single dose. Dr. Bell replied that she wasn't sure anyone knew the answer, but it was consistently the case. In some of the very early studies where a modified IgM assay was used, which was much more sensitive than the usual IgM assay, one could see IGM coming up even sooner. Dr. Treanor responded that if these rapid responses occured because people are somewhat primed by exposure to other enteroviruses, then one might see a difference between the kinetics of the antibody response in a population like Kazakhstan and the U.S. population. He wondered whether children in Kazakhstan respond more rapidly to a single dose of hepatitis A vaccine than children in the U.S., where perhaps background rates of enterovirus infections might be lower or where there's a much lower rate of background hepatitis A transmission. Dr. Bell replied that all the pre-exposure immunogenicity data shown were U.S. data.

Dr. Baker noted that a public health conclusion for the comments about outbreaks in the U.S. is that all food handlers should be immunized, and wondered if any thought had been given to that strategy. Dr. Bell said there was no objection to vaccinating food handlers. Restaurants should be reminded that often food handlers do have other indications for vaccination. When this question has been studied from an economic point of view, it has never appeared to be a favorable policy largely because of the turnover among food handlers. In fact, as hepatitis A vaccine was about to be licensed, a number of the large restaurant chains appeared to be interested. While a few have adopted it, not as many as might be expected have done so,

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probably because of staff turnover. Dr. Baker then asked why everyone with hepatitis was hospitalized in Kazakhstan. Dr. Victor replied that this was a lingering practice from the Soviet Union era.

Dr. Kathy Neuzil asked whether the concentration of specific IgG or antibody against hepatitis A in commercial IG preparations was changing over time. Dr. Bell responded that the concentration of anti-HAV in commercial IG preparations is not routinely measured. There has been some theoretical concern that perhaps the antibody concentrations have been falling in IG, but no clinical evidence that the efficacy of IG has changed.

Dr. Dale Morse wondered if the FDA had any comments. Dr. Baylor responded that one of the downsides was that it is an off-label use. The limitations of the data presented are indicative of the fact that this would not support an indication alone. However, the FDA recognizes that flexibility needs to be written in.

Dr. Ciro Sumaya asked what the basis was for the U.K. recommendation for IG. One of the slides seemed to indicate that if the post-exposure period is greater than seven days, then the recommendation is for IG rather than vaccine. Dr. Bell replied that, according to the Dr. Crowcroft in the U.K., the reason was that the Italian study cut off at seven days, so there were no data past that. She suspected there was concern that vaccine did not work as well in the second week after exposure. Dr. Crowcroft thinks the actual practice is quite variable in the U.K. and they do continue to distribute a fair amount of IG. Dr. David Salisbury added that the updated guidance issued at the beginning of this year had not changed this part of the hepatitis A guidance. It still says to use a one-week cutoff, based on all the evidence available at the end of last year. However it does say that the HNIG that should have an antibody level of at least 100 IU per ml.

Dr. Treanor referred to the fact that the vaccine is the primary prophylaxis mode for many countries and wondered if there was information about the rate with which that prophylaxis fails in countries that use it routinely. Dr. Bell responded that the U.K. only had 700 or 800 hepatitis A cases a year, which would not yield much information about failures. In Canada much of the vaccine has been used in outbreak settings, for which vaccine is already recommended. Dr. Naus added that there was information about one situation in Canada in a school and some additional cases in a day-nursery setting, where there were a number of failures among children who had received the vaccine. Canadian guidelines were also based on the Italian study. While Canada has a permissive recommendation about administration of IG more than seven days out from exposure, there is probably very little IG use now because of the preferential statement to administer vaccine.

Dr. Bill Schaffner asked about the availability of IG. Dr. Bell replied that Bayer, the one manufacturer, was continuing to make IG. There is another market for IMIG in this country, which may be larger than the public health market. Some patients with immune deficiency apparently use large volumes of IMIG. She didn’t believe Bayer's production schedule had recently been interrupted, but since this is a shrinking market, the distribution may be somewhat spotty.

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Dr. Neil Halsey from Johns Hopkins had two comments. First, the wording of this statement strongly implies a preference for IG, but the data do not support such a preference, especially in the first week. He felt the two sentences should be combined, indicating that either can be used and the committee should decide whether there would be a preference. Second, the guidelines for pre-exposure prophylaxis for travelers need to be revised. To best of his knowledge, travel clinics are just about only using vaccine and ACIP guidelines are out of touch. Dr. Bell responded that in the most recent statement, the wording in terms of travelers is much more permissive, downplays IG, and has shortened the recommended time interval. Dr. Halsey indicated that for pre-exposure, only vaccine is needed, while the guidance still implies the need for immune globulin.

Dr. Harry Keyserling asked whether it would be appropriate to have a special category with higher standards for healthcare workers, since the implications of infection and transmission are compromised and should be different. Dr. Bell thought the need for prophylaxis after exposure to hepatitis A in hospitals was extremely unusual. Dr. Keyserling said that was true for exposure in hospitals from patients, but it would more likely be exposure within families, which a healthcare worker would report to employee health.

Dr. John Temte, American Academy of Family Physicians, wondered if there was any sense about the distribution between rural and urban areas in terms of the required use of prophylaxis. Dr. Bell said in the old days, the large communitywide outbreaks of hepatitis A often occurred in urban areas, so the need for post-exposure prophylaxis after household contact was probably greater in urban areas. These days, without those communitywide outbreaks, there's probably no difference between those two settings.

Dr. Jeff Duchin from NACCHO asked about the implications of the trend towards younger children in both of those groups, and whether that would have been significant if this study was larger. Perhaps transmission is more likely among younger people and they were overrepresented in the vaccine group. Dr. Victor said that was possibly the case. In a pilot transmission study conducted the season before this study was implemented, secondary attack rates in the age group from zero to six years were about 35 to 40 percent, compared to adults, where they were under 20 percent.

Dr. Barbara Kuter from Merck added some information to the immunogenicity data presented. First, to address the question about the use of the vaccine in individuals less than 40 versus greater than 40 years of age, particularly for healthcare workers, there are data suggesting that the 50-unit dose of VAQTA has a pretty flat response across all age ranges. Also, regarding the kinetics of response, Joe Bryan from the U.S. military did a randomized cross-over study between the two available vaccines. That paper pointed out some differences in the kinetics of response, particularly at the early time points of two and four weeks, and some differences with regard to the levels of antibody obtained between the two vaccines.

Dr. Pickering asked whether the ACIP members were ready to vote on the general recommendation as presented, or did they still have questions about specific aspects of the

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recommendation. There would be a chance to look at the manuscript produced, with more detail about specific subgroups.

Dr. Kathy Neuzil said she preferred something in between, based on what Dr. Bell had said about giving the two [vaccine and IG] together. Dr. Bell reiterated that the current recommendation was that the two can be given together if there is an indication -- a pre-exposure indication for vaccine. In other words, if someone is seen post exposure, give them IG, and if there is a reason to give them vaccine as well, that ability already exists. The question is whether there are any circumstances in which IG does not have to be given post exposure.

Dr. Dale Morse agreed that there were a number of nuances to consider and his preference was to discuss them before voting. If the paper hasn't been published and discussed in the literature yet, he wondered why the recommendation was coming forward for a vote. Dr. Bell replied that the abstract and tables were among the materials that the committee received ahead of time.

Dr. Abramson said he sensed that a number of people were still trying to deal with specific groups, such as the immunocompromised and people with chronic underlying disease. He suggested sending something out to ACIP for comment and bringing it back at the June meeting. Dr. Treanor added that, ultimately, the committee would probably approve the general principle of using the vaccine, the only issue being whether there should be a specific list of people that should get IG instead.

Dr. Abramson asked whether the committee was willing to approve the overall principle, i.e., vaccination as a main means of prophylaxis and then take on the nuances about the specific subgroups. Dr. Treanor said he wished there was more information about how this strategy has worked in other countries. Hearing that there may have been failures in Canada is unsettling, but basically the data would support the recommendation without having to look at every single set of conditions before voting.

Dr. Neuzil felt the recommendation could be interpreted as saying vaccine is inferior. She was comfortable with vaccine recommendation from the data presented, and the other advantages of vaccine, such as the simplicity and the long-term protection that IG does not provide, but the language needs editing.

Dr. Lieu felt the issue of whether IG is preferred to vaccine or whether vaccine is considered equivalent to IG really needed to be part of the vote. Dr. Baker suggested delaying the vote just to edit the one sentence that implies an either/or rather than a preferred recommendation. Dr. Greg Wallace, CDC, reminded the committee that the specific language has to be agreed upon before the VFC vote. The decision was to return to the issue the next morning and make a decision then.

ROTAVIRUS VACCINE

Update on U.S. Rotavirus Vaccination Program

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Dr. Umesh Parashar, National Center for Immunization and Respiratory Diseases (NCIRD)

Dr. Parashar reviewed a number of key milestones that had occurred during the previous calendar year. About a year ago, the U.S. FDA licensed Rotavirus Vaccine, Live, Oral, Pentavalent (RotaTeq®), which was subsequently recommended for routine immunization of all U.S. children.

Another vaccine, Rotavirus Vaccine, live attenuated (Rotarix), made by GlaxoSmithKline, has not yet been submitted to the FDA for U.S. licensure, but has been licensed in more than 70 other countries, including those in the European Union. A large clinical trial was done and the vaccine has now been introduced into immunization programs in several Latin American countries, including Brazil, Panama, Venezuela, and El Salvador.

In November of 2006, the Global Alliance for Vaccines and Immunization approved the investment case for purchase of rotavirus vaccines for use in the public sector in GAVI-eligible countries, which are countries below an income cutoff of $1,000 GNP per capita. The initial investment case signaled approval for purchase of the vaccine for GAVI-eligible countries in Latin America and Eastern Europe. Clinical trials of both vaccines are ongoing or soon to start in Africa and Asia, and only when those data become available will a broader recommendation be issued.

RotaTeq is a reassortant vaccine made by Merck. By genetic reassortment, human antigens have been introduced into a bovine strain. There are five reassortants included in the vaccine against G1, 2, 3, 4, and P8, and these are essentially the GNP types of 80 to 90 percent of strains in the U.S. It is a liquid preparation given directly to the infant by mouth in three doses, and recommended at two, four, and six months of age routinely.

Data from the large vaccine effectiveness trial indicate that RotaTeq is highly efficacious against hospitalizations, emergency-department visits, and office visits for rotavirus gastroenteritis. Rate reductions range from 96 percent against hospitalizations to about 85 percent for office visits. The trial enrolled about 70,000 infants, and was designed to look at intussusception, an adverse event associated with a different rotavirus vaccine used in the U.S seven years ago. The data include cases of intussusception, broken down for each of the three doses. The primary safety endpoint was cases of confirmed intussusception within 42 days of any dose. There were a total of six cases of intussusception in vaccine recipients and five in placebo recipients. The relative risk, not adjusted for the multiple comparisons made, was about 1.2, indicating no evidence of any association of this vaccine with intussusception.

RotaTeq has now been licensed in Europe, Australia, Canada, and many other locations. Outside the U.S., the largest user in the public sector is in Nicaragua, where a demonstration project was launched in October 2006 for routine immunization of all infants in that country. The vaccine is being donated by the manufacturer for a period of three years for the entire birth cohort.

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Rotarix, the vaccine made by GlaxoSmithKline, has been tested in a similar large trial. This vaccine is based on a single strain of Serotype G1P[8] rotavirus, a human strain that is, by far, the most common single strain globally. In the past 10 years, about 60-80 percent of rotavirus strains seen in hospitalized children are of this serotype. It's a lyophilized product, given by mouth in two doses after reconstitution with a buffer preparation. When this vaccine was tested in a large efficacy trial, primarily in Latin America, it showed about 85 percent efficacy against severe rotavirus disease and disease leading to hospitalizations. This trial was also large enough to look at the risk of intussusception. Over 30,000 infants got vaccine and placebo. There were six cases of intussusception in vaccine recipients and seven in placebo, with a relative risk lower than one. For both Dose 1 and Dose 2, there was no excess of intussusception in the vaccinated groups. This vaccine may be submitted to the FDA for licensure sometime in the future.

Rotavirus kills more than half a million children globally each year. In the U.S., there are few deaths, but a large number of hospitalizations and other severe health outcomes. The vaccine looks promising for prevention of severe disease and deaths in developing countries.

Update on Rotavirus Disease Burden and Vaccine Effectiveness Monitoring
Dr. Daniel Payne, National Center for Immunizations and Respiratory Diseases (NCIRD)

The New Vaccine Surveillance Network (NVSN) is a prospective, population-based, acute gastroenteritis surveillance platform for three U.S. counties. Another wing of the NVSN is the acute respiratory illness (ARI) platform. The three counties are Davidson County, Tennessee (surveillance conducted by Vanderbilt University), Monroe County, New York (University of Rochester), and Hamilton County, Ohio, (Cincinnati Children's Hospital Medical Center). The epidemiological data collected include parental interviews; medical-chart reviews; clinical outcomes from inpatient, emergency-department (ED), and outpatient-clinic visits; and laboratory data. Enzyme immunoassays (EIA) are performed at the hospital, and rotavirus-positive-by-EIA samples are sent to CDC for further typing.

The objective of acute gastroenteritis and rotavirus surveillance is to directly estimate the annual burden of rotavirus gastroenteritis among children under three years old in the three counties, and to monitor the effectiveness and impact of rotavirus vaccination. The data presented were from surveillance conducted between January 1 and June 30, 2006.

Dr. Payne showed a chart that described the curve for rotavirus cases. February, March, and April accounted for a substantial amount of the AGE cases captured among less than three-year-olds. Forty-four percent of all of AGE cases under three years old were found to be rotavirus positive by EIA. They were fairly consistent statistically across the three surveillance sites. Another stratification of percent rotavirus-positive by EIA is by provider type – hospital, emergency department and outpatient clinic. The hospital and ED percent rotavirus-positive is 50 percent, which is on the higher edge of what would have been expected from previous publications, and about one-quarter of outpatient clinic AGE cases were rotavirus-positive during this season.

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Rotavirus burden was calculated and adjusted for differential specimen collection and differential enrollment practices. The 2000 census data were used as a denominator. For children under three years old (rates per 10,000 children), some site variability in hospitalization rates is seen, but the aggregate total rate is 28.9 rotavirus hospitalizations per 10,000 children in these counties. This matches very well with some of the published estimates that use indirect methods, in particular, the National Hospital Discharge Survey of rotavirus hospitalizations under five, which was 27.4 per 10,000. Although 28.9 per 10,000 is an aggregate, the burden of this disease falls very heavily upon the February, March, and April months of the year. Looking at hospitalization among under-three-year-olds by month, one can see that in March, for instance, the rotavirus AGE burden is approximately six times that for all other pathogens combined.

All EIA-positive rotavirus samples are sent to CDC, where they are tested for strain types. The G[1]P[8]strain is most common, about 80 percent, as expected. No G3 or G4 strains were found, and the G9-strain proportion was a bit lower than would have been expected from previous published reports. Interestingly, the G[12]P[6] strain was found in over 3 percent of the sample, which will be watched carefully in future surveillance.

One objective of the NVSN rotavirus effectiveness studies is to determine post-marketing vaccine effectiveness in the three NVSN communities. Cases will be collected during the 2007 rotavirus season, as well as the following season. Two different control methods will be used: community cohorts and comparison with other NVSN surveillance controls based on vaccination status. In the current data there were no vaccinees, since the vaccine was only licensed in February 2006.

A limitation of the study is that several untypables or mixed-strain specimens were found, which are being further analyzed by CDC. Also, one year of surveillance data places limits on conclusions because of the very small *n*, but further surveillance years should help to verify some of the specific trends.

In conclusion, the rates of rotavirus hospitalizations found are fairly consistent with published estimates and those previously presented to the committee. But 2006 appears to have been a mild rotavirus season in the Rochester, New York area. Half of the acute gastroenteritis hospital and emergency-department visits were for rotavirus. This was consistent across sites, but a little higher than expected. Approximately 96 percent of the strains detected had matching antigens covered by the current rotavirus vaccine. Results show the strength of the NVSN platform to monitor trends of rotavirus burden, strain prevalence, and also vaccine effectiveness in upcoming years.

Summary of RotaTeq Vaccine Reports to VAERS
Ms. Penina Haber, CDC Immunization Safety Office
Dr. Manish Patel, National Center for Immunizations and Respiratory Diseases

Since March 2006, about 3.6 million doses of RotaTeq vaccine have been distributed in the United States. From March 1, 2006 to February 15, 2007, VAERS received a total of 567 reports pertaining to any RotaTeq vaccination. Of those, 51 percent were after RotaTeq

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vaccine alone and 57 percent were after Dose 1. Most frequently reported adverse events were diarrhea and vomiting.

Looking at onset interval in days, about 50 percent of reports were between zero to two days and over 30 percent did not have information about the onset interval. As of February 15th, 35 reports of IS have been confirmed. Of those, 17 were 1 to 21 days post vaccination and 11 of those were one to seven days. No deaths were reported. Reports of onset interval ranged as high as 73 days. Between two and six days post vaccination, there are 11 reports.

For the 17 reports of intussusception by Dose 1 and Dose 2 from onset interval Day 1 to Day 21, there were nine reports for Dose 1, and of those, seven were between two and six days. For Dose 2, there are eight reports, including one on Day 0, the day of vaccination. No cases were reported after dose 3 within 1 to 21 days. Overall, the mean and median age of symptom onset was 21 and 20 weeks, and the range was 10 to 37 weeks. Forty-three percent of reports were male, though gender was not reported in 11. Of the 17 reports within 1-21 days of RotaTeq vaccination, five had surgical reduction and another five had surgical resection. Six percent of the 17 reports within 1-21 days had contrast enema reduction.

Lab results from tissue or stool or both specimens have been very limited. Of the reports within 1-21 days, 4 were tested and none was positive for rotavirus or adenovirus, which is known to be associated with intussusception. One stool sample tested positive for vaccine strain at Day 6, which is expected after RotaTeq administration.

Data from the VSD study show that, as of February 14, 2007, 28,377 children were vaccinated, which included six out of eight sites of the participating study of the VSD. No intussusception report within 30 days was found following RotaTeq vaccination. Data on uptake by age group in weeks and dose number show that about 61 percent of the vaccination went to Dose 1, 30 percent to Dose 2, and 9 percent to Dose 3.

The Merck Phase IV study is a prospective review of the original active surveillance. The study population is a large insured population in the U.S., with an annual birth cohort of about 100,000 a year. The planned study size will be 44,000 vaccinated children. Rates of intussusception and overall vaccine safety will be monitored and compared with rates in several control groups. The study period will be 30 days post vaccination for each dose. So far, 1,354 RotaTeq recipients were followed up through September 30, 2006, and no case of intussusception was found. Over 16,000 first-dose vaccinees were enrolled by December 2006, and those data are currently being evaluated.

Interpretation of the Data

The primary question to be addressed is whether the observed number of intussusception reports to VAERS exceeds the expected number of cases likely to occur by chance alone. To calculate the expected rates of intussusception, two key data elements are necessary: the age-stratified baseline rate of intussusception, and the number of vaccine doses administered and the age at which these doses were administered.

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Regardless of the data source, intussusception rates increase several-fold during the first six months of life, illustrating the importance of age-adjusted analysis. Data from the Healthcare Utilization Project, or HCUP, captures about 85 percent of national inpatient hospitalizations. Looking at annual background intussusception rates per hundred thousand for the years 1993 through 2004, it can be seen that the rates increase dramatically between birth and 24 weeks of age. However, rates may vary depending on the data source. Background rates of data from the Vaccine Safety Datalink (VSD) and the Healthcare Utilization Project (HCUP), rates appear to be reasonably similar. The calculations presented used VSD background rates, as VSD is a robust source of data. Rates were also categorized by age of onset: 6 to 14 weeks, 15 to 23 weeks, and 24 to 35 weeks. The background incidence of intussusception varies dramatically between these age groups and the three-dose RotaTeq series is being administered according to this schedule, which is close to the ACIP-recommended schedule.

The second important data element for calculating expected rates is the number of doses administered. Although the exact number of doses administered to date is unknown, approximately 3.6 million doses were distributed by the manufacturer through the end of January 2007. Of the 28,000 doses of vaccine administered within VSD, 57 percent were given to infants 6 to 14 weeks of age, 31 percent were given to infants 15 to 23 weeks of age, and 12 percent administered to infants 24 to 35 weeks of age. These proportions are similar to the proportion of Doses 1, 2, and 3 that were administered within VSD. So in essence, the calculations presented by age throughout the rest of the presentation are similar to the calculations by dose.

Two time windows of potential intussusception risk after RotaTeq vaccination were used: 1 to 21 days and 1 to 7 days after vaccination. The previous experience with Rotavirus Vaccine, Live, Oral, Tetravalent (RotaShield®) identified these as possible risk windows and because of biological plausibility. As of February 14th, 2007, VAERS had received 35 confirmed reports of intussusception; 50 percent, or 17, of these reports were within 1 to 21 days after RotaTeq administration and of these 17 reports, 11 were within one to seven days of RotaTeq vaccination. Categorizing the VAERS intussusception reports by age of onset, it was found that within 1 to 21 days of vaccination, seven cases were in the first group, 6 to 14 weeks; nine cases were in the second group; and one case was in the third group. In the second age window of one to seven days after vaccination, five cases were in the first age group, 6 to 14 weeks; six were in the second group; and none were in the last group.

These data were used to assess the observed versus expected calculations for the first time window of interest, which is the 1-to-21-day time period after vaccination. VAERS has received 17 reports within 1 to 21 days of vaccination, whereas one would expect approximately 52 cases of intussusception to occur by chance alone within this time period, after adjusting for age. For these expected calculations, the manufacturer's distribution data were used, and VSD was used for the background incidence of intussusception and the age at vaccine administration. The data indicate that the number of observed cases does not exceed the expected number within the 1-to-21-day window, and the reporting rate is 0.32. In addition, the observed number of cases does not exceed the expected within each of the three age strata.

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Within the one-to-seven-day window, VAERS has received 11 cases of confirmed intussusception. Approximately 17 cases would be expected to occur by chance alone after adjusting for age. Again, the observed number of cases does not exceed what one would expect to occur by chance. Although the numbers are small for each of the three age strata, the observed numbers are also within the expected for the three age strata.

Several assumptions should be kept in mind when interpreting the data. First, baseline intussusception rates can vary depending on the source of the data. The VSD data may not be nationally representative, but they are very robust for that HMO population. The completeness and accuracy of the ICD-9 code for intussusception are not well known. For example, some evidence suggests that databases may actually underestimate the true background rate. Intussusception cases may be discharged from the emergency department or short-stay setting, and they would be missed if one just used inpatient databases. In fact, one study suggests that approximately 40 percent of intussusception cases may be managed in the ED or short-stay setting, making the expected number of cases actually higher.

Another assumption regards the reporting completeness of intussusception to VAERS. Indirect evidence suggests that the reporting of intussusception is common. Since the RotaShield experience, awareness of potential intussusception after vaccination has been high among healthcare workers. For instance, in the data presented on the current RotaTeq vaccine, half of the VAERS intussusception cases were outside the 1-to-21-day window and many of these cases were as far as 45 to 60 days after vaccination.

The third assumption involves the number of doses administered. Although there is distribution data from the manufacturer, it is unclear whether there is substantial lag time between the distribution and administration of vaccine doses. Past experience suggests that the delays tend to diminish as vaccine coverage rises. Background IS rates vary depending on the age at which the children receive the vaccine. VSD data was used to determine the age of vaccination for the expected rate calculations and compared with data from U.S. immunization registries, they appear to be similar.

In summary, the observed reporting rates of intussusception did not appear to be greater than rates expected to occur by chance alone. Nonetheless, these data are dynamic and need to be interpreted with limitations. The CDC continues to support the ACIP recommendations for routine immunization of all U.S. infants with three doses of RotaTeq at two, four, and six months. Ongoing monitoring and refinement will be critical, and plans are in place to provide healthcare providers and public health authorities with current updates.

Discussion

Dr. Abramson asked what the confidence interval was for the reporting rate around that first week. If there was absolutely no association, one would think it would be fairly even out across the days. Dr. Melinda Wharton responded that the data in question was from the case-control study where there was active case finding in hospitals, and there is near certainty that all of the cases were found. However, cases soon after vaccination are more likely to be reported and it is actually quite remarkable that so many late cases were reported. It does

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appear that there is clustering the first week, but the comparison to that isn't with how many cases are at later intervals but how many cases are expected in that first week. If there were unbiased ascertainment, where cases that occurred later are actually known as opposed to relying on people to report them, the graph would probably look very different.

Dr. Ban Allos wondered how the message in the media became so distorted and what could be done to make sure that doesn't happen again. Dr. Patel noted that the media headline was different from the body of what was presented in most of those articles.

Dr. Janet Gilsdorf asked if the criteria for hospitalization had been standardized. Dr Payne replied that there was a series of inclusion and exclusionary criteria, which were implemented to standardize criteria across the three sites.

Dr. Baker asked whether each of the three sites was tested according to some standardized protocol. Dr. Payne replied that all AGE cases were enrolled in the study according the inclusion and exclusionary criteria. However, in normal practice the EIAs are differentially applied. There was standardization for differential specimen collection and differential enrollment. Sometimes specimens weren't able to be collected from all the other patients due to a number of factors. Dr. Baker then asked whether, in terms of ongoing disease-burden estimates, these sites had registries or a mechanism for seeing unvaccinated, partially vaccinated children and rates of disease. Dr. Payne replied that starting this year, detailed information was being collected on vaccination status of all the cases and exactly how many doses of how many vaccines study enrollees had received.

Ms. Stinchfield asked about data on use of the vaccine in special populations, such as premature infants in neonatal intensive care units, with or without GI problems; or perinatally exposed HIV infants; and if there was any guidance for clinicians. Dr. Payne replied that the sample size was very small from the first year, so it has not yet been possible to stratify beyond general age ranges and some calendar splits.

Dr. Jane Seward, NCIRD, referring to the apparent clustering in the first seven days, noted that the majority of those cases were reported early in October, and at the time some wondered if they may have represented an unrecognized adenovirus outbreak. The fact that they haven't continued to be reported in clusters as the months progress is reassuring.

Dr. Stan Grogg commented that by the expected versus the number of cases, it might appear that the vaccine is protective against intussusception, and that's not what the media have said. Dr. Patel responded that the rate ratio of 0.32 does certainly imply that, however it likely reflects underreporting within that time window of 1 to 21 days. As the 1-to-7-day window closes, the rate ratio goes up and reporting is more complete.

Dr. Sam Katz, IDSA, asked how many of the reported intussusceptions were corrected or remedied radiologically, in contrast to those that went to surgery. Dr. Patel replied that of the 35 cases, 13 were reduced by barium enema, 8 required surgical resection, 12 required surgical reduction, 2 reduced spontaneously, and 2 were still undergoing investigation.

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Dr. Parashar cautioned that one should be careful not to interpret those rates to be protective, even though statistically significant for 1 to 21 days. There are too many assumptions in the data, such as reporting completeness and doses distributed versus doses administered, etc. At this point, the only take from the data is that it's not higher than what would be expected.

Dr. Plotkin shared a headline from the Bucks County local newspaper: "New childhood vaccine put on hold. The government says it's unknown whether the recently approved RotaTeq is responsible for a potentially life-threatening bowel obstruction." He said it was not surprising that the press got it wrong because reading the FDA statement without any prior knowledge creates a number of doubts. The question of how to communicate safety questions applies to all vaccines. Organizations could avail themselves of expertise in communication issues and the CDC and FDA should synchronize their statements when important issues come up. Since RotaShield was taken off the market for a safety issue, an estimated 400,000 American children have been hospitalized because of rotavirus, which might have been prevented by a vaccine. Two companies went to a great deal of expense to develop a safer vaccine. If there is a small excess risk, one would hope that the impact of the announcement would be much smaller than those cases not prevented by rotavirus vaccine during the interval. Dr. Schuchat added that communication needs to be speedy, nimble and flexible and that there was good communication between FDA and CDC. However, those agencies do not control the media and the headline writers are not the same people who write the articles.

Dr. Paul Offit, Children's Hospital, Philadelphia, referred to the report that over 28,000 children now have been inoculated with RotaTeq through the VSD. Looking back on the RotaShield experience, he asked if there was there a number administered to the VSD that signaled there may have been a problem. Dr. Haber recalled that there was no rapid cycle at that time, but it could be shown retrospectively, if the rapid cycle was used after a few weeks.

Dr. Parashar cautioned that though it is reassuring that there were 28,000 doses given with no cases reported, in that age group less than half a case would be expected. Going back to RotaShield, with a 30-fold risk two weeks after vaccination, it could have been picked up sooner, but if the risk elevation is substantially smaller, power to do more at this state is very limited.

Dr. Davis said he thought that if the relative risk with this current vaccine were as high as was seen with RotaShield, then it would be appearing now. The new vaccine has exceeded the number of doses administered by which an elevated relative risk was detected with RotaShield. In essence, the time period during which this would have been picked up had the relative risk been 25 or 30 has already been exceeded.

Dr. Georges Peter, Brown Medical School, noted that considerable efforts had been made over the years to educate medical writers with varying success, but headline writers had not been targeted to the same extent. Often the public just reads the headline and not the story. He then asked whether there were any data available from registries on whether or not pediatricians and family physicians are actually following the guidelines, in terms of administration of the first dose at 6 to 12 weeks and the second dose at the appropriate

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interval. Some preliminary data indicate that a significant portion of doses may be given at an older age, which is not desirable. Dr. Parashar referred to the slide with the VSD dose distribution by age to answer the second question. Dr. Schuchat responded to the comment about headline writers pointing out that inflammatory headlines help solicit reports.

Dr. Abramson closed this session by saying he sensed the ACIP was happy going forward on this issue.

THIMEROSAL: REVIEWING THE EVIDENCE
Dr. Jay Liebermann, Pediatric Infectious Disease Specialist, University of California, Irvine

Dr, Abramson introduced this session by saying that since ACIP members rotate and it has been awhile since the evidence around thimerosal and its potential side effects has been discussed, ACIP members had asked for a review.

Dr. Liebermann explained that preservatives are required by the FDA for use in multi-dose vaccines, except for certain live viral vaccines, due to episodes of bacterial contamination of biological products that occurred early in the twentieth century; for example, Staphylococcus aureus contamination that led to local infections, systemic infections, and even deaths. Thimerosal is an organic mercury-containing preservative that has been used in more than 30 U.S. licensed vaccine since the 1930s. The primary purpose is to prevent microbial growth during storage and use. It is also used in the manufacturing process for some vaccines, for example, to inactivate vaccine antigens in the whole-cell pertussis vaccine.

There are three forms of mercury. One form is an organic mercury, of which the two primary forms and ethyl and methylmercury. Ethylmercury is the form used in some vaccines. Mercuric salts are found in batteries and elemental mercury, e.g., quicksilver. Mercury is ubiquitous in the global environment; 95 percent of environmental mercury resides in soil and is released into the environment by burning fossil fuels such as coal and petroleum. It can also be released from rock erosion and volcanoes. It has been estimated that increases in power-plant emissions and industrial uses over the past century have tripled the amount of environmentally available mercury. Atmospheric mercury can be deposited on the surface of bodies of water, where elemental mercury is converted to methylmercury, usually by bacteria, and ingested by fish. The principal source of human exposure for organic mercury is fish consumption, particularly fish higher in the food chain. For an example, a can of tuna contains about 28 micrograms of methylmercury. Mercury can also be found in breast milk if the mother has concentrations in her system and in some cosmetics used by certain ethnic groups, as well as some herbal remedies and dental amalgams.

Mercury is a known neurotoxin, and the fetal brain appears to be especially susceptible to exposure to organic mercury. There have been outbreaks described with high-dose exposures. One was in Japan in an area called Minimata, where industrial pollution heavily contaminated the ocean waters with mercury. When locals ate contaminated fish, it caused many cases of mercury poisoning, deaths and infants born with severe developmental disabilities, including cerebral palsy, mental retardation, and seizures. In Iraq, there was an incident of grain

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contamination in the early seventies, causing many cases of mercury poisoning and deaths, and infants were also born during that time with severe developmental disabilities. In this case, researchers were able to document to some degree a dose-related response, higher levels being associated with more severe disability.

In the 1980s, two large cohort studies tried to correlate prenatal methylmercury exposures with neurodevelopmental outcomes. One study in the Faroe Islands was able to show an association between mercury levels in the mother's hair and cord blood and neurodevelopmental outcomes at seven years of age. This study is extremely important because the data were used to try to determine a level of mercury exposure to the fetus at which or below which one would not see effects on neurodevelopmental outcome. These were used to develop federal guidelines for safe levels of mercury exposure. A similar study was done in the Seychelles and no association was found, although the exposure to mercury was about the same. The reason for the difference is not clear. In the Seychelles, exposure is through fish, which they eat often. In the Faroe Islands, most of the mercury exposure comes from eating pilot whales, which are contaminated with other things such as PCBs. The role PCBs might be playing in the neurodevelopmental outcomes is not clear.

Thimerosal is about 50 percent ethylmercury, whereas methylmercury is the predominant form of organic mercury in the environment. Many childhood vaccines contain between 12.5 to 25 micrograms of mercury. Through the eighties, it was in flu vaccine and various diphtheria/tetanus/pertussis vaccines. In the late eighties and early nineties, as hepatitis B and Hib vaccines were added to the immunization schedule, there were now more vaccines in the childhood immunization schedule that contained thimerosal.

A goal of the 1997 FDA Modernization Act was to compile a list of drugs and foods that contained intentionally introduced mercury compounds and provide a quantitative analysis. The FDA concluded that infants who received thimerosal-containing vaccines at several visits could exceed the total mercury exposure recommended by Environmental Protection Agency guidelines. These guidelines for exposure were set to avoid toxicity to the fetus. They were based on studies of oral ingestion of methylmercury, usually through fish. It was assumed that, since digestion was going on daily over months, the half-life of methylmercury was about 50 days. The aim was to develop a no-effect level that would be safe and then put in a safety factor. For the EPA, that factor was about tenfold and they set the level at 0.1 micrograms per kilogram per day of methylmercury. FDA guidelines were a little higher because of how they analyzed the data and their safety factor, but these are not toxic levels, they are safe levels, set to minimize the chance of neurodevelopmental problems. Looking at different ages, specifically females in the first six months of life by different weights and different body percentiles, and calculating by the different standards for mercury (EPA, FDA, WHO, etc.), one can ask what an acceptable or safe level of mercury would be for that daily exposure.

These exposure limits had a number of assumptions. For vaccines, there’s an assumption that the toxicity and pharmacokinetics of ethylmercury in thimerosal and methylmercury are the same, but exactly how they relate is unknown. There's some evidence that ethylmercury is excreted faster in the stools, and some evidence in monkeys that less goes to the brain. They

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also assume that the effects of low-dose oral exposure daily are the same as a bolus IM injection and that the susceptibility of the infant to toxicity is the same as that of the fetus. There are also many assumptions when making the leap from what is happening to a developing fetus to giving an injection at two and six months of age. However the conclusion was that children receiving all possible thimerosal-containing vaccines could receive quite a bit of thimerosal compared to the EPA guidelines - 200 micrograms by six months of age. For girls, the recommended upper limit was between 65 and 106 micrograms depending on weight, and by two years, 275 micrograms.

In 1999, a joint statement by the AAP/FDA U.S. Public Health Service urged manufacturers to remove thimerosal from vaccines as soon as possible, as a precautionary measure to maintain the public's trust in immunization. There was no evidence at the time of any harm caused by the low levels in vaccines. The big uproar came from pediatricians who saw their immunization schedule potentially disrupted.

Thimerosal as a preservative was removed from most childhood vaccines by 2001 and the last lots of thimerosal preservative-containing vaccines expired in January 2003. It is still being discussed only because of ongoing litigation in both state courts and the Vaccine Injury Compensation Program. Thimerosal is still contained in some of the flu vaccines routinely given to children since 2004. There are also vaccines that contain trace, often unmeasurable, levels of thimerosal.

During the nineties, the number of persons reported to be receiving services for autistic spectrum disorders increased substantially. Rates are tenfold higher than in the 1970s; in the *MMWR*, rates ranged from 4.5 to almost 10 per thousand eight-year-olds. Newspapers have reported that one in 150 children has autism. A study published in *Nature Genetics* from the Autism Genome Project analyzed genes from more than 1100 families with at least two children with autism. There is some very promising research identifying some loci of genes on chromosomes, particularly Chromosome 11.

While researchers are getting closer to understanding where autism comes from, especially regarding the strong genetic component, they still do not know if an environmental hit is also necessary. There’s some evidence that it occurs in a susceptible host in whom something else happens. Prenatal exposures, such as Thalidomide, have been linked with autism. Interestingly, those children who developed autism had very specific birth defects, which suggested a specific time of onset. Congenital rubella, as well, had been associated with autism. To date, there's no good evidence that postnatal exposure to anything is linked with the onset of autism, but the concern about mercury in thimerosal in the vaccines remains. A paper published in *Pediatrics* several years ago looked at autism and some of the neurologic characteristics, comparing it to the known neurotoxicity of mercury. In comparing the two, they were dissimilar.

The Institute of Medicine was commissioned by the CDC and the NIH to review specific vaccine-safety topics, including vaccines and autism. In their 2001 report, they concluded that the evidence was inadequate to accept or reject a causal relationship between exposure to thimerosal from vaccines and autism, ADHD, speech and language delay. The reason was

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that there were no published epidemiologic studies examining the potential relationship between thimerosal exposure and neuro-developmental disorders. They did conclude, however, that because mercury is a known neurotoxin and because prenatal exposures to methylmercury have been documented to negatively affect early childhood development, a potential biological mechanism could at least be hypothesized and was worth investigating.

To test this hypothesis, ideally there would be a double-blind, randomized, placebo-controlled trial, randomizing children to get thimerosal-containing vaccines or not and following them for many years. However the sample size would be prohibitive and it couldn't be done from an ethical standpoint either, since the goal was already to remove thimerosal from vaccines. This leaves retrospective cohort studies, looking at a well-defined cohort, their exposures to thimerosal and gradations of exposure, and neuro-developmental outcomes. In addition, ecological studies can track changes in incidence of autism and other neuro-developmental disorders as the use of thimerosal changes.

The first published study, from Denmark, was a population-based cohort study of all children born in that country between January 1990 and December 1996, a total of almost half a million. Their health care system was able to track and compare children vaccinated with thimerosal-containing vaccines with children vaccinated with thimerosal-free vaccines, in general, the diphtheria/tetanus/pertussis vaccines as they evolved. The use of thimerosal was discontinued in 1992. They were able to identify 440 cases of autism and 787 with other autistic spectrum disorders. They found that the risk of autism and autistic spectrum disorders did not differ significantly between groups. For example, for autism, the risk ratio was 0.85, showing no link between getting vaccines containing thimerosal and the development of autism and autistic spectrum disorders. In addition, they found no evidence for a dose-response association.

The next big study was done in the U.S., using the Vaccine Safety Datalink project, which was developed as a screening study and initiated in late 1999. The study was devised to examine the association between thimerosal exposure from childhood vaccines by one, three, and seven months of age and various diagnoses, including autism, speech and language delays, tics, and ADD. This study was in two phases; the first phase at two managed-care organizations (HMOs A and B) looking at all children born between January 1992 and December 1998. The second phase was done at a third managed-care organization (HMO C). The preliminary findings showed a statistically significant dose-response association between exposure to thimerosal at three months of age and any of various neuro-developmental disorders.

These findings were discussed at a meeting in Georgia, in early June 2000. Several consultants were invited to review the findings and advise the CDC. They were ultimately presented at the June ACIP and then at the Institute of Medicine. The meeting was the focus of the articles in *Rolling Stone* and *Salon*, which suggested that something nefarious was going on because the final published report findings were different from the preliminary findings. They differed because after peer review the authors corrected errors and refined their analytic methods, adjusting for utilization of healthcare services. The major influence on when children got the vaccine was how often they went to the doctor, which would also

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influence diagnoses and behaviors. They also extended the follow-up period, so they had more diagnoses. But the fact that the final results differed from the preliminary just fueled suspicions that something was being hidden.

In the published paper, in Phase I, the cumulative thimerosal exposure at three months was associated with tics. At HMO B, the cumulative exposure at three and seven months was associated with language delays, with relatively low relative risks. In Phase II at HMO C, there were no significant associations between cumulative thimerosal exposure at one, three, or seven months and speech or language delay, ADD, or tics. Only HMO B had a sufficient number of cases of autism to perform an analysis, and even in the preliminary analysis, autism was not significantly associated with thimerosal exposure. The conclusion was that there was no evidence of a clear association between thimerosal exposure in infant vaccines and specific neuro-developmental disorders. But results among the HMOs were inconsistent, and so further investigation was recommended.

The next study was a retrospective cohort study looking at over 100,000 children born in the U.K. between 1988 and 1997, which evaluated the relationship between exposure to thimerosal via DT or DTP vaccines and neuro-developmental outcomes. There was some evidence for higher risk of tics with increasing doses at four months, but no negative associations were found between thimerosal exposure and ADD, general developmental disorders, and unspecified developmental delay.

A problem with these cohort studies is that diagnostic accuracy of outcomes such as ADD or autism is not perfect. For example, in the study just presented, 90 percent of the tics were transient. The doses of thimerosal also differ among the studies. Cohort studies are best used to quantify a risk to exposure rather than to prove its absence.

Dr. Liebermann then talked about ecological studies. In 2000 the Institute of Medicine presented data showing the amount of thimerosal in vaccines and cases of autism diagnosed in California by year of birth. The data show increases in the amount of thimerosal given to children by birth cohort and increases in the rates of diagnosis of autism, and they track fairly well. The rate of autism rose in the mid-eighties, even before an increase in thimerosal. However, anything that increased in the nineties tracks with diagnoses of autism, including use of home personal computers and cell phones. This kind of data only shows that two things were increasing at the same time. It says nothing about a possible association.

An ecological study in Denmark analyzed data from almost 1,000 children diagnosed with autism over 30 years. Thimerosal was used in childhood vaccines from the early fifties until 1992, and there was no trend for an increase in autism up through 1990. From 1991 to 2000, the incidence of autism increased, after thimerosal was discontinued from vaccines, suggesting no relationship between thimerosal and autism in Denmark.

In Sweden, a similar ecological study analyzed inpatients diagnosed between two and ten years of age with autism over a 12-year period. It looked at the average cumulative dose of thimerosal using vaccine-coverage levels. Thimerosal was eliminated by 1993, after which the data show no decline in autism, in fact, it continued to rise. From 1980 to 1996 there was

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almost a doubling in cases. Looking at all these studies, the Institute of Medicine report in 2004 said the evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism.

There have been studies showing an association: two ecological studies and three studies using passive reporting data, all by the same authors, who are the only ones who ever found a relationship between MMR vaccine and autism. Quoting the Institute of Medicine, "These studies cited have serious methodological flaws. Their analytic methods were nontransparent, making the results uninterpretable and therefore noncontributory with respect to causality." They used the VAERS database to calculate an incidence of neurodevelopmental disorders and heart disease following thimerosal-containing versus thimerosal-free DTaP vaccines. It might be possible with rare events, like intussusception or Guillain Barre, but not autism. They found an exponential distribution link between autism, speech disorders and heart arrest, and thimerosal dose. VAERS has many limitations. It's passive and there's underreporting, incomplete reporting, and, certainly, bias. It can't be used to calculate incidence and the cases weren't verified. These authors also did an ecological study with U.S. Department of Education data. They compared autism to thimerosal exposure by birth cohort and showed a linear relationship - as thimerosal in vaccines increased, autism increased. However, that does not prove causality and how they actually got their numbers is not clear.

A paper published by Sarah Parker and colleagues carefully analyzed the studies looking at autism and thimerosal exposure, emphasizing the quality of the studies. How good are the data? Are exclusion criteria defined and outcome measures precisely described? Is there a basis for the sample size? Is bias controlled? The paper concluded that while the studies that do not support a relationship are not perfect, one can understand the methodology. The studies that do support a relationship are worthless to evaluate any possible association between thimerosal and neurodevelopmental disorders.

Since the IOM report, there have been two new studies. In the U.K. a longitudinal study of more than 14,000 children determined the ages at which they got thimerosal-containing vaccines, calculated levels of mercury exposure, and compared them with development at between 6 and 91 months of age. Again, the results showed no evidence of any harmful effect of early exposure to thimerosal on neurological or psychosocial outcomes. Indeed, the unadjusted results suggested a beneficial effect of thimerosal exposure. For example, those who had thimerosal had less hyperactivity and better model development. When results were adjusted for possible confounders, eight of the nine significant associations actually showed a beneficial effect, not suggesting that thimerosal is protective, but no evidence of harm. The only negative association was poor pro-social behavior at 47 months.

The last study, published this past year from Montréal, looked at almost 30,000 children and evaluated the relationship between the development of pervasive developmental disorder and changes in vaccines, thimerosal exposure as well as MMR. The cumulative exposure to thimerosal increased and decreased over time. By 1996, it was out of the vaccines. There were a total of 182 children with pervasive developmental disorders. Looking at average thimerosal in the vaccines and diagnoses of autism by birth cohort, the same trend of increases in cases over time can be seen, even in those infants who were not exposed to

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thimerosal. This seems to be the most compelling evidence of no association. If thimerosal is responsible for autism, as it is removed from vaccines, cases of autism should decline, but that is not happening.

Data from California from 2002 to 2006, which has been submitted for publication, indicates that cases of autism in three- to five-year-olds and six- to nine-year-olds have continued to increase. There's absolutely no evidence of any decrease in cases of autism since thimerosal has been taken out of vaccines. Instead, cases have continued to climb. The science shows that in well-designed epidemiologic studies, there's no association between thimerosal exposure from vaccines and autism. The ecological studies show that autism does not go down when thimerosal is removed from childhood vaccines. Studies in tissue cultures and animals provide interesting information about toxicity, but they do not translate to what is going on in children.

Finally, Dr. Liebermann talked about unintended consequences. For example, the birth dose of hepatitis B vaccine is universally recommended to prevent against failures of screening, but hospitals discontinued the routine birth dose in 1999, after the joint statement until thimerosal-free vaccines became available. However, by 2006, vaccine-coverage rates for the birth dose were still below the 1999 levels. As a consequence, hundreds of children in the U.S.were born to hepatitis B-positive mothers and, for various reasons, not screened. The infants did not get their dose of hepatitis B vaccine and, therefore, were at risk of becoming chronic carriers of hepatitis B. Concerns about vaccine safety and the fear that the MMR vaccine caused autism caused MMR vaccination rates to fall in the U.K. with subsequent outbreaks of these vaccine-preventable diseases. Fear of thimerosal caused some high-risk children to avoid the recommended flu vaccine. So there are real consequences to every decision made.

California has passed legislation banning thimerosal-containing vaccines for children under three years and pregnant women in that state. A provision was put in for an exemption in case of emergency or vaccine shortage. In fall 2006, there was a delay in shipping some doses of flu vaccine for children three years of age and younger because one virus in the vaccine was slow growing. A group of medical organizations requested an exemption, which was granted. There are no data to show how this influenced flu vaccines in California, but flu vaccines are time-dependent and not having vaccine makes it very hard to vaccinate children. Anything that limits the availability of vaccines for children potentially puts them at risk.

In conclusion, the evidence does not support an association between thimerosal and autism. The consistency among these well-designed studies lends strength to their individual conclusions. Autism is increasing and research should be directed towards areas of more promise.

Discussion

Dr. Harry Hull asked if there were any other possible reasons why the diagnosis of autism might be increasing. For example, there was something in the popular press recently saying that autism is going up but mental retardation is going down because it's being reclassified, or

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that support programs for families with an autistic child might be reaching more children who are diagnosed with autism. Dr. Liebermann replied that part of the increase is related to changes in diagnostic criteria and accessibility to services. But among pediatricians, there's also a sense of a true increase, which is why it's important to investigate what is leading to that increase.

Dr. David Salisbury noted that the levels reported in the U.K. schedule were lower than those experienced in the U.S. However, the vaccines were given at two, three, and four months in the U.K. rather than two, four, six, in part because children are actively called in through registers. The fact that the U.K. studies showed no association is important because the ages map across quite reasonably and compliance with the recommended ages for vaccination is very tight.

VACCINE SUPPLY
Dr. Greg Wallace, MD, CDC/NCIRD

Dr. Wallace addressed three topics related to vaccine supply: influenza vaccine distribution; implementation of new vaccines and specifically how the process works; and a brief update on varicella zoster-based vaccines.

Influenza Vaccine Distribution

In the eighties, about 20 million doses of influenza vaccine were made annually, nearly all distributed each year, but by today's standards, there was relatively low use. Into the nineties, the amount of vaccine produced increased from about 30 million doses to over 85 million, but there was greater variability in the amount of vaccine produced and not distributed. This year, over 110 million doses were produced and more than 100 million have been distributed.

Recent history shows both problems and improvement over the last several years. In 1999, vaccine was distributed on time and most of what was produced was distributed. In 2000 and 2001, there were delays, which led to considerable scrambling to produce late-season vaccine. By then, demand was down and even though there were many complaints about not being able to get vaccine, much of the vaccine produced wasn't distributed. In 2002, a record number of doses was produced (95 million), but it exceeded demand, so a significant amount remained undistributed. The following year, production was closer to expected demand: 80 to 85 million doses. That vaccine was mostly distributed, but there was a report of pediatric deaths in November, causing many requests for new vaccine. Most of the late season production was never distributed because demand waned rapidly.

There was a real shortage in 2004 when a manufacturer dropped out late. In 2005, capacity for the manufacturer who dropped out was mostly restored, but production was delayed. This year, early projections were for over 100 million doses and even more if an additional vaccine was licensed. Since early December 2006, over 102 million doses have been distributed, almost 20 million more than have ever before, but there continue to be concerns over timing, equity, and supply-demand mismatches.

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A cumulative distribution curve shows the variability that occurs in October. In 2006, 2005 and 2004, the shortage year, while distribution is modest, it continues into January. The same data on a monthly cumulative curve show the vaccine mostly coming out in September with production over by October. However, the peak of distribution is usually in October, which can be awkward for planning because a week or two of delay can make a big difference.

One of the big concerns is about equitable distribution, both regionally and by provider type. Most years, there are reports that a state doesn't have any vaccine. This year there is a secured data network that manufacturers and major distributors provide data to voluntarily, which makes it possible to evaluate how vaccine is distributed by HHS region. The data on the distribution rate over time, or the number of doses per thousand, indicate very tight agreement among regions, so everybody is basically getting the same amount of vaccine no matter what the time period.

The other common concern is distribution by provider type. Data on distribution by provider type show that no matter what the time period, private providers receive 40 percent or more of the vaccine distributed. Vaccine does not get distributed to providers last. There is also survey data suggesting that around 40 percent of the public seek their flu vaccine from their private provider. For distributors, there is an initial increase in September, but it flattens out quickly. For state and local health departments, the federal government and the military, equilibrium is not reached until well past the November time period. Even though they're a relatively smaller part of the influenza vaccinators, there's clearly room for improvement here as far as equitable distribution over time.

In summary, there have been overall improvements in distribution. It's a very complex and dynamic system with multiple variables and some improvement is still needed in the public-sector distribution.

Implementation of New Vaccines [Routine Pediatric Vaccines since 2000]

Dr. Wallace described the process for the implementation of new vaccines. After FDA licenses the vaccine, ACIP votes to approve it, and a vote for a VFC resolution follows. Next CDC secures a vaccine contract and grantees can purchase vaccine through those contracts. They can use three different funding sources: the VFC funding, 317 grant funding, and state and grantee funding. Sixty-three grantees purchase vaccine directly through CDC contracts; 60 of those 63 grantees are VFC eligible (three Pacific islands are not VFC grantees).

Dr. Wallace then showed a table of new vaccines implemented since 2000, including dates of FDA approval; the ACIP approval, which would be the same day that the VFC resolution was approved; date of the CDC contract; and when the *MMWR* was published. A relatively rapid, stepwise process can be seen, which occurs with the most variability around the timing of the *MMWR* presentation.

For pneumococcal conjugate vaccine and the number of grantees who are using VFC funding, 317 funding, and state and grantee funding, there is a leveling out after six or seven months.

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There's a gap between the number of grantees using 317 funding and VFC funding and another gap between state and 317 funding. But since its inception to the present, eventually almost everybody was using 317 funding as well.

In contrast, there was a very tight progression from FDA licensure to *MMWR* publication for MCV4. For this vaccine, CDC contracts represent currently about 45 percent of the market. There are a few reasons for the relatively slower uptake and CDC being a smaller percent of the market. People were aware of the relative shortage or demand-production mismatch, so CDC contracts were prioritized based on the VFC population. As that supply eases, this may change. Initially more vaccine uptake was occurring in college freshmen, which would account for CDC being a smaller percentage. As it becomes more of a routine 11- to 12-year-old vaccine, a change will be seen.

TDaP, also an adolescent vaccine, was ready to come out of the chute right away. Public health was more excited about the TDaP because of the pertussis-outbreak responses needed. Here 317 comes up pretty quickly and there is always a gap between state and 317 funding. A common complaint is that a new vaccine cannot be implemented until the *MMWR* is published, but that clearly wasn't the case for this vaccine. For TDaP, CDC is about 50 percent of the market.

For rotavirus vaccine, the same pattern of a quick uptake and an early gap between funding sources is seen. Right now, CDC is about 65 percent of the market, which has been common in the past, where the VFC program leads implementation, particularly for an infant vaccine. For HPV vaccine there are data for only six months, but utilization of VFC has been on a rapid uptake. It's too early to know what will happen with 317, but CDC contracts already account for about half of the market.

In summary, VFC funding leads implementation of new vaccines. The extent and timing of the 317 and grantee funding gap vary varies considerably by vaccine and over time, without addressing the question of whether or not there's enough 317 vaccine to implement some of these programs. The time lines for implementation are relatively efficient, although the funding for 317 and state funding may not be adequate. In conclusion, the state funding for any of the vaccines never exceeds half of the grantees, so there's certainly a gap there.

Update on the Varicella-based Vaccine Supply

Varicella-zoster virus bulk is used to manufacture the varicella, MMRV, and zoster vaccines. Merck recently announced that they are having lower than expected yields in their bulk product and have ceased producing the bulk while they work on addressing the yield issues. They currently have a fair amount of bulk available and expect to have an adequate supply for all the vaccines, although MMRV supply may be limited in the future and may run low late in this calendar year.

As has been done for other vaccine-supply issues recently, CDC convened an ad-hoc supply group that includes ACIP, CDC, FDA, and other stakeholders to meet with the manufacturer regularly and will follow this issue closely. In the *MMWR* coming out on Friday [February

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23, 2007], the main message is that there will be no changes in the recommendation even if MMRV becomes in short supply late in the year. CDC projects there will be adequate varicella and MMR supply, and the two would be equivalent to administering one MMRV dose. Vaccine supply will continue to be monitored by the stakeholder work group and at any time, if MMRV is not available, varicella vaccine and MMR are equivalent. Updates will be provided as necessary.

Discussion

Dr. Julie Morita mentioned that the influenza vaccine distribution data were extremely helpful for showing that private providers were actually getting the bulk of vaccine and in addressing issues raised by the press.

Dr. Ciro Sumaya asked whether there really were breakups or delineations in aggregate data within states and what was the lowest level of useful data on distribution and supply. The basis for the question was to get a better sense of any variability occurring at lower levels that isn't picked up at the national and public-health levels. Dr. Wallace replied that he did not go beyond the HHS level, not only because there were a lot of data to evaluate, but breaking it down by state and by provider would be a much bigger process. The data do provide good information about the equity issues, in that there are some areas for concern that need approval. This information has been useful in discussions with manufacturers and distributors, but the main point is to allay the overall sense that Wal-Mart gets vaccine before everybody else.

Dr. Sumaya asked how shortages were defined, specifically for influenza. Dr. Wallace said he thought a shortage was actually defined by the press or by individuals who had not yet received their vaccine. Dr. Baker asked whether distribution referred to when the vaccine is shipped or when it's received. Dr. Wallace said it was when it was received, but clarified that both the manufacturers and the major distributors ship their vaccine within 24 hours of release and it gets to at least the next level within 24 to 72 hours, so shipping and receiving are essentially the same. If it is going to a middleman rather than to a private provider, that information is also captured.

Dr. Tamara Lewis, America's Health Insurance Plans, suggested that the increasing gaps were related to the ability to absorb price increases. Without an increase in immunization budgets, states are not able to absorb the cost of new vaccines and so some new ones are dropping off the state's list. So far, VFC and insurance companies have been able to keep pace, but the cost issue around new vaccines is going to become critical and there will be more gaps. Dr. Wallace responded that the same could be said for the 317 grantees, who are purchasing more different kinds of vaccine but without the same coverage. Dr Abramson commented that there would probably be discussion on vaccine financing in June and that the National Vaccine Advisory Committee had been given the task of trying to deal with those issues.

Dr. Jon Temte, American Academy of Family Physicians, asked where the mass immunizers fit into the distribution by provider type. That's the biggest concern from individual clinicians who have the perception that the large-scale retail outlets get vaccine before they do. Dr.

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Wallace was not sure what percentage they represented. He noted that in one region even the mass vaccinators go through a middleman, so they do not necessarily get their supply by this time in September.

Dr. Georges Peter, Brown Medical School, asked when the herpes zoster vaccine statement would be published and whether there were any measures of the uptake of that vaccine. Dr. Pickering said the statement was expected to be completed sometime the end of February or in March [2007]. Then it will begin the clearance process, so it would be several months before it is published in *MMWR*. Dr. Joan Benson of Merck added that there has been a significant interest in Zoster Vaccine, Live (Zostavax®) by healthcare providers.

Dr. Jeff Duchin from NACCHO acknowledged that, as 317 funds are increasingly used for vaccine, it takes away money for infrastructure for vaccine programs at state and local levels. He also noted that some states don't distribute vaccine until the official *MMWR* publication, which creates an uncomfortable time period during which the vaccine is available to those who can pay cash but not to those who receive it through VFC or 317. Finally he noted that the ACIP has recommended HPV for a target group in 11- and 12-year-olds, yet there's a very permissive recommendation for VFC women up to 18. He asked how the vaccine would be allocated with such a broad cohort. Dr. Wallace responded that the CDC contract was not restricting the use of HPV or how much can be ordered based on supply. Dr. Haupt added that there has been a remarkable uptake of the Human Papillomavirus (Types 6,11,16,18) Recombinant Vaccine (Gardasil®) since licensure and there is no supply problem for all the cohorts that have been recommended.

Phil Hosbach, sanofi pasteur, pointed out that publication of recommendations in the *MMWR* also has an impact in terms of when the health plans will actually put it on their formularies and allow it to be reimbursable. So while VFC is getting the vaccine, the private side of the same office is not getting reimbursed. He also pointed out that the total cost of vaccines needed to be put into perspective relative to the total expense of healthcare. Dr. Pickering noted that provisional ACIP recommendations are placed on the ACIP Web site shortly after clearance and there is an attempt to expedite all of the *MMWR* publications. Dr. Wallace added that TDaP may be slightly different than the other vaccines, so even if VFC got here right away, it is only about a quarter of the market.

Dr. Baker asked whether health plans recognized what is on the Web in the same way they recognize the printed publication. Dr. Lewis said the America's Health Insurance Plans were very cognizant of the NIP Web site and used it consistently. Dr. Lett added that in Massachusetts they attach the provisional recommendations and send a letter to all the health plans as soon as there's a vote and they're available on the Web site, to encourage reimbursement.

Dr. Katz, IDSA, said that a study about funding published by the Institute of Medicine several years ago showed enormous variation from state to state. Some states use all their 317 money to purchase vaccine, others use it for infrastructure, and then there's a gradation in between. Dr. Wallace added that what states report on how they're planning to use the money and how they actually spend it can vary as well, even from year to year. Dr. Dean Mason, Wyeth

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Vaccines, stated that the good news was that 32 million dollars have been appropriated for 317 fund increase this year, the result of an intense lobbying effort by a number of immunization coalitions.

Dr. Katz then asked whether flu vaccine through the CDC contract represented only a small proportion of the total flu doses purchased historically. With the recommendations for routine immunization of children and the CDC contract becoming even more important to the national framework of vaccine purchases, he wondered what the proportion of total purchases was for the CDC contract and whether was it increasing. Dr. Wallace replied that the absolute number of doses in the contract has been increasing on the magnitude of 1 or 2 million more doses a year, but it is still probably less than 10 percent of the aggregate. However, CDC is 50 percent of the market for sanofi's 0.25 cc vaccine licensed for 6- to 35-month-olds and has been consistently since the full recommendation was made.

Dr. Abramson noted the concern about financing and supply, but reminded the group that many others were trying to deal with these issues.

INFLUENZA

Update: Seasonal Influenza Epidemiology, Virologic Surveillance and Antiviral Drug Resistance

Dr. Ban Mishu Allos, ACIP Influenza Workgroup Chair
Dr. Anthony Fiore, MD, CDC/NCIRD

Dr. Allos opened the Influenza session with a summary of progress in influenza-prevention efforts made in recent years. There are now more timely population-based data and more effectiveness data based on lab-confirmed infection instead of just URI illness. Critical questions being addressed include the need for two doses of influenza vaccine in children, which was not understood five years ago.

Vaccine coverage has improved among infants and toddlers, and rates for the elderly and adults are rebounding after the shortage season of 2004/2005. Manufacturing capacity has expanded, there is increased availability of preservative-free formulations, and new formulations are in the pipeline. There's also improved flexibility for providing vaccine in innovative settings, such as schools. However, coverage rates are still too low in many groups at high risk for complications. Effectiveness and safety studies are needed yearly, especially as recommendations are expanded. Implementation is difficult; flexibility in scheduling and capacity are needed and supply delays or shortages continue. Public demand is fickle and messages are sometimes confusing in such areas as the optimal time for administering influenza vaccine.

Dr. Allos reviewed some of the milestones in recommendation changes. In 2000, ACIP voted to expand the recommendation for all adults 50 and older, moving closer to what the pediatricians have always known, that risk-based recommendations rarely are effective in getting the people at risk vaccinated. In 2004, all children between the ages of 6 and 23

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months were recommended for vaccination, as well as women who would be pregnant during the influenza season. In 2005, people with respiratory compromise or who have trouble handling their secretions were added. Then last year, ACIP voted to include children ages 24 to 59 months and their household contacts. This was paradigm shift, from vaccinating to prevent death or hospitalization to preventing visits to the emergency department and other outpatient settings.

Criteria for expanding vaccination recommendations include safety, effectiveness, morbidity and mortality, and hospitalizations. This involves looking at outpatient and emergency-department visits, and indirect effects, especially preventing illness among contacts, in addition to feasibility, cost effectiveness, and vaccine supply. Regarding expanding the recommendations to older children between the ages of 6 and 18, it is important to note that children who are household contacts of younger children, people at high risk and the elderly are already recommended for annual vaccination. If the recommendation is expanded to include children ages 5 to 18 years of age, morbidity and mortality would be reduced in the children who are themselves vaccinated. Communitywide morbidity and mortality might be reduced by indirect effects. However, it may create an expectation of immediate implementation of immunization programs for this age group, which could be difficult to meet and might exacerbate vaccine supply shortages and distribution delays. Planning for recommendation and expansion requires input from many groups: epidemiologists, immunologists, vaccine-safety experts, immunization program managers, communications experts, manufacturers, economists, education officials, funding entities, and the general public.

A possible time frame for modifying influenza vaccination recommendations is as follows: in 2007-2008, expand recommendations to include all school-age children 5 to 18 years old, address critical issues and develop roll-out plans. A summary of scientific and implementation issues surrounding this expanded recommendation could be presented at the October 2007 meeting, after which ACIP could assist manufacturers, immunization programs, and public-health communication experts in planning for actual implementation in 2008 and 2009. By 2010, recommendations could be expanded to include household contacts and caregivers of school-age children. After the appropriate surveillance studies are done and the need is assessed, ACIP might move to a universal vaccination recommendation in 2012.

Dr. Fiore presented the most up-to-date influenza surveillance data, through February 10th. First, he showed a map representing current influenza activity across the country, as estimated by state epidemiologists. Since October 1, 2006, about 92,000 specimens have been tested for influenza viruses; about 9 percent of these were positive. Among the 8300 influenza viruses, about 7,000 or 83 percent were Influenza A, and some 1400 were or 17 percent were Influenza B viruses. Twenty-eight percent of the A viruses have been sub-typed: 88 percent were H1, and 12 percent were H3 viruses. The CDC has characterized 161 of these viruses through February 10th. Of the 99 H1N1s characterized, 94 percent were similar to the New Caledonia-like virus represented in the vaccine and 6 percent had somewhat reduced titers to New Caledonia. In 2007, only seven H3N2 viruses have been characterized so far. Four are similar to the Wisconsin-like viruses represented in the vaccine, and three had reduced titers to these viruses.

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For Influenza B, 55 viruses were tested. Over the past couple of years both Influenza B lineages have been circulating; this year, 67 percent were B/Victoria. Of those, 49 percent were similar to the B/Ohio strain, which is represented in the vaccine, and 51 percent had somewhat reduced titers. The remaining 33 percent of the viruses were of the Yamagata lineage. At this point, 6.7 percent of all deaths are reported as being due to pneumonia or influenza; this is measured against a seasonal baseline, but the defined epidemic threshold has not yet been exceeded.

Laboratory-confirmed influenza-associated pediatric hospitalizations are monitored in two population-based surveillance networks. The Emerging Infections Program (EIP) data indicate hospitalization rates for young children, zero to four years old, and 5- to 17-year-olds, for this influenza season and previous seasons. Rates this season are similar to the past couple of years, but distinctly below the 2003-2004 season. Data from the New Vaccine Surveillance Network has the advantage of going back a couple of more years for comparison, but it also just has data for zero- to four-year-olds.

Surveillance for pediatric deaths began in the 2003-2004 season when it became a reportable disease. As of February 15, 2007, CDC has received 15 reports of influenza-associated pediatric deaths. Ten children were five years of age or older, three had underlying conditions that might have contributed to severity, five had no known underlying conditions, and two, as of yet, have unknown previous health status. Four children had MRSA bacteremia and nine were unvaccinated. One child was vaccinated. In 2004-2005 and 2005-2006, there were 44 and 48 deaths respectively, as compared to the first year of reporting, 2003-2004, when 153 deaths reported.

Dr. Fiore then talked about antiviral drug resistance during the 2006-2007 year, with reference to the emergence of adamantane-resistance Influenza A viruses. Last year was predominantly an H3N2 year, and two of eight H1 viruses were adamantane resistant, while 192 of 209, or 92 percent, of the H3N2 viruses were adamantane resistant. There fewer adamantane-resistant isolates so far in 2006-2007, and relatively fewer H3N2s thus far globally to characterize. For H1N1s, 5 of 199, or 3 percent, have been shown to be adamantane resistant, compared with 24 of 54, or 44 percent of the H3N2 isolates, which is roughly the same as what's being seen among U.S. isolates. Slightly lower proportions are adamantane resistant: 1 of 91, or 1 percent, for H1N1; and 3 of 10, or 33 percent, for H3N2. In contrast, resistance to the neuraminidase inhibitors, oseltamivir and zanamivir, remains rare. A large global-surveillance network published a paper last year in which, among the many thousands of the isolates tested, less than 0.5 percent were resistant to one or the other of the neuraminidase inhibitors. So far, none of the 437 isolates tested at CDC has had resistance to these two drugs.

In the October 2006 ACIP meeting, manufacturers talked about their projected capacity and ACIP asked them to provide information at this February meeting. GlaxoSmithKline estimates that in 2007-8, there will be 35 to 40 million doses of the adult vaccine available, which is 10 million more than for the current season. About one-third of these are Influenza Virus Vaccine, Trivalent, Types A and B (Fluarix®), which has trace thimerosal and will

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come from the Dresden facility. The other two-thirds are Influenza Virus Vaccine, Trivalent, Types A and B (FluLaval®), from the Canadian facility. FluLaval has thimerosal preservative and is sold in multidose vials. GSK is currently conducting studies of pediatric vaccine with trace thimerosal, and a thimerosal-free pediatric vaccine is under development.

MedImmune makes Influenza Virus Vaccine, Live, Intranasal (FluMist®), a live attenuated vaccine, also known as CAIV-T, which is a thimerosal-free presentation and administered intranasally. For 2007-8, there will be about 7 million doses of FluMist. The vaccine is currently licensed only for 5- to 49-year-olds. Licensure for a younger age group might occur before next influenza season. Capacity could ramp up to as many as 20 million doses in 2008-2009 and between 35 and 90 million doses after that.

Novartis projects 45 million doses per year over the next three to five years. They plan to shift most production to preservative-free vaccine and are expanding their influenza vaccine capacity, using cell culture-based influenza vaccines, with the possibility of limited quantities as early as 2008 and up to 50 million doses possibly available by 2012. A significant percentage of the cell-based vaccine will be preservative-free.

Sanofi pasteur provided no new information, but a statement at the last meeting read as follows: "A new enclosed facility is under construction that will double sanofi pasteur's capacity in 2008-9 and allow for production of 100 million doses of influenza vaccine. In 2007 or 2008, sanofi pasteur expects to build a new fill-and-formulation facility that would allow for an expansion over the 8 to 9 million doses of preservative-free vaccine."

In summary, taking into account that these projections are subject to change based upon strain characteristics, what strains are chosen, licensure issues, production issues, etc., there could be as many as 130 million doses available for the upcoming influenza season. Twenty million of these could be preservative-free doses, but only one manufacturer is currently licensed to supply preservative-free TIV to young children; the LAIV is a thimerosal-free option for children over the age of five right now, with pending licensure for lower ages. Over the next three to five years, taking all of the manufacturers' projections together, there could be as many as 150 to 200 million doses, and manufacturers hope they will have increased preservative-free capacity.

Dr. Fiore then discussed the current ACIP statement and changes proposed for the upcoming ACIP statement. There are four key issues for the 2007 recommendations. First, vaccine composition would be decided at the VRBPAC meeting on February 28th, after ACIP. That section of the statement will have to change if composition is changed. Second, the use of adamantanes should continue to not be recommended because of the greater than 30 percent resistance still present among H3N1 strains in the U.S. this season. Third, there's a change for children ages six months to less than nine years who received a single dose during their first year of vaccination instead of the recommended two doses: these children would receive two doses in their second year of vaccination. Finally, the age groups and the risk groups for whom routine vaccination is recommended has not changed, even though there has been some rearranging of the text and wording changes.

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To improve readability and usability, the recommendation has been reorganized, starting with a summary and followed by the core of the recommendations. A new methods section describes studies and how they were selected and used to make recommendations. Effectiveness and safety are considered separately for TIV and LAIV, and results from new studies comparing TIV versus LAIV are presented. Recommendations on how individual vaccinators and immunization programs should give the vaccine and the antiviral section at the end have been expanded.

The core of the recommendations reads as follows: *"Vaccination is recommended for any person who wishes to reduce the likelihood of becoming ill with influenza or transmitting influenza to others should they become infected, depending on vaccine availability. Healthy, non-pregnant persons ages 5 to 49 can choose to receive either trivalent, inactivated influenza vaccine or live attenuated influenza vaccine. All others should receive TIV."*

The recommendation that anyone who wishes the vaccine should be vaccinated has been there for the last couple of years, but now is highlighted. There's no preference in this year's recommendations for TIV versus LAIV. The second part of the recommendations has the groups recommended for TIV; it reads as follows:

"All persons in the following groups should receive annual influenza vaccination with TIV. Vaccination efforts should focus on delivering vaccination to these persons as well as contacts or caregivers of children less than six months old if vaccine supply is limited.

"All children aged 6 to 59 months old, all persons aged greater than 50, children and adolescents who are receiving long-term aspirin therapy; women who will be pregnant during the influenza season; adults and children with a variety of chronic conditions listed here; adults and children who have immunosuppression; adults and children who have any condition that compromises respiratory function and the handling of respiratory secretions or that can increase the risk for aspiration; and, finally, residents of nursing homes and other chronic-care facilities.

"In addition, to prevent transmission to persons such as those identified above, all persons in the following groups should receive annual influenza vaccination with TIV or LAIV unless contraindicated: First healthcare workers. Secondly, healthy household contacts (including children) and caregivers of children who are 0 to 59 months of age and adults greater than 50 years of age; and healthy household contacts (including children) and caregivers of persons with medical conditions that put them at higher risk for severe complications from influenza."

The main change is *"including children"* because it has not been well understood that child contacts are an important group. It includes older children living with younger siblings, older folks, and/or other people with the variety of different chronic conditions that can lead to severe influenza.

Dr. Fiore then drew attention to a change regarding children ages six months to less than nine years who received only one dose in their first year of being vaccinated. In the 2006

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recommendations, it was clearly stated that all children ages six months to less than nine years who were getting vaccinated for the first time should get two doses. But inevitably, some of these children only got one dose in that first season. The issue was whether these children should get two doses or one dose in their second year. In the June 2006 meeting, both published and unpublished data were presented on this topic. At that time, the ACIP work group recommended and the ACIP agreed that the data were not sufficient to determine if one or two doses should be given to these children; one dose was recommended for a variety of different reasons, including feasibility.

However in October 2006, the AAP Committee on Infectious Diseases reached a different conclusion, looking at roughly the same data. The first paper, Englund, et al., in *Pediatrics*, came to the conclusion that, when the Influenza B antigen was changed for the second season, children who had only received one dose in that first season of being vaccinated and then got one dose in the second season had a decreased immunologic response to the Influenza B antigen, compared to children who received two doses in that second season. Then a paper that looked at ILI-type outcomes, by Allison, et al., published in the *Journal of Pediatrics* late last year, concluded that, in consecutive seasons when the influenza vaccine antigens were unchanged, the effectiveness against ILI in the second season was significantly less for 6- to 21-month-old children vaccinated for the first time who received one dose at both seasons, compared to the 6- to 21-month-old children who received one dose in their first season and two doses in the second season.

Based on those papers and discussions with colleagues at AAP, looking at feasibility and vaccine supply issues, the work group concluded that ACIP should change its recommendation to harmonize with that of AAP. The new language proposed is: *"The ACIP now recommends two vaccine doses for children aged six months to less than nine years who received an influenza vaccine for the first time in the previous season but who did not receive the recommended second dose of vaccine within that first season."*

Next Dr. Fiore turned to language about thimerosal in the statement: *"No scientifically conclusive evidence has demonstrated harm from exposure to thimerosal preservative-containing vaccine. Persons recommended to receive TIV may receive any age- and risk-factor appropriate vaccine preparation depending on the availability."* Little has changed from last year, but several paragraphs review the evidence and reiterate the concern about the health impact of not vaccinating some groups, such as young children and pregnant women who are eligible for vaccination, because of concerns about thimerosal.

Another new issue is a need to better emphasize and improve vaccination coverage among healthcare workers. The statement this year is slightly reworded from last year: *"All healthcare workers as well as those in training for healthcare professions should be vaccinated against influenza annually. Facilities that employ healthcare workers should provide vaccine to workers by using approaches that maximize vaccination levels. Higher vaccination coverage levels would likely protect healthcare workers, their patients, and communities; improve prevention of influenza-associated disease and patient safety; and reduce disease burden. Influenza vaccination rates among healthcare workers should be regularly measured and reported."*

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The recommendations note the new Joint Commission on the Accreditation of Health Organization regulations that require accredited organizations to offer vaccination and measure vaccination coverage among staff. Also noted are various professional organization proposals and state health-law requirements that healthcare workers be vaccinated or provide a written statement declining vaccination. There have been a number of comments that the recommendation needs to be even stronger, so a proposal is to add: *"All healthcare workers should be offered vaccination, and those who refuse influenza vaccination for reasons other than medical contraindication should be required to provide a signed declination."* The Healthy People 2010 objective of 60 percent coverage is also noted, along with a reference to additional professional society recommendations and state regulations that require vaccination unless healthcare workers can provide written declination.

Finally, Dr. Fiore addressed language making immunization programs and vaccinators more flexible in terms of getting late-season vaccine, and getting vaccine in settings that are not traditional. The section entitled "Timing of Organized Vaccination Campaigns" reads, *"Vaccination clinics should be scheduled through December and later, if feasible, with attention to settings that serve children 6 to 59 months of age; pregnant women; and other persons aged less than 50 years at increased risk for influenza-related complications; persons aged 50 or greater; healthcare workers; and household contacts of healthy children age 24 to 59 months; and persons at high risk, including children aged 0 to 23 months to the extent feasible. Planners are encouraged to develop the capacity and flexibility to schedule at least one vaccination clinic in December."*

Some of the language is reminding individual providers when influenza seasons typically peak and emphasizing the benefit of providing vaccination throughout the season: *"Vaccine should be administered starting in late September and October and should continue through January and beyond because influenza activity typically peaks in February or March in the majority of seasons. Healthcare providers should be alert to potential vaccination opportunities during all healthcare encounters, including diagnostic or minor surgical procedures, as influenza season approaches. And whenever influenza vaccine is available, office staff should advocate or offer vaccination whenever patients contact medical-care facilities, including during requests for services such as prescription refills or appointment requests."*

Dr. Fiore repeated the recommendation against the use of amantadine drugs, which says, *"Amantadine and rimantadine should not be used for the treatment or prevention of influenza in the United States until evidence of susceptibility to these antiviral medications has been reestablished among circulating Influenza A virus subtypes."*

Discussion

Dr. Baker hoped the media would pick up the message that providers should continue to vaccinate into December and January and noted that the language about the peak of the season should be in both statements, not just in the providers' statement. Dr. Harry Hull said that since ACIP is now recommending two doses for children, the statement should be clear that

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that second dose should be given even late into the influenza season because influenza viruses may be circulating until April or May and children need to have that benefit of the timing effect of two doses. Dr. Julie Morita said that as an AAP member and ACIP member, she welcomed the harmonization in the revaccination recommendation for children less than nine years of age because it makes it easier to educate providers.

Mr. Rob Beck asked if the two-dose program for part of the target audience would change projections of the available supply of vaccines. Dr. Fiore replied that it is hard to know how many children just received one dose when they should have gotten the two doses. NIS data should help clarify that concern.

Dr. Baker asked whether existing registries included influenza vaccination, because that would be a way of getting that data: one versus two doses. Dr. Fiore pointed out that a December 2006 *MMWR* publication looked at the six sentinel registries. Coverage ranged from 6 percent to 50 percent among the six registries.

Dr. Duchin asked what the recommendation would be for a child under nine years of age who received one dose in the first season, didn't receive a dose or received one dose in the second season and is now coming in the third season, still under age nine. Dr. Fiore replied that such a situation had not been specifically addressed. Presumably this applies only to the second season of eligibility for vaccinations, so the recommendation would probably be just one dose in subsequent seasons.

Ms. Stinchfield was interested in the timing of the school-age group. If ACIP recommends the vaccine for this fall, after clinics, hospitals, and health departments have already ordered, implementation could be difficult. Dr. Bocchini mentioned that the statement this year seemed to limit the two doses to just the second year after the child received one dose in the initial year. Dr. Abramson clarified that the two doses are only a one-time occurrence, so if a child got two doses in the second year, in the third year, it would go back to one.

Dr. Morse was concerned that if the projection for 130 million dose capacity in 2007-2008 is solid and ACIP does not change the recommendations, there could be a lot of extra vaccine for the coming year.

Dr. Schaffner asked whether there was any truth to the rumor that VRBPAC might be considering adding a fourth antigen next year. Dr. Baylor responded that the issue of adding a second B strain comes up every year at the influenza VRBPAC. There will be discussions this time, but no vote.

Dr. Schaffner then informed the group that the National Foundation for Infectious Diseases has launched an educational activity to make sure adults and children with diabetes get vaccinated against influenza. Last November, the NFID held a roundtable with representatives from more than 15 medical and public-health organizations and all agreed that improving immunization rates in this group is an important goal. The NFID is developing a comprehensive monograph to provide further details on specific strategies and models. It's available on the NFID Web site. Comments and suggestions are welcomed.

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Dr. Kristin Nichol, as chair of the National Coalition for Adult Immunization Advisory Committee, seconded the importance of enhancing influenza vaccine delivery to people with diabetes. Current immunization rates in this high risk group lag substantially below the national 2010 health goals.

Dr. Wallace, CDC, doubted whether 130 millions doses would be made this year. Regarding the [vaccination of the 6-to-59 age group] last year, he did not believe there would be more vaccine available for those 0 to 18 years of age than there is currently this year. Dr. Margaret Rennels, GSK, said that the 130 million doses was a goal, not a promise. It is not known what strains will be chosen, what the yield will be, or if a plant may become contaminated or a fill line may go down. Dr. Marie Mazur said that CSL Biotherapies hoped to have its influenza vaccine in the market this year. Most of its production is thimerosal free, and there is also a thimerosal-free indication.

Dr. Kathleen Coelingh from MedImmune asked whether the recommendation about timing of influenza vaccines was meant to be a prohibition on administering vaccine whenever it becomes available.

Dr. Jon Temte, American Academy of Family Physicians, asked whether there was a cut off point after which CMS will not cover administration of influenza vaccine in a given year.

PUBLIC COMMENT

Diane McGowan introduced herself as a board member of Families Fighting Flu, a nonprofit, volunteer-based organization made up of families and healthcare practitioners who have experienced first-hand the death of a child due to the flu or have had a child experience severe complications from the flu. She told the story of how her family had lost their healthy 15-year-old son to influenza two years ago. She noted that there have been at least 15 pediatric deaths from influenza this season, some of whom were older, healthy, school-age children not within the current recommendation. She urged the ACIP to expand the current recommendation to include the new age group, so that more lives would be saved.

Mr. Scott Lassiter said he believed that CDC and the pharmaceutical companies are ignoring data that indicate concerns and dangers regarding thimerosal, even though their goals are laudable. He quoted an expert epidemiologist who questioned the design and conclusions of studies presented at this meeting. He then recounted his son's experience with mercury poisoning, urging the ACIP to consider removal of thimerosal from all vaccines.

Ms. Lyn Redwood disagreed that there is no scientifically conclusive evidence that demonstrates harm from exposure to thimerosal-preserved vaccines. She mentioned over 20 peer-reviewed toxicological studies published in highly credible journals since 1999, which document harmful effects of thimerosal in animals, primates, and humans at vaccine levels exposure. These articles were dismissed by today's presenter as not being informative. However, Ms. Redwood argued that the discussion should not be about whether thimerosal causes autism, but is it appropriate to inject a known neurotoxin at levels in excess of federal

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safety guidelines into pregnant women, infants, and children? There is the capability to produce thimerosal-free vaccines and she urged the committee to reconsider its recommendation.

Mr. Gary Stein told the committee about the loss of his daughter five years earlier from complications of influenza. She was not vaccinated, as are millions of children and adults in the U.S. today. He urged the committee to help other families by recommending universal influenza vaccination. As a founding member of Families Fighting Flu, he applauded the decision to expand the pediatric recommendation last year up to 59 months and urged the committee to pass a universal pediatric, if not total universal, influenza vaccination recommendation.

Ms. Karen Beauvais told the committee about her son, who received over 277 times more than the EPA's allowable amount of mercury in his infant vaccines and then plunged into regressive autism. After three years of receiving chelation therapy, he still tested very toxic to mercury. Arguing that thimerosal was a poison that should not be ingested by a pregnant woman or an infant, Ms. Beauvais implored the committee to change its policy before more families are impacted by autism.

Dr. Deborah Wexler, representing 122 organizations, urged ACIP to immediately recommend universal childhood and school-aged children vaccination against influenza. This is needed to simplify the current targeted recommendation, sustain and build manufacturing capacity, and provide benefits to individuals by reducing morbidity and mortality, providing herd-immunity protection, and enhancing vaccine access for all who wish to be vaccinated. She read a statement in support of universal vaccination for all school-aged children and teens through the age of 18.

LCDR Stephen Kay related the experience of his two children who were recovering from mercury poisoning. He read a statement from the family’s developmental pediatrician, Dr. Nathanson-Lippitt, which outlined her findings on the effects of heavy metal build-up in children, many of whom develop symptoms of autism. Lt. Cmdr Kay stated that he was not anti-vaccine, but pro safe vaccines, and urged the committee to remove both thimerosal and aluminum from vaccines.

Dr. William Redwood, a front-line healthcare provider in a large emergency department, stated that in 19 years as a practicing physician he had never diagnosed anyone with sepsis or respiratory failure secondary to influenza. He felt the more important issue was proactively educating the public on common-sense ways to prevent transmission of a range of communicable diseases spread by direct contact. He added that he was seeing increasing skepticism toward ACIP, not only around influenza, but also other vaccine-related diseases, such as hepatitis B at birth. He felt parents were becoming increasingly skeptical about what they perceive as offering up their children for vaccine testing, giving rotavirus vaccine and intussusception as an example. He urged the committee to step back and regain the public's trust, and make reasonable recommendations for vaccine based on sound evidence.

Dr. Rick Zimmerman expressed concern about the low rates of healthcare worker vaccination

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coverage. He had reached the conclusion that declination would create an enormous administrative burden and suggested that hospitals use EMTs or nurses to take the vaccine to the floors or provide incentives, such as a lottery for paid time off.

Vote

Dr. Abramson asked if the committee wanted to pull out any of the recommendations for a separate vote, while Dr. Fiore reviewed all the recommendations on the slides.

Dr. Hull said he thought the American Academy of Pediatrics had said that the two doses in the second year only applied to the second year of life. Dr. Joe Bocchini responded that since there was less opportunity for exposure to natural infection and the highest risk would be in the second year, the emphasis would be to provide two doses in the second year. Subsequent to that, there would be increased opportunity to be exposed to influenza naturally and perhaps less need for more than one dose. Dr. Hull said that since there were only data on the second year and in the spirit of being harmonized with the American Academy of Pediatrics, the recommendation for two doses should be restricted.

Ms. Stinchfield pointed out that the sentence that reads "*Vaccination is recommended for any person who wishes to reduce the likelihood of becoming ill with influenza or transmitting influenza to others should they become infected, depending on vaccine availability,"* essentially reads universal influenza vaccination. She suggested that a compromise might be to recommend it for any person, including school-aged children, so they are highlighted.

Dr. Susan Lett thought clarifying language about the third season would be helpful for clinicians. It can say there are no data, but people are going to ask the question.

Dr. Treanor felt there was no real reason to specify that vaccination should not begin until late September if the vaccine is available earlier. In addition, if making people sign a declination form is a waste of administrative time, then it should not be recommended. The more important question is whether declinations are actually an effective strategy for increasing vaccination rates. Dr. Abramson replied that in his experience they do increase rates and make people think about protecting themselves and their patients as well. Dr. Kathy Neuzil was in favor of including declinations as just one of a number of approaches that might maximize vaccination levels, rather than focusing on just one.

Dr. Plotkin noted that the first part of the second paragraph emphasizes TIV and then underlines that contacts or caregivers of children less than six months of age should be vaccinated. It seems to be excluding live attenuated vaccine for caregivers or contacts of children under six months of age but in fact there isn’t any such exclusion. The recommendation should be rephrased.

Dr. Abramson asked for further comments and when there were none, he asked those who had arrived late to declare whether they had conflicts of interest.

Dr. Dale Morse: no conflict.

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Dr. Kathy Neuzil: no conflict.
Dr. John Treanor stated that he had a conflict.
Dr. Ciro Sumaya; no conflict.

Dr. Abramson noted that the VFC vote would take place after the break. He then asked for a motion for adoption, which would include the minor suggestions that will be edited in later.

Dr. Allos moved that the committee accept the recommendation.
Ms. Stinchfield seconded the motion.
Dr. Sumaya: In favor.
Ms. Stinchfield: In favor.
Dr. Neuzil: In favor.
Dr. Morse: In favor.
Dr. Morita: In favor.
Dr. Leiu: yes.
Dr. Hull: yes.
Dr. Gilsdorf: yes.
Mr. Beck: yes.
Dr. Baker: conflict.
Dr. Allos: yes.
Dr. Abramson: yes.

The motion passed.

VFC Resolution on Influenza Vaccine Recommendations
Dr. Angela Calugar, CDC/NCIRD

Dr. Calugar presented the updated Vaccine For Children program (VFC) resolution related to influenza vaccines. The purpose of this resolution is to revise the previous resolution from February 2006 to recommend that children who received only one dose in the first year at vaccination should receive two doses in their second year at vaccination.

There were no changes on the first page besides the purpose. On the second page, under Recommended Influenza Vaccine Schedule, the wording closely matches Dr. Fiore's initial recommendations, and this text will be updated to match it exactly with the final recommendation which ACIP voted on: *"All children ages six months to less than nine years who receive influenza vaccine for the first time should be given two doses. Children who receive only one dose in the first year of vaccination should receive two doses in their second year of vaccination."* There were no other changes to the VFC resolution.

Discussion and Vote

Dr. Jeff Duchin, representing NACCHO, asked whether VFC could provide vaccine to any child or parent who wished their child to be vaccinated in addition to the target groups, since the new recommendation and the old suggest that anyone who wishes to avoid influenza

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should be vaccinated. He felt it would be difficult to carry out that recommendation if VFC restricts access to only those in the target groups. Dr. Calugar explained that this statement was in the previous resolution voted on February 2006. It implies that, if there is enough supply, all children aged 6 months to 18 years are eligible to receive influenza vaccine. Dr. Duchin asked whether that would be taken into consideration when VFC vaccine is allocated. Dr. Wallace responded that vaccine allocations are allocated based on available supply. VFC resolutions do not make vaccine.

Dr. Hull asked whether the committee could vote before the changes in language were made. Dr. Wallace replied that the committee had the updated version, which reflected the new ACIP recommendation: *"All children aged six months to less than nine years who receive influenza vaccine for the first time should be given two doses. Children who receive only one dose in the first year of vaccination should receive two doses in the second year of vaccination."*

Dr. Allos moved that the committee accept the language on the slide and adopt the VFC recommendation. The voting proceeded as follows:

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

The motion passed.

Interagency Pandemic Influenza Vaccine Prioritization Workgroup Update
Dr. Ben Schwartz, National Vaccine Program Office (NVPO)

Dr. Schwartz began his presentation by explaining that it was necessary to prioritize pandemic influenza vaccination because everybody is assumed to be susceptible to a pandemic virus, but the U.S.-based production capacity currently is not sufficient to make vaccine rapidly for the entire population and the earliest doses of pandemic vaccine currently are projected to become available about 20 weeks after identification of the pandemic virus. He illustrated the large gap between the current U.S. based capacity to produce influenza vaccine for a pandemic and what is projected as the national need, representing the entire U.S. population. Assuming that two doses will be required per person at 90 micrograms per dose, the pandemic

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will spread much more rapidly than the amount of vaccine produced in an entire year.

A number of government initiatives have been implemented, with over $1 billion going to increase vaccine production capacity, develop and license new pandemic vaccine production technologies, particularly cell-culture-derived vaccine, and evaluate adjuvanted vaccine formulations. Some results presented recently on the potential effectiveness of candidate H5N1 vaccine formulations suggest that adjuvanted vaccine formulations may allow the use of vaccine with more than 90 micrograms per dose.

John Treanor's study suggests that 90 micrograms of unadjuvanted sanofi vaccine produced in the U.S. yielded a protective antibody response in 54 percent of vaccine recipients after two doses. By contrast, studies done with other vaccines suggest that, at lower antigen doses, similar or higher immune response can be achieved, although different assays and study population were used. The results reported in a press release by GSK have not yet been published in a peer-reviewed journal. These studies suggest that, as production capacity increases, it may be possible to stretch the number of doses made by using an adjuvanted formulation, thereby decreasing the amount of antigen needed in each dose.

In the spring and summer of 2005, the ACIP and NVAC jointly evaluated the potential priority groups for pandemic vaccination, taking into consideration vaccine supply and efficacy, the impacts of pandemic disease by age and risk group, potential impact on critical infrastructure and on healthcare, and the ethical basis for pandemic vaccine prioritization. Recommendations adopted unanimously by both of these advisory committees are included in the 2005 HHS Pandemic Plan and provide guidance for state and local planning.

Many of the same groups recommended for annual vaccination are included in the highest priority tier for pandemic vaccination, including healthcare providers, high-risk groups, household contacts of young infants, immunocompromised people, and pregnant women. In fact, it is not until over 100 million people have received vaccine that critical infrastructure outside of healthcare is recommended for prioritization.

The committees considered the goal of mitigating adverse health outcomes in a pandemic as being above mitigating societal and economic impacts. The pandemic severity assumptions used were based on a 20 to 30 percent attack rate and a case fatality rate of up to 1 percent. The committees also emphasized the certain benefit associated with vaccinating high-risk individuals versus the unclear benefit of vaccinating people in critical infrastructure sectors. Absenteeism due to illness or caring for family members at the peak of a community outbreak was estimated at 10 to 15 percent and the committee recognized the data suggesting a much greater mortality risk among vulnerable persons than others in the general population.

Since the recommendations were made a year and a half ago, there have been a number of reasons why they should now be reconsidered. A set of public engagement meetings coordinated by CDC at the end of 2005 identified preserving essential services as the most important goal for the public and stakeholders who participated in these meetings; protecting those at high risk of severe influenza disease rated second. National planning assumptions now assume a more severe pandemic, based on extrapolation from 1918, with a 2 percent case

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fatality rate, and assumptions on absenteeism are up to 40 percent, based on additional absenteeism if schools are closed and people need to care for their children or are reluctant to go out or to work. Pandemic response strategies have evolved, such as the community-mitigation guidance that CDC put out earlier this year, and there has been additional analysis of critical infrastructures.

The priority groups for pandemic vaccination are being reconsidered by a working group made up of several federal agencies. The process involves presentations on key issues by key stakeholders from public health and from Homeland Security, consideration of ACIP and NVAC recommendations and National Infrastructure Advisory Council (NIAC) recommendations on critical infrastructure, results of public engagement and stakeholder meetings, a decision-analysis process, and written comments in response to a request for information.

The NIAC analysis of critical infrastructure for a U.S. pandemic looked at functions of critical infrastructure in key resource sectors, which included maintaining national and homeland security, ensuring economic survival, and maintaining health and welfare. The committee considered the interdependencies among sectors and the work force needed to retain the most critical functions and activities. The process included surveys of operators within these various sectors, a review of existing data and plans, and interviews with subject-matter experts. The results of the NIAC analysis are available on the Department of Homeland Security Web site. Overall, NIAC identified critical workers in three tiers with almost 17 million workers. The largest group is healthcare followed by emergency services and information technology. Employees who are most essential to providing the most critical functions in each of these sectors numbered 12.4 million, three-quarters of those in healthcare and emergency services sectors.

To summarize, as a proportion of the entire critical infrastructure work force of 85 million people, the top tier represents only about 14½ percent and all three tiers only about 20 percent of the work force. When expressed as a proportion of the entire U.S. population, the first tier is about 4 percent of that population and all three tiers about 5½ percent. Excluding healthcare and emergency services, the proportions are relatively small. When ACIP and NVAC considered critical infrastructure, estimates were 9 million individuals in healthcare and emergency services and about 9 million people in the other sectors, so NIAC's estimates are actually more parsimonious.

Recent public-engagement and stakeholder meetings have provided important input regarding prioritization. Participants in Las Cruces, New Mexico included over 100 persons of culturally diverse backgrounds, a large portion of whom were Spanish-speaking. A second public-engagement meeting in Nassau County, on Long Island, New York, had 130 people, many of whom were older individuals. In fact, from both public-engagement meetings together, 31 percent of the population was 65 years of age or greater. The stakeholder meeting in Washington, D.C., included representatives of about 90 different government and community organizations and critical infrastructure sectors.

A severe 1918-like pandemic was assumed, but there was no assumption of increased

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mortality among young, healthy individuals, as occurred during 1918. Uncertain vaccine timing and supply was assumed, and vaccination was considered in the context of other pandemic-response measures, including border strategies to delay the pandemic, community mitigation strategies to decrease impact, antiviral treatment and prophylaxis, as well as planning by government and businesses.

The 10 potential goals for a pandemic vaccination program basically include occupational function and occupational risk, as well as the potential risk among various groups of the general public. Participants were asked to rate the goals on a seven-point scale. The highest rated goal was to protect people working to fight the pandemic and provide care for those with pandemic illness, followed by those who provide essential community services, then children and those who are most vulnerable to infection due to their jobs. Interestingly, people who are most likely to get sick or die did not rate as highly in any of the meetings.

To summarize, the highest rated goals were the same in all of the meetings. The values underlying those goals included the importance of maintaining critical societal functions; protecting those who would help others during the pandemic; and protecting children, who represent the future. The key message seems to be the importance of balancing and simultaneously considering multiple purposes for pandemic vaccination.

The working group has drafted prioritization guidance. Once it becomes available, one to two months are anticipated to get comments from additional public and stakeholder meetings; from a Web-based, public-engagement process; written comments; as well as ACIP and NVAC input. The guidance should be finalized before the June ACIP meeting. The working group also will be considering pre-pandemic vaccine prioritization and the approach to modifying guidance at the time of a pandemic once the severity and epidemiology of disease is known.

Discussion

Dr. Baker asked where a woman who is 34 weeks pregnant would fall in these groupings. If children are being valued, then the death of the mother would be a severe threat to the baby. Dr. Schwartz replied that was important to balance the needs of national and homeland security, critical infrastructure, pandemic response, and the needs of vulnerable populations.

Dr. Allos commented that the only other time vaccine recommendations were taken away from the ACIP and given to other federal agencies was with smallpox. She then noted that it is tricky to assign priorities because it appears to assign value to different people's lives. In addition, she worried that saying vaccine should be given to transportation workers could become enormously complicated, for example, proving someone is a truck driver and deciding which truck drivers to vaccinate. Finally, she asked about estimates as to how long the absenteeism might be as high as 20 or 40 percent and what the preparations were for such a contingency. Dr. Schwartz replied that high absenteeism would probably be only a couple of weeks out of an 8- to 12-week outbreak. The community-mitigation guidance suggests closing schools for 12 weeks, so that already means 10 percent of the work force is likely to be absent for that three-month period. Regarding giving this guidance to other federal

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agencies, Dr. Schwartz explained that many different sectors have a stake in pandemic influenza vaccination and prioritization, especially critical infrastructure sectors such as Homeland Security or the Department of Defense. A working group representing the various departments increases involvement and buy-in to the results of the process. ACIP will be asked for comments and endorsement of the final guidance.

Dr. Plotkin suggested that the ACIP might consider a recommendation to immunize the population with an H5N1 vaccine now. There are data indicating that the current strains would make good vaccines even if there is more mutation of the H5N1. A recommendation from ACIP would stimulate manufacturers to make a vaccine and consider putting a fourth strain into the vaccine.

Dr. Rennels asked what was meant by pre-pandemic vaccine prioritization -- is it prioritization before the pandemic, or stockpiling or vaccinating before the pandemic? Dr. Schwartz replied that it refers to the vaccine made before a pandemic against strains with pandemic potential, and so it would include stockpiled H5N1 vaccine, for instance. He said the working group would be providing guidance on prioritization of this vaccine, but not be making recommendations for a particular strategy for when or how it's used. Dr. Baylor added that there would be a discussion at the next VRBPAC about the licensure of an H5N1 vaccine. As part of that, VRBPAC would discuss prime boosting as well as cross-protection and other strategies for immunization against a potential strain.

Dr. Zimmerman expressed concern that there may not be enough vaccine for the large numbers of people within the prioritized groups, particularly in the first few weeks or few months, and that vaccine might just go to the most advantaged, the best informed, and the richest. He noted that in a time of polio-vaccine shortage, Britain used a lottery.

Dr. Foster asked how long the vaccine will last in storage and whether there was possibility of using it up before it expires in storage. Dr. Baylor said the FDA was looking at stability, date, and duration of protection. Dr. Gellin further clarified that the majority of stockpiled vaccine remains in bulk, so that the required dose could be formulated at the time it is needed. New science would potentially allow it to be formulated through an adjuvant, even if there has been a loss of “potency” over time.

Review of Safety Data on Influenza Virus Vaccine, Live, Intranasal (FluMist®)
Dr. Robert Walker, Vice President, Clinical Development, MedImmune

Dr. Abramson reminded the committee that efficacy data had been presented in October and that the *New England Journal of Medicine* had a report about the cold-adapted influenza vaccine and its efficacy and safety. There is an application before the FDA to expand its use down to one year of age and ACIP may vote on recommendations in June.

Dr. Walker presented a comprehensive safety summary for children within the proposed indication, as well as relevant data for children outside the proposed indication, to assist the members of the committee in developing recommendations for FluMist. The AV019 or Kaiser study was a placebo-controlled trial, conducted in over 9,000 children, 1 to 17 years of age.

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In pre-specified safety analyses, a signal for asthma/reactive airways disease, a coded diagnostic term in the HMO database, was initially found in children 18 to 35 months of age within 42 days of vaccination, where the rates were 2.2 percent in FluMist and 0.45 in placebo. In post-hoc analyses conducted to better understand the signal, an increased risk through 59 months of age could not be ruled out. For children 12 to 59 months of age, the rates were 0.69 in FluMist and 0.20 placebo.

The medical visits for asthma/RAD were not temporally clustered within the 42-day period. There were no hospitalizations, and most of the visits were associated with standard medication use. There was no increased risk in children five years of age and older. In fact, rates of asthma/RAD were significantly decreased in some analyses of older children who received FluMist versus placebo. A limitation to the Kaiser study was that it was not prospectively designed to specifically assess the risk of asthma. Nonetheless, based on the observations from this study, MedImmune decided not to seek initial approval for FluMist in children under five, pending additional study.

Soon after the initial approval of FluMist, MedImmune undertook the CP111 pivotal study to evaluate safety and comparative efficacy in children under five. CP111 was a randomized, double-blind, multinational study that used an active control of injectable influenza vaccine, or TIV. It enrolled 8,475 children who were 6 to 59 months of age. All children, including those with underlying medical conditions, were eligible to participate except those with recent wheezing, severe asthma, or immune compromise. The primary endpoint was the relative efficacy of FluMist versus TIV against culture-confirmed modified CDC influenza-like illness, or CDC ILI. For the purposes of the protocol, modified CDC ILI was defined as fever plus either cough, sore throat, or runny nose and nasal congestion.

Since an important safety objective was to further investigate the asthma/wheezing signal identified in the Kaiser study, CP111 used a prospectively defined safety endpoint termed "medically significant wheezing" or MSW. This endpoint required a medical diagnosis of wheezing associated with other respiratory findings or with initiation of bronchodilator therapy.

All children received their first vaccinations by the end of October. With the onset of influenza circulation more than two months later, the proportion of children with influenza was statistically significantly reduced in the FluMist group compared to the TIV group. Overall, for the season, there were 338 cases in TIV and 153 cases in FluMist, representing a 55 percent reduction in influenza cases caused by any matched or mismatched strain in FluMist compared to TIV.

For the standard safety comparisons, rates of serious adverse events were similar in the two treatment groups and rates of reactogenicity events were as expected. FluMist recipients had more runny and stuffy noses, and TIV recipients had more injection-site reactions. For the pre-specified safety endpoint of medically significant wheezing, there was no increased risk observed in FluMist recipients among those children two years of age and older. A statistically significant increase was seen, however, in children under two years of age in the two-dose group within 42 days after Dose 1, where the incident rates were 3.2 in FluMist and

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2.0 in TIV. This increase after Dose 1 in children under two years of age occurred primarily among children ages 6 to 11 months.

In terms of severity of MSW, the proportion of children under 24 months of age with MSW who had tachypnea, dyspnea, retractions, or hypoxemia within 42 days after Dose 1 was similar: 27 percent for FluMist, 26 percent for TIV. Twelve children were hospitalized with MSW within 42 days after a dose: 0.5 percent of all FluMist recipients and 0.2 percent of all TIV recipients in this age group. No child was treated in an ICU or received mechanical ventilation, and there were no deaths because of MSW. Children in the two treatment groups who were hospitalized with MSW appeared to have comparable illness severity based on the length of hospital stay, discharge diagnoses, and treatment received in the hospital.

Recurrences of MSW were also examined. Children with at least one additional MSW episode or with two or more episodes were balanced between the two treatment groups. Thus there was no evidence that children with MSW post vaccination with FluMist were predisposed to subsequent episodes of MSW compared to children who wheezed post vaccination with TIV over the approximately seven months of follow up on the study.

After completing the planned analysis of the study data, a post-hoc risk-benefit analysis was conducted. The objective was to evaluate both safety and efficacy endpoints over the same time interval, extending from first vaccination through 180 days after the last vaccination. Endpoints included protection from influenza, that is, culture-confirmed, modified CDC ILI, as well as medically significant wheezing and all-cause hospitalization. The risk-benefit endpoints were analyzed by grouping according to whether they had a prior history of wheezing or asthma. Base prior-history information was obtained at the time of screening and was based on responses by the parent and medical staff to two questions: Does the subject have a past medical history of wheeze? Has a diagnosis of asthma ever been made?

The results of the risk and benefit analysis for FluMist versus TIV for the 6500 children in the study without a prior history of wheezing or asthma were reported. In the youngest age subset, children 6 to 11 months of age, a statistically significant benefit was seen for flu prevention. Twenty-nine fewer cases of influenza resulted for every 1,000 children vaccinated with FluMist versus TIV. This benefit, however, was offset by risk of MSW -- 19 more cases per 1,000, though not statistically significant -- and by risk of all-cause hospitalization: 34 more cases per 1,000, which was statistically significant. Based on the increase in hospitalizations for this age group, MedImmune is not seeking an indication in children under 12 months of age. Further study in this age group is needed to determine whether FluMist caused these hospitalizations, most of which were common pediatric diagnoses occurring over 42 days post vaccination.

In each of the four older age subsets, a statistically significant benefit for flu prevention was seen, despite the fact that the study was powered to demonstrate statistical significance only across the entire population of 6 to 59 months. In contrast to what was observed for the youngest children, the trends for MSW and all-cause hospitalizations were generally in the direction of benefit although this was not statistically significant. Only in the 12- to 23-month subset was there evidence of some low risk of MSW. Four cases per 1,000 were observed,

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which is in contrast to the benefits seen in terms of reduction in influenza, 35 fewer cases per 1,000, and reductions in hospitalizations, 8 per 1,000 in children treated with FluMist vs. TIV.

For the group of children 12 to 59 months of age without a history of wheezing or asthma, the overall risk-benefit profile for FluMist appeared highly favorable. Based on these findings, this is the population for which MedImmune is seeking an expanded indication for FluMist.

The risk-benefit for the remaining 1700 children in the study who had a prior history of wheezing or asthma was also assessed. Despite smaller numbers in this group, the benefit for influenza prevention was statistically significant for children in the 12- to 23- and 24- to 35-month subsets. For children with a history of wheezing or asthma, non-statistically significant trends towards increased MSW and increased hospitalizations were seen for all but the 48- to 59-month subset. Although this risk profile was not associated with statistical significance and so is different from hospitalizations in children 6 to 11 months of age, these trends suggest a need for caution. Therefore, until further studies are available, MedImmune is not seeking an indication in children under 59 months of age with a history of wheezing or asthma.

CP111 was designed as a pivotal efficacy and safety trial, and the number of children evaluated was quite large. However, CP111 was one of 13 studies in young children included in the safety summary provided to the FDA in support of the proposed expanded indication. These 13 trials provided safety information on more than 30,000 children 6 to 59 months of age. Nine were placebo-controlled studies and accounted for more than half of the children whose data were summarized. Three studies were TIV controlled, and CP111 contributed most of the children in this category of studies. One study was uncontrolled. In a safety summary provided to the FDA, these trials provide data about rates of serious adverse events. Nearly all SAEs were hospitalizations. The analyses of these studies included all children regardless of history of wheezing or asthma.

In the nine placebo-controlled trials, rates of serious adverse events through 180 days after last vaccination were assessed for the 12,000 children 12 to 59 months of age. SAEs included wheezing, pneumonia, and gastroenteritis, which were selected because of the findings from CP111 regarding medically significant wheezing and hospitalizations where lower respiratory tract and gastrointestinal infections were the most common diagnoses. Across the nine placebo-controlled trials, rates of SAEs were nearly the same for FluMist recipients as for placebo recipients for all four categories of SAEs analyzed.

In children 6 through 11 months of age, rates of SAEs were higher than in the older children, but rates in FluMist recipients were generally lower than those in children in the placebo group. For pneumonia SAEs, rates were comparable for FluMist and placebo, thus the observation from CP111 regarding hospitalizations in FluMist recipients compared to TIV recipients in this age group was not seen in the combined SAE analyses of the placebo-controlled trials.

Finally, there are data from a recently published head-to-head comparative study of FluMist and TIV in asthmatic subjects 6 to 17 years of age. While children with asthma are currently

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excluded from the label, these are the only data from a large comparative trial that directly address safety of FluMist in children with chronic underlying lung disease. Asthma exacerbations in this study, assessed within 42 days after vaccination, occurred at similar rates in TIV and FluMist recipients. This was true when looking at all exacerbations as well as specific categories of exacerbations, including hospitalizations, unscheduled clinic visits, and increased asthma medication use. Thus there was no evidence from the study that receiving FluMist resulted in worsening asthma control compared to TIV over the six weeks following vaccination.

In conclusion, in the CP111 study, FluMist demonstrated superior efficacy against both matched and mismatched influenza strains compared to TIV. Although not discussed in today's presentation, high efficacy for FluMist has also been demonstrated in six large placebo-controlled trials. The safety of FluMist for children less than 12 months of age and in the children less than 59 months of age with a history of wheezing or asthma needs further study. In children 12 to 59 months without a history of wheeze or asthma, FluMist appears to have a highly favorable risk-benefit profile. Approximately 80 percent of the children between 12 and 59 months in CP111 fit this description. Review of placebo-controlled trials supports the safety of FluMist in children 12 to 59 months. Data to support the proposed indication in children 12 to 59 months without a history of wheeze or asthma are currently under regulatory review.

Discussion

Dr. Abramson asked how the children with history of wheezing or asthma had been chosen. He wondered if any had developed a history of wheezing in between the first and second dose and if so, of those who were hospitalized, how many were actually hospitalized for wheezing versus other non-related reasons? Dr. Walker responded that overall the rate of hospitalization for MSW was very low, 0.5 and 0.2 percent. Chart reviews revealed that half of the children had a prior history of wheezing and half did not. However, the majority of children hospitalized in this study were hospitalized with common pediatric problems, mostly gastroenteritis, oftentimes rotavirus gastroenteritis and lower respiratory tract and upper respiratory tract infections.

Dr. Neuzil asked whether the population included in the CP111 study was all vaccine naïve, or could they have had prior vaccination? Dr. Walker replied that they stratified based on whether or not the children had been previously vaccinated or not. About 20 percent had been previously vaccinated and 80 percent of those were in the two-dose group. Dr. Neuzil asked whether this made any difference in the analysis of the medically significant wheezing. In other words, since the first dose is the concern, did having had a prior vaccination mitigate the wheezing? Dr. Walker responded that the data seemed to indicate it was an age-related phenomenon and not prior vaccination, and that it was related to a history of asthma or wheezing, regardless of whether they were in the one-dose group or the two-dose group. Dr. Neuzil noted that the youngest children would have had fewer opportunities to receive a dose of vaccine and then asked about the large time interval of 180 days. If broken up in smaller time intervals, was any effect closer to the vaccine seen? Dr. Walker replied that the hospitalizations were mostly late-occurring events, beyond 42 days; 180 days was chosen as a

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way of standardizing and representing most of the influenza surveillance period that was assessed. Most of the hospitalizations were really the late-occurring events. Dr. Neuzil went back to the question of how well past history can be identified in a population beforehand. It appeared that parents were asked about recent wheezing or severe asthma, but then the charts were used for the post-hoc analysis. Dr. Walker replied that what was used was a composite of both what the parent provided and what the medical team provided.

Dr. John Iskander reminded the committee that post-licensure safety data jointly published by CDC and FDA in *JAMA* a little over a year ago indicated that, among episodes of wheezing reported in post-licensure safety surveillance, the primary risk factor was prior history of wheezing. He also wondered about the reliability of using either history or chart review to identify a prior history of wheezing illness, given that alternate, nonstandard terms like bronchitis are sometimes used to hide or obfuscate diagnoses such as asthma. Dr. Treanor added that this also raised the question of whether those who analyzed the charts could determine whether or not the subject had actually developed MSW during the trial.

Dr. Treanor asked whether the Wyeth trials involved children this young. Dr. Walker replied that most of the placebo-controlled trial data reviewed came from some of the Wyeth studies involving children typically 6 to 35 months of age. Dr. Treanor noted that Wyeth also did comparative trials with TIV and those studies did not show an increase in wheezing. Dr. Walker added that one of those studies was the TIV/FluMist comparative study in 6- to 17-year-old asthmatics. Another study, similar in design but in younger children with a history of recurrent respiratory tract infections, also showed superior efficacy and no increase in post-vaccination wheezing. Dr. Treanor wondered if the variability between studies appearing to show an association with wheezing and other studies not showing an association could potentially reflect strain-to-strain differences in the reassortants from year to year. Dr. Walker replied that the two studies, AV019 and CP111, were conducted in different populations of children, in different years, so they did have different vaccine strains.

Dr. Morse asked whether, using a composite history of wheezing from the parents or the doctor, it was possible to determine which was more important for the association. Dr. Walker replied that they were additive and that the best ability to isolate the risk was based on information from both the parent and the physician rather than one or the other.

Dr. Abramson reminded ACIP members that they would be asked to make a recommendation for a vaccine that has better efficacy, but has increased risk for wheezing and hospitalization in those with a history of wheezing. He asked if there were any questions now for which answers could be brought to the June meeting.

Dr. Jon Temte, American Academy of Family Physicians, wondered if any of the analysis was done looking at children for whom the definition of wheezing or asthma was based on past use of medication for wheezing or asthma, and whether that was broken out as a definition. Dr. Walker replied that the information related to wheezing collected from the Kaiser study included medication use. However, on CP111, a yes or no response from parents was adequate to differentiate children with and without the risk.

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Dr. Treanor wondered how severe the MSW really was and whether the children who developed it after the first dose received the second dose anyway. Dr. Walker replied that about 40 percent of children who wheezed after the first dose went on to receive the second dose. Most did not wheeze with the second dose.

Dr. Abramson asked if anyone in the public wanted to speak. There was no response, so the meeting was adjourned at approximately 5:09 p.m.

Friday, February 22, 2007

UNFINISHED BUSINESS

The second day began with finalizing the hepatitis A post-exposure recommendations, carried over from the previous day. Dr. Bell went over the revised wording for this draft recommendation. The current ACIP recommendation for post-exposure prophylaxis says to use IG as soon as possible after exposure. Vaccine, if also recommended, can be given at the same time. The current wording further states that the results of a clinical trial comparing vaccine and IG are needed to determine if vaccine alone can be used.

Dr. Bell recalled that the previous day there was discussion about current recommendations for pre-exposure use of hepatitis A vaccine, which include all children ages 12 to 23 months; catch-up vaccination of older children in areas with existing programs, with some permissive language for other parts of the country; persons at increased risk, including travelers, people with chronic liver disease because of the risk of more severe consequences, and men who have sex with men and illicit drug users.

The randomized clinical non-inferiority trial conducted in Kazakhstan found that hepatitis A vaccine efficacy was similar to that of IG, that is, the non-inferiority 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 is assumed, the point estimate of vaccine efficacy was 80 percent with the upper bound of 64 percent. The proportion of outcomes among vaccine recipients was slightly higher than among IG recipients, although not statistically so. Putting this in context, the risk of hepatitis A among vaccine recipients was never more than 1.5 percent greater than among IG recipients. The study provided evidence, consistent with many previous studies in IG recipients, that IG might attenuate clinical illness when given after exposure.

Dr. Bell enumerated a number of reasons why one might want to be able to use hepatitis A vaccine post exposure. It offers a number of advantages over IG and provides the flexibility to use the vaccine in some circumstances post exposure where it might be quite beneficial. But not all populations were studied in the post-exposure clinical trial, most importantly, people over 40 years old and people with medical conditions. This trial took a number of years to complete. The number of index cases of hepatitis A recruited is now equivalent to about a third of all U.S. hepatitis A cases reported in a year. It won't be possible to answer the

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remaining questions about populations not studied in this clinical trial because no further data are expected with respect to use of vaccine alone post exposure.

The proposed wording for patients with chronic liver disease and immunocompromised persons indicates a preference for IG. This is predicated on the fact that these populations are known to have a poorer response to vaccine pre-exposure. Also, chronic liver disease patients appear to have more severe outcomes and a higher risk of death following hepatitis A.

For persons older than 40 years or not considered “healthy”, the draft wording simply states that there are no data. The rationale behind this proposed wording is that there's little information in the pre-exposure literature one way or the other and little information on which to base a preference for IG.

Another issue was what can be learned from those countries that have been using vaccine for three to six years. Vaccine is essentially all that is used in Canada and IG is very difficult to get there. Dr. Naus polled people around the country and received one report of what appeared to be a chain of transmission in a couple of child day care centers and a household in late 2003/early 2004, where there might have been some breakthrough infections. In the U.K., most people are thought to be using IG and vaccine - some are using mostly vaccine, and some are using IG. She had no information with respect to the performance of vaccine. They have only 700 or 800 hepatitis A cases a year and so they would not be in a position to ascertain breakthrough infections with any regularity.

A group called the Viral Hepatitis Prevention Board provides information about viral hepatitis in Europe. Their survey indicated that three countries in Western Europe use vaccine alone, while most other countries are using both vaccine and IG. They were not aware of any particular concern one way or the other about the use of vaccine in a post-exposure setting.

Dr. Bell went over the rewritten wording:

"Unvaccinated persons who recently have been exposed to HAV should receive a single dose of vaccine at the age-appropriate dose for pre-exposure use or IG as soon as possible. The efficacy of IG or vaccine, when administered more than two weeks after exposure, has not been established. For people who receive vaccine, the second dose should be administered according to the licensed schedule to complete the series.

IG should be used for children less than 12 months old, for immunocompromised persons, for persons who have been diagnosed with chronic liver disease, and for 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. The post-exposure efficacy of hepatitis A vaccine in persons less than two years or greater than 40 years and persons with medical conditions has not been studied."

Discussion

Dr. Allos wondered if the sentence that begins "*Efficacy of IG or vaccine has not been*

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established," might be misinterpreted to mean that vaccination might not be effective, period, not just for post-exposure prophylaxis. Dr. Bell said this sentence was lifted directly from the current statement with the addition of "*or vaccine*." She agreed that adding "*vaccine*" might now have introduced some point of confusion and agreed to do some further editing.

Dr. Treanor asked about confidence that the current system in place would effectively detect failures of this strategy and whether it was working as well as desired. Dr. Bell replied that hepatitis A is a reportable condition in all jurisdictions in the country, so all the health departments collect this information. There is now also enhanced surveillance in six or seven jurisdictions, so it's likely that such an assessment could be made.

Dr. Neuzil pointed out another potential source of confusion - the statement that vaccine in persons younger than two has not been studied. The most common group will be children 12 to 23 months of age because that's where vaccine is routinely recommended, and yet some of them may not have received it yet when they've been exposed. She recommended that there be a line in the recommendation specifically for that group, saying children 12 to 23 months of age should receive the recommended hepatitis A vaccine. In addition, Dr. Neuzil felt the group should decide whether to say "*also immunoglobulin*" or not, with a special decision for the 12-to-23 month age group because they're targeted for universal vaccination, but they fall in between the two age groups in the recommendation.

Dr. Bell said the trial in Italy, which did not have IG as a comparison group but did use vaccine at the licensed pre-exposure dosage, went down to age one. She did not know how many children aged one to two there were in that trial. However, the sentence is not exactly correct if one includes the results from the earlier Italian trial. That could make a difference, or the committee might prefer an additional, explicit sentence about children 12 to 23 months.

Dr. Abramson thought just saying that *"the post-exposure efficacy of hepatitis A in persons greater than 40, and persons with medical conditions has not been studied"* covers the essence. Further details can go into the text. He asked if the committee wanted to have "*less than two*" in there, since it was already not recommending it to children less than one. Dr. Neuzil preferred to either take out *"less than two*" or add another sentence because, otherwise, there are two different age groups in the same paragraph and Dr. Abramson agreed.

Dr. Susan Lett said she thought that the previous day the group had suggested that immunocompromised people and perhaps older people with liver disease should get IG and vaccine, but this was not reflected in the new wording. Dr. Bell responded that immunocompromised people don't respond as well to the vaccine, but there's no recommendation explicitly for pre-exposure vaccination of all immunocompromised people. They don't necessarily have worse hepatitis A outcomes, so the recommended groups for pre-exposure prophylaxis include chronic liver disease patients but not all immunocompromised people.

Dr. Morse said he was uncomfortable with the last sentence because of questions about people less than age two and greater than 40. He felt it would be useful to see more of the Canadian data, then either remove the "*two*" or say *"immunoglobulin can be used for children less than*

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two". As for people over age 40, he noted that the U.K. recommends using immunoglobulin for people age 50 and above, and thought it would be useful to see the data they used to substantiate that recommendation. He noted that the average of age of participants who got either vaccine or immunoglobulin in Kazakhstan was around 12. He wondered how many study participants were actually over age 20 or 30, in order to give any useful information. Also, there were higher ALTs, a measure of liver function, in the vaccine recipients than those that received immunoglobulin. The U.S. has a much older population that's not immune, and this might create problems.

Dr. Baylor was uncomfortable with the definitiveness of some of the wording. Instead of saying "*unvaccinated persons who recently have been exposed to HAV should receive a single dose of hepatitis A vaccine or IG,"* he preferred "*should receive IG"* and then, "*based on the limited data can receive hepatitis A vaccine.*" Such flexibility is more acceptable since the data do not support that indication for the label. The recommendation is using IG, but hepatitis A vaccine may be used based on the limited data.

Dr. Greg Wallace reminded the group that if this was an affirmative vote, there would be a VFC vote, so it was important to sort out the language before the vote. He suggested using the following wording regarding efficacy: *"The efficacy for post-exposure prophylaxis of IG or vaccine, et cetera."* That qualifier makes it clear that the committee is talking about vaccine efficacy for post-prophylaxis.

Dr. Ciro Sumaya worried that by having the sentence that says: "*Persons administered IG, for whom hepatitis A vaccine is also recommended, should receive a dose of vaccine simultaneously with IG."* in the second paragraph, it could be misinterpreted. He suggested putting that sentence in a separate paragraph, disengaging it from the sentence that precedes it now.

Dr. Hull commented that the recommendation should explicitly state that people who have gotten one dose of hepatitis A should be vaccinated with a second dose.

Dr. Treanor asked for clarification on what the committee was actually recommending: A) "Vaccine and IG are completely equivalent and you can give whatever you want, depending on what's better for you"; B) "IG is what you should probably give most of the time, but if it's not around or, for some reason, you'd rather give vaccine, that's okay"; or C) "We really think you should mostly use vaccine, but you could use IG if you want to." Dr. Abramson agreed that further editing for clarification was needed and asked the committee members if they were ready to vote or if they wanted to see more data first.

Dr. Lieu said there would probably not be more data between now and June, but that more clarification was still needed as to whether the committee is saying that vaccine and IG are equivalent, or that there's a preference for one or the other. Dr. Abramson asked whether the committee needed more data before making a decision. Dr. Allos reiterated that there would be no more data, perhaps for years, and that the data presented the previous day would be published in a peer-reviewed journal.

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Dr. Morse felt it might be worth re-examining the currently available data to see how many study participants were over age 20 and 30, and whether the numbers were large enough to reach any conclusions. There might be age-related details in the U.K. and Canadian data.

Dr. Gilsdorf said that what was missing was an analysis by the working group about which of the three options Dr. Treanor mentioned was preferred. It would help to have the pros and cons of each one presented very clearly. The consensus was to put off the vote until June.

DIPHTHERIA AND TETANUS TOXOIDS AND ACELLULAR PERTUSSIS ADSORBED, INACTIVATED POLIOVIRUS AND HAEMOPHILUS INFLUENZAE b CONJUGATE (TETANUS TOXOID CONJUGATE) VACCINE COMBINED (PENTACEL®)
Dr. Patricia Joyce, National Center for Immunization and Respiratory Diseases

Pentacel, a combination vaccine being developed by sanofi pasteur, is a five-component vaccine, comprising DTaP-IPV-Hib. It has been used in Canada exclusively since 1997 in their childhood vaccination schedule. Pentacel is almost identical to Diphtheria, Tetanus, Five Component Acellular Pertussis, Inactivated Poliovirus and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed) (Pediacel®), which has been used in Europe. Pentacel and Pediacel differ in the force of the polio component. In Pentacel, the poliovirus is grown in human diploid cells, whereas in Pediacel, it is grown in vero cells. Sanofi pasteur has submitted a Biological License Application to the FDA for use of Pentacel as a four-dose, primary series in children at 2, 4, 6, and 15 to 18 months.

Dr. Joyce showed a slide demonstrating the components of various DTaP vaccines. Pentacel is based on the sanofi pasteur product Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (Daptacel®), combined with PRP-T and poliovirus vaccines. However, in Pentacel, the pertussis components are slightly different from those in Daptacel. Pentacel contains twice the amount of pertussis toxin and four times the amount of FHA. The diphtheria component is equivalent to that contained in Daptacel. The Hib component is identical to ActHIB. The tetanus component is similar to Daptacel plus an additional amount, conjugated to PRP. Pentacel is administered intramuscularly in a 0.5 ml volume. Liquid DTaP-IPV, also known as Quadracel vaccine, is used as a diluent for lyophilized ActHIB. Pentacel is thimerosal-free.

Pentacel was contrasted to other DTaP combination vaccines, such as Combination Acellular DTP and Hib Conjugate Vaccine (TriHIBit®), which is licensed only for the fourth dose of the DTaP and Hib series, and Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Hepatitis B (recombinant) and Inactivated Poliovirus Vaccine Combined (Pediarix®), which was licensed by the FDA in 2002 and recommended by the ACIP in February 2003. Pediarix is licensed for three doses only at 2, 4 and 6 months, and is not approved for booster doses.

If Pentacel receives FDA approval for the requested schedule of 2, 4, 6, and 15 to 18 months, the vaccine would fit into the childhood immunization schedule as follows: Pentacel doses given at 2 and 4 months would provide doses one and two of the primary series for DTaP,

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poliovirus, and Haemophilus B. The third dose, given at 6 months, would provide the third dose of the series. A dose given at 15 to 18 months will provide the fourth dose of DTaP and Hib and an extra, or fourth dose, of IPV.

If the FDA licenses Pentacel for use in the United States, the vaccine will be presented for consideration by the ACIP. In preparation for that review, the following measures are proposed to examine pertinent issues related to Pentacel and other combination vaccines: form an ACIP combination vaccine working group; review data on immunogenicity and safety; and consider the need to update the combination vaccine statement in the *MMWR*.

Dr. Susan Lett asked Dr. Joyce to describe the antigens in the DTaP vaccines and the lyophilized part of the vaccine. Dr. Joyce responded that the vaccine, as it is being manufactured in Canada, consists of two vials, one of which is a 0.5 amount of liquid DTaP-IPV. This is equivalent to Quadracel, which is not licensed in the US. Liquid DTaP-IPV is drawn from one vial and mixed with lyophilized Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), (ActHIB®) in a second vial, then drawn back into a syringe, ready to inject. Pentacel has no hepatitis B component, whereas the combination vaccine Pediarix does.

IMMUNIZATION SAFETY OFFICE STUDY AND SURVEILLANCE UPDATES
Dr. Robert Davis, CDC/ISO

Dr. Davis's first presentation was an update on Guillain Barré Syndrome (GBS) among recipients of meningococcal conjugate vaccine (MCV4; trade name Menactra), covering the period from October 2006 to January of 2007. He presented data from the Vaccine Adverse Event Reporting System (VAERS) and from the Vaccine Safety Datalink (VSD), showing the observed compared to the expected rate calculations and age and season-stratified analyses, followed by a discussion on limitations of the data.

GBS is a rapidly evolving polyradiculoneuropathy that generally manifests as a symmetric motor paralysis. This was reported on previously in the *MMWR*, where cases of GBS following receipt of MCV4 were reviewed. In October 2005, five cases were originally reported to VAERS. In April 2006, there were three additional cases reported to VAERS and published in the *MMWR* and in October 2006, nine additional cases of GBS were reported.

Dr. Davis discussed two new cases through January of 2007, making a total of 19 cases that have occurred less than 6 weeks after MCV4 receipt as reported to VAERS. Four confirmed cases of GBS have also been reported in 13- to 19-year-olds, but those have an onset interval greater than 6 weeks following receipt of vaccination so were not included in discussion or analysis. Of the 19 cases of GBS following administration of MCV4 with an onset interval of 2 to 33 days, 17 occurred in children 11 to 19 years old. Information from managed-care organizations within the VSD indicates that approximately 94 percent of MCV4 recipients were 11- to 19-years old.

Dr. Davis then presented information on the number of GBS reports to VAERS within 6 weeks of MCV4 administration by age at onset. There was one case among 11-year-olds, two

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cases among 15-year-olds, two cases among 16-year-olds, three cases among 17-year-olds, seven cases among 18-year-olds, and two cases among 19-year-olds.

The VSD Rapid Cycle Project from April 2006 through January 2007 indicates that 156,542 doses of MCV4 have been administered and no cases of GBS have been observed among those recipients who were 11 to 19 years old. The expected number of cases was zero to one, based on the background incidence rate of GBS in this population.

In the VAERS Observed, 1.78 cases per million person-months have been observed. HCUP data show 1.57 expected cases per million person-months and VSD data show 1.59 expected cases per million person-months. If these data represent the true magnitude of increased risk after vaccination with MCV4, then there are 0.89 excess cases per million person-months, and there are 17 observed cases and 10.8 expected cases divided by 6.93 million doses, or close to one excess case per million doses of MCV4 administered.

Among 11- to 14-year-olds in the VSD, the rate ratio is 0.25, with confidence intervals ranging from 0.1 to 0.2. Among 15- to 19-year-olds, the rate ratio is 2.48, with confidence intervals from 1.30 to 4.55. So the risk for GBS after MCV4 is, in fact, greater among 15- to 19-year-olds compared to 11- to 14-year-olds. One reason for this difference might be that 15- to 19-year-olds routinely receive their vaccinations at the end of the summer in preparation for school, while the 11- to 14-year-olds receive them throughout the year. In addition, there are frequently circulating infections associated with risk for GBS. Even though this has been controlled for this season, there may be residual confounding due to seasonality in this data.

In summary, for 11- to 19-year-olds, there is no statistically significant evidence of an increased risk of GBS after MCV4 vaccination, although there appears to be a small increased risk for GBS after MCV4 vaccination in the 15-to-19 age category.

The inherent limitations of VAERS require that these findings be viewed with caution. Substantial uncertainty exists regarding the risk estimate using either the HCUP or VSD background incidence rate. However, the timing of neurologic symptoms within 1 to 5 weeks shown in previous presentations remains of concern. The completeness of GBS reporting to VAERS is unknown. Under-reporting of GBS after MCV4 vaccination would raise the risk estimates. However, there has been no surge in GBS reports to VAERS after any of the three prior *MMWR* publications, and this would be expected if underreporting were marked. Also, the VSD has limited ability to detect rare adverse events, so not finding any GBS in that population of 156,000 vaccinees does not offer substantial reassurance regarding MCV4 safety in terms of risk for GBS.

Harvard Pilgrim has begun a larger study to provide a more definitive assessment. Data regarding the risk for GBS following MCV4 is expected in approximately 2 years. This study period is necessary to accumulate the required number of cases to attain sufficient statistical power to answer this question. In addition, an ongoing evaluation of GBS following MCV4 vaccination is being performed using the VSD Rapid Cycle Project.

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Dr. Davis proceeded to present an update of the ongoing thimerosal-autism case-control study. High doses of methylmercury exposure cause a range of neurologic impairments. Low-dose methylmercury exposure can also lead to more subtle neuro-developmental deficits, as shown by Grandjean et al., 1998. Thimerosal contains approximately 49 percent ethylmercury. The previous ACIP recommended immunization schedule could have led to mercury exposure exceeding the EPA safety limits for methylmercury exposure. Since 2001, all U.S. licensed vaccines recommended for children 6 years of age and younger have been manufactured in thimerosal preservative-free formulations with the exception of some formulations of inactivated flu vaccine.

Ecologic studies have found that autism rates have continued to increase even after thimerosal has been removed from vaccines, as shown by Madsen (2003), Stehr-Green (2003), and Fombonne (2006) in three different countries. The Autism Cohort Study by Hviid in 2003, with a population-based cohort of almost half a million children, showed no association between thimerosal and risk for autism. Verstraeten (2003), in a larger observational cohort study within the VSD, found no statistically significant association at any time in the analyses between thimerosal exposure and risk for autism.

In 2004, the IOM published a statement that the evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism, and that many of the epidemiologic research recommendations of the committee's 2001 report on thimerosal and a range of neurological developmental disorders are either under way or have been completed. Thus available resources should be focused on causes of and treatments of autism.

In terms of the protocol development for the current case-control study, Abt Associates successfully competed for a contract competition in 2002. Input was provided by CDC staff, principal investigators from the VSD participating managed-care organizations, and a panel of independent, external expert consultants. The final analysis plan was approved by each of these external expert consultants. The primary research question was whether there was an association between the diagnosis of autistic disorder and the level of mercury exposure from vaccines and immunoglobulins. The study follows a 3-to-1 matched case-control design. Mothers are recruited from three managed-care organizations within the VSD. Children's age is 5 to 11 years, with birthdates ranging from January 1994 to December 1999. All children received vaccines during the period when thimerosal-containing vaccines were used frequently and, hence, became a relevant study population from which to draw the case-control population.

A parent interview is being administered to both cases and controls and allows collection of extensive data on confounders such as family demographics, medical history, and other relevant data. A Social Communication Questionnaire is being administered only to controls as a screening tool. SCQ-positive control children are then excluded from the study and replaced with normal controls. The mercury exposure periods being examined include prenatal mercury exposure, mercury exposure at birth through 28 days of life, and mercury exposure at one through seven months of life. There will also be joint analyses combining these exposure periods in various manners. Clinical case assessment is being done through clinical interviews with the mother; the Autism Diagnostic Interview-Revised, otherwise

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known as the ADI-R; and an interview designed to measure if the child is having regressive autism. The clinical assessment of case children is being done with the Autism Diagnostic Observational Schedule (ADOS). Measures of cognition include the Raven's Colored Progressives Matrices test and the Mullins Scales of Early Learning.

Regarding power calculations for autism spectrum disorder, a sample of 320 autistic spectrum disorder children and 960 matched controls will be obtained. For prenatal exposure, this will provide 80 percent power to detect an odds ratio of 1.8 for every 12.5 micrograms increase in mercury received by the children. For the birth to 28 days exposure, this will provide 80 percent power to detect an odds ratio of 1.9 per 12.5 micrograms increase. And for the birth to seven months' exposure, this will provide 80 percent power to detect an odds ratio of 1.1 per 12.5 micrograms increase. Currently there are a total of 233 children with confirmed autistic spectrum disorder. The target is an additional 27 children with autistic disorder and an additional 60 children with autistic spectrum disorder. Complete data collection is anticipated by July of 2007.

Discussion

Ms. Stinchfield stated that she was looking forward to the day when all vaccines are thimerosal-free and wondered if some of the influenza vaccine manufacturers could comment on that possibility. Phil Hosbach, sanofi pasteur, replied that they currently do have an unpreserved formulation of influenza vaccine, in a pediatric dosage form of 0.25 ml as well as a 0.5 ml formulation. Current capacity is about 8 to 10 million doses, depending on demand. They have never entirely sold out of the 0.25 ml dosage, including this year, but plan on expanding their fill-and-finish capability to continue to increase the availability of that product. Their new facility will expand influenza vaccine capacity to about 100 million doses. By then, around 2009, they will probably be able to transfer everything to unpreserved vaccine. Dr. Michael Decker, sanofi pasteur, further explained that the limitation is not the ability to remove thimerosal. Unpreserved vaccine must be packaged in single-dose containers and no one in the industry had the manufacturing capacity for the single-dose containers when the thimerosal issue arose. It takes half a decade or more to bring the new manufacturing facilities on line.

Dr. Rennels said that GSK is working toward bringing thimerosal-free vaccines to the market, both from the Canadian and the Dresden production plants; however, this will not be in time for the next influenza season. Dr. Marie Mazur reported that CSL Biotherapies was working hard to be in the [U.S.] market this fall. The Australian company had removed thimerosal in 2003 and most of their capacity has been converted to making a thimerosal-free product for the U.S. adult population. They are building additional capacity for 20 million doses of thimerosal-free product by 2010.

Mr. Beck asked about the current availability of thimerosal-free vaccine dosages today as a substitute for receiving a thimerosal-containing vaccine. Mr. Hosbach replied that his company was able to manufacture and sell sufficient quantities. The issue was whether the doctors are stocking them. They have not yet sold out of thimersal-free vaccine. Dr. Baker agreed that whether or not a child gets thimerosol-free vaccine often depends on whether the

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site has it or not.

Dr. Sam Katz asked whether the children in the study were being evaluated clinically only, or were their serum specimens or other specimens being obtained for eventual genomic analysis or other testing. Dr. Davis replied that they were not obtaining biologic specimens from either cases or controls. However, if someone were to submit a proposal to do, for example, a gene-interaction analysis, they would be willing to contact patients and see if they would be amenable to providing swab smears for future analysis.

Dr. Jane Quinn said that GSK had recently announced the FDA approval of formulation changes that remove residual thimerosal from their hepatitis B-containing vaccines, which include Hepatitis B Vaccine (Recombinant), (Engerix-B®), Pediarix, and Hepatitis A Inactivated and Hepatitis B (Recomninant) Vaccine (Twinrix®). These products will be in inventory with new NDC codes over the course of this year.

Dr. Bill Schaffner asked whether the fact that the study was not obtaining any biological specimens implies that they are also not measuring mercury in its various forms in both the cases and the controls. In addition he asked for clarification of the role of the Social Communication Questionnaire in the study design. Dr. Davis replied that with the change in birthdates, it was felt that trying to obtain current mercury levels in biologic specimens of either the mother or the child would actually add more “noise” for the amount of data that could be utilized in the study design. In addition, they were concerned about the possibility of having more trouble obtaining the required number of study participants if they had to donate blood or other specimens. Regarding the SCQ, this is a way to screen a general population for evidence of communication disorders that have been linked to an increased risk of being diagnosed as autistic spectrum disorder.

Dr. Paul Offit, Children's Hospital of Philadelphia, wondered whether the study results would be available for the omnibus autism proceedings scheduled to be heard in mid June of this year. Dr. Davis felt this was highly unlikely. If data collection is completed in July of 2007, data analysis would take anywhere from 12 and 18 months, and writing, clearance, submission to a journal, acceptance, and publication would probably take another 6 to 12 months. Study authors would not want to release the data before peer review. However, the thimerosal and the neurodevelopmental study has been completed, written, gone through clearance, and is being submitted to a peer-reviewed journal. Autism is not part of that study. It looks at neuro-developmental outcomes among population-normal children with varying rates of exposure to thimerosal in these same time periods.

Next, Dr. Iskander presented safety updates on two recently licensed, adolescent and adult acellular pertussis vaccines, in addition to safety data on the newly licensed herpes zoster vaccine. Data sources included VAERS, VSD, and an evaluation of the use of TDaP during mass vaccination of healthcare personnel in an outbreak setting. VAERS, a spontaneous reporting system for vaccine adverse events, is well suited for preliminary safety evaluation of new vaccines. It is subject to well-defined limitations common to other passive surveillance systems. VAERS has recently upgraded its adverse event coding system to conform with international standards. The VSD network serves as the primary U.S. safety system for

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testing vaccine-safety hypotheses that emerge from VAERS or other sources. Rapid Cycle Analysis allows timely surveillance of new vaccines, but the network's size may limit rare event detection and study - specifically, events with an incidence of 1 in 10,000 vaccinees or rarer.

Through the end of January 2007, VAERS had received a total of 1,379 domestic adverse event reports for licensed TDaP products. Two-thirds of reports involved females and just under half involved adolescents 11 to 18 years of age. Eighty percent of the reports involved the sanofi pasteur product Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed (Adacel®). This, most likely, reflects differences in market distribution between that product and the GlaxoSmithKline product product Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed (Boostrix®).

Approximately two-thirds of reports have involved adverse events with onset within 24 hours of vaccination. Just over half have been reported by healthcare providers. Nearly 90 percent had recovered from the event at the time of the report. Consistent with pre-licensure data, most are systemic complaints, such as fever, pain, and headache, along with injection-site reactions. Five percent of reports met regulatory criteria for seriousness. Most of these involved hospitalization. The regulatory definition does not require any determination of causal relationship to vaccination. The breakdown between the two licensed products, among serious events, is similar to the overall adverse event breakdown. Two of the three reported deaths involved adults who died from complications of underlying cardiac disease. The third case, which has been presented to the ACIP previously, involved an adolescent male who died of a previously undiagnosed cardiac arrhythmia two weeks following vaccination.

Among eight reports of Guillain Barré Syndrome following TDaP, half occurred at very brief intervals following vaccination and half involved at least one co-administered vaccine. All reported case-patients are in various stages of recovery. A variety of vaccine mix-ups involving TDaP have been reported. Other vaccines involved have included pediatric DTaP as well as Pediarix. Among these reports, no serious clinical outcomes were reported.

Additional safety data on TDaP was collected following a suspected pertussis outbreak in which healthcare providers at a major medical center were offered the vaccine. More than 4500 were vaccinated. Vaccinees were surveyed for solicited and unsolicited adverse events as well as medically attended events after two weeks. Serious adverse events, as defined in federal regulations and in VAERS, were monitored for a two-month period. The overall survey response rate approached 60 percent. Respondents did not differ demographically from the group of vaccinees as a whole. Rates of solicited local and systemic adverse events ranged between 7 and 18 percent. Rates of solicited adverse events did not differ significantly between persons who had received Td or TT in the previous two years compared to longer intervals from a prior vaccination.

In summary, most adverse events reported following TDaP were non-serious and had a close temporal relationship to vaccination. Deaths were not consistent with a causal relationship to vaccine, and GBS reports were not clustered by plausible onset interval or single vaccine exposure. Among healthcare providers receiving the vaccine who were actively followed up,

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there was no increased risk of local or systemic reactions compared to pre-licensure data, even among those vaccinated more recently with Td or TT vaccines.

Next, Dr. Iskander reviewed emerging safety data regarding zoster vaccine. The total number of VAERS reports received through mid January, along with the net dose distribution through January, was shown. The number of serious adverse events reported to date is less than ten, and no post-vaccination deaths have been reported. The median age of persons involved in VAERS reports for zoster vaccine is 65, with a 3-to-1 female-to-male ratio. The median symptom onset interval following vaccination is one day.

The most commonly reported adverse events were injection site reactions. Rashes are both zosteriform and nonzosteriform types and systemic reactions included pruritus and fever. Rashes described as being zoster and nonzoster-like did not differ in terms of onset interval or patient demographics. VAERS does not routinely receive photos of rashes involved in adverse events, so these are based on textual symptoms descriptions contained in the regional reports. Medical errors involving zoster vaccine have occurred among both adults and children. Vaccines involved in the mix-up have included varicella vaccine and Measles, Mumps, Rubella and Varicella Live Vaccine (ProQuad®), as has been the case with a TDaP. No serious outcomes have been reported.

Within the Vaccine Safety Datalink, safety surveillance is being conducted in two age strata of potential vaccinees. Among 50- to 59-year-olds, with the possible anticipation that there may be some off-label use, a cohort of 563,175 persons will be under surveillance. Among persons 60 years of age and older, just over 660,000 persons will be under surveillance. This conforms to the FDA license and ACIP recommendations for use of this vaccine. The specific sites and populations were shown.

Adverse events selected for active surveillance include events judged to be plausible following Zoster Vaccine, Live (Zostavax®) or related vaccines, events that have been commonly reported to VAERS, and chronic underlying medical conditions of importance in those greater than or equal to 60 years of age. Events falling among the previously listed categories were noted. Unlike in VAERS, rates of these events will be compared between vaccinated and unvaccinated cohorts. Analyses will be adjusted to account for confounding of vaccination status by underlying disease status.

In summary, to date, VAERS safety data for zoster vaccine is consistent with pre-licensure data and events anticipated on the basis of knowledge of the vaccine product and the target population for vaccination. The vast majority of reported events have been non-serious and demonstrate close temporal proximity to vaccination. Preventable vaccine administration errors have been reported. Active surveillance for selected adverse events among the cohort of over one million people is proceeding within the VSD.

Discussion:

Mr. Beck asked what the comparable number of vaccinations would be for the 1,379 reported cases. Drug manufacturer representatives indicated they did not have that specific

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information at hand.

Dr. Baker asked about the period of time for which reports on adverse events for zoster vaccine would be taken. Some of these events could occur much later and theoretically be biologically related. Dr. Iskander replied that they do not routinely exclude from the initial analysis any event regardless of its onset interval. They do present data in terms of median days to onset, but there are no time limitations either on reporting or on analysis.

Dr. Baker's second question was about TDaP and the more than 4000 people who were vaccinated during the outbreak. She noted that one of the barriers to getting recommended groups vaccinated with TDaP is this limitation of a prior TT or Td, and these are very reassuring data. She wondered about loosening the limitation because currently, for example, a 13-year-old who received TT one year previously because he had stitches in his head could not be protected against pertussis, due to the two-year cutoff limitation and the five years that FDA thinks is most desirable. Dr. Iskander replied that the current wording suggests that intervals as short as 18 months are permissible and there may be permissive wording allowing even shorter intervals. Dr. Decker further explained that the current recommendation contains enough "wiggle room" so that anyone be vaccinated. He referred to a study of about 8,000 people in Prince Edward Island, where the vaccination intervals between prior Td and subsequent Adacel were as short as 18 months, and which found no relationship between local adverse events and the timing of prior Td. The only relationship, a "soft" one, was with the number of prior AP doses and had nothing to do with the Td. Dr. Wallace added that both his branch and the safety division receive distribution data on an annual basis. The unanswered question is really the gap between the number of doses distributed and how many were actually administered. It is not useful to break that data down on less than an annual basis, especially with new vaccines where the pipeline is still being filled, as has been demonstrated by some of the analysis of the rotavirus vaccine and MCV4.

Dr. Karen Broder agreed that the data about intervals were very reassuring. In the healthcare worker population, the rates of the selected local adverse events and subjective fever were not higher in the healthcare workers who reported receiving Td or TT less than two years earlier than in the healthcare workers who had a longer interval. Those data are consistent with the permissive recommendation to use TDaP in populations less than two years. Dr. Abramson asked about the percentage of hospitals that are implementing the TDaP. Dr. Broder promised to email that information or have it available for the June meeting.

Dr. Ciro Sumaya asked how the administration errors with zoster vaccine compared with other vaccines. Dr. Iskander replied that, based on anecdotal and unpublished data, despite an increase in alerts on consumer safety websites, more errors with this vaccine are not being seen. With more vaccines being licensed, especially vaccines with similar contents (varicella vaccine, a zoster vaccine, and an MMR-varicella vaccine), and new types of medical practices taking on vaccination, this may just be part of a general trend. Fortunately, most of these errors do not result in adverse clinical outcomes, but it certainly warrants further attention. There are some data in the process of being submitted for publication involving tetanus toxoid vaccine and PPD mix-ups, along with other kinds of mix-ups.

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Dr. Baker returned to the interval issue and pointed out that the language says to wait 2 years, which is a barrier for post-partum women and health care workers, for example. She recommended that the committee reconsider the 2-year restriction.

Dr. Nancy Messonnier, NCIRD, said the general impression was that uptake of vaccine in healthcare workers was low because the recommendations were just published. In the several pertussis-like illness outbreaks investigated this year in hospitals, use of the vaccine before those events has been low. The data were not in, but she thought a plateau had not yet been reached.

Dr. Harry Keyserling wondered if the vaccine manufacturers or the FDA had considered making similar antigen-containing vials look different, which would certainly contribute to fewer errors. Dr. Adrian Dana reported that Merck had been looking at errors and mix-ups in vaccine, specifically the Zostavax and Varicella Virus Vaccine Live (Varivax®) vials. After calling practitioners, it appears that mix-ups occur because vaccines are kept in the freezer and whoever takes them out doesn't look carefully or isn't aware there are different vaccines. Merck tried, when licensing Zostavax, to be sure that the generic name contained the word "zoster" first and not "varicella."

Dr. Abramson asked whether there were any official recommendations on the Merck web site about what should be done if the varicella vaccine is mistakenly given instead of the zoster, or vice versa. Dr Dana replied that manufacturers really were not in a position to give official medical guidance. It would depend in which way the mistake went – if the person received an inadequate dose or a higher dose than what was intended.

Dr. Mark Feinberg informed the group that planning had been launched for a study to address some of these issues, specifically looking at total diphtheria content received by adolescents and adults, timing of the receipt of those varying content levels and rates of both local and systemic reactions.

Dr. Iskander noted that this discussion belongs under patient-safety, which focuses on root-cause analysis. Follow-ups of VAERS reports can be done, but the simple question of why errors happen can trigger a very complex, root-cause type of analysis.

Dr. Wallace pointed out that when people are looking for guidance for errors, including cold-chain errors, they usually end up going to the grantees and then eventually CDC must struggle to give guidance with limited data and information. It would be very helpful if manufacturers could provide more information so that better advice can be provided.

Dr. Jeff Duchin, NACCHO, addressed the complications at the clinical practice level with the increasing number of vaccines and the complexity of the schedule. Currently the VFC program provides funding for site visits to practitioners who administer VFC vaccine. These site visits focus on vaccine-safety issues, administration errors, and quality of clinical practice to improve the quality of practice and decrease errors. A similar mechanism is needed for adult vaccines, which would allow qualified public health professionals to be brought into the community to do this type of training.

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HUMAN PAPILLOMAVIRUS VACCINE
Dr. Janet Gilsdorf, ACIP, HPV Vaccine Workgroup Chair

Dr. Gilsdorf updated the committee on some of the group's activities, which include reviewing data from clinical trials, reviewing new epidemiological data on HPV infection, and considering additional modeling and cost-effectiveness analyses. GSK has announced that they plan to file for FDA approval in April of 2007. In anticipation of possible licensure of that vaccine, the workgroup will develop recommendation options for use of the bivalent HPV 16/18 vaccine for ACIP consideration. It will also update the ACIP statement to include bivalent HPV vaccine when it is licensed. The working group plans to review the bivalent HPV vaccine Phase III data in June 2007 and present options for bivalent HPV vaccine recommendations in October 2007.

Quadrivalent HPV Vaccine – Gardasil
Dr. Eliav Barr, Head of HPV Vaccine Programs, Merck Research Labs

Dr. Barr presented an update of efficacy findings in the clinical program for Gardasil. There are four efficacy studies: one that involved an HPV-16 vaccine prototype with efficacy through four years, and three studies of Gardasil, the quadrivalent vaccine with follow up through an average of 2.8 years (two Phase III studies) and 5 years (one Phase II study).

The presentation focused on updated analyses of the efficacy and population impact of Gardasil, including one further year of follow-up in the Phase III efficacy studies relative to the data set presented to ACIP last year. Other studies are ongoing. As Scandinavian subjects end their participation in the Phase III trials, they will be enrolled in a long-term effectiveness follow-up program. Towards the end of this year, it is anticipated that results for a study in mid-adult age, which examines the efficacy of Gardasil in 24- to 45-year-old women, will become available. Such women have continuing risk of development of HPV infection disease and precancerous lesions. Like all vaccines, HPV vaccines have a lower immunity by age at which the first dose is given. Merck felt it was more prudent to make claims about efficacy in adult women using efficacy data rather than relying on extrapolations from immunogenicity, particularly since the minimum protective anti-HPV level has not been demonstrated.

Merck has ongoing studies in men looking at both genital disease and infection and anal disease. Studies of Gardasil are being conducted or are in the planning phase in various immunocompromised populations, including solid organ, bone-marrow transplant and bone-marrow transplant patients and HIV-positive patients. A large program to encourage and manage uptake in the developing world is being conducted in collaboration with PATH, a nongovernmental organization.

Dr. Barr then focused on the results of the updated efficacy analyses for Gardasil. The Phase III trials had been analyzed using pre-specified target endpoints, and the first set of these were

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used to conduct the analyses that served as the basis for licensure. But the studies continued for an additional year and are still on-going.

There was another pre-specified milestone for analysis, relating to an evaluation of the impact on the overall rates of CIN 2/3 or AIS (caused by vaccine or non-vaccine HPV types). The trigger for this analysis was met in summer 2006. The results now represent about a year of follow up above and beyond the follow-up included in the original analyses. The main analysis population is women who were naïve to the relevant HPV types at enrollment, remained free of infection with the relevant types through one month post completion of the vaccination regimen, and who received 3 doses of vaccine/placebo within a one-year time frame. Dr. Barr focused mostly on the overall impact of CIN 2/3 and adenocarcinoma *in situ*, as well as other endpoints, regardless of the causal HPV type, in two populations.

Dr. Barr showed the database submitted for licensure in 2005 and the updated results. Subtracting out the numbers for each endpoint reveals that, in the intervening period, 35 cases of CIN 2/3 caused by HPV 16 and 18 developed, of which 34 occurred in the placebo group and one in the vaccine group. The last case is unusual and may reflect contamination. With respect to vulvar and vaginal pre-cancers, efficacy remained high.

A single case of HPV 16-related CIN 3 in the group that received Gardasil was described. This analysis had the benefit of testing for common non-vaccine HPV types, which revealed that this woman had been infected with HPV 52 at baseline, remained infected for the next three years, and had an abnormal Pap test at Month 32-1/2 that led to a biopsy. The biopsy showed CIN 3. It was positive for both 52 and 16. This was the first detection of HPV 16. The next month, the patient underwent definitive therapy because she had a CIN-3 lesion. A biopsy was taken at that time, and a LEEP specimen was divided into four pieces, as per the study protocol. All of these lesions were typed, and all were positive for HPV 52 but not for HPV 16.

No cases with similar patterns were observed in placebo subjects in Protocol 015, the study in which this case was seen; that is, a situation where a case is called an endpoint case, the subject is positive for a vaccine and a non-vaccine HPV type, and the only time that there is detection of the vaccine type is on a single biopsy. There is reason to suspect that the case may represent contamination, however, it meets endpoint definition and is reported as a case in the group that received Gardasil. This subject was not tested for anti-HPV levels because the subject was not in the consistency lot sub-study of this protocol.

Analyses were conducted to evaluate the efficacy of Gardasil with respect to HPV 6/11/16/18-related cervical, vulvar, and vaginal disease, the broad spectrum of disease, including low-grade abnormalities. Efficacy remained high. In the period since the closing of the last analysis data set, another two cases were observed in the group that received Gardasil, including the one case described above, plus 65 cases in the placebo group. So the efficacy actually went up slightly, and the 95 percent confidence interval is tightened. The same is true with vulvar and vaginal lesions, including genital warts.

A similar pattern is seen with the new cases. As is the case with the HPV 16-related CIN 3

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lesion described previously (and included here as well), the second additional case of CIN was a woman who was chronically HPV-56 infected at baseline, had remained infected, and had HPV-56 infection in every CIN 1 lesion found; in one LEEP specimen, she was HPV-18 positive. These cases may point out limitations of using highly-sensitive HPV typing for definitive determination of causality. But overall, the vaccine's efficacy was high and remained so. The results through three years of follow up are exactly as expected, given that the high efficacy of Gardasil has been demonstrated through Year 5 of follow up. The data presented represent a much larger data set that confirms those Phase II results.

Dr. Barr then talked about the impact in the general population. The clinical trials enrolled women regardless of baseline HPV status. Because Gardasil is a prophylactic vaccine, the primary analyses were conducted in women who were naïve to the relevant HPV types (prophylactic efficacy). However, it was also of interest to evaluate the impact of the vaccine among the general population of women regardless of the baseline HPV status. The enrollment of the clinical trials program for Gardasil did not exclude women who were infected with HPV at baseline, and thus there was a substantial amount of infection at baseline, which obviously impacted the population-impact findings.

The results for HPV 16/18-related cervical cancer, vulvar cancer, and vaginal cancer efficacy, using surrogates, which include HPV-infected women at baseline, show that the efficacy or percent reduction, particularly for CIN, has improved between the original analysis database and the current database that includes an additional year of follow-up. In the intervening time period, 20 cases were observed among subjects who received Gardasil, as opposed to 50-54 cases in the placebo group. All of the cases in the group that received Gardasil were due to prevalent HPV infection. In the placebo group, only 14 were due to prevalent infection, and the rest were due to incident infection. Thus the benefit of the vaccine becomes more apparent. With VIN 2/3 and VaIN 2/3, the efficacy is already high,. There is much less prevalent disease, as the time-to-event curves demonstrate.

At the beginning of the follow up, the cumulative incidence is comparable, since all cases were due to infections present at baseline, which Gardasil and other prophylactic vaccines would not impact. However, after a period of time, the curves diverge and continue to do so. Women remain at risk for HPV 16/18-related CIN 2/3 and AIS, but there is a flattening of the curve in the group that received Gardasil. As these women are followed for longer periods of time, a broadening of the split and a better percent reduction will be seen.

The same results are seen with the overall incidence of CIN caused by the four types as well as vulvar and vaginal lesions. There were 22 cases in the group that received Gardasil since the last time analyses were done and 97 in the placebo group, demonstrating the unmasking of the efficacy of the vaccine. For vulvar and vaginal lesions, there were four cases in the group that received Gardasil and 90 cases in the placebo group. The time-to-event curves have slightly different Y-axis scales: one 6 percent and one 5 percent. But the results are exactly the same as for CIN 2/3. The external genital lesions are pretty much flat and now there are very few cases. The same is true with CIN, and the curves continue to diverge over the course of time. Women continue to be at risk for developing these infections and diseases over this entire period of time, even well into their twenties.

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Dr. Barr then turned to the overall incidence of disease regardless of the causal HPV types. The first population was one that was intended to be completely HPV naïve. Testing was conducted for 14 common HPV types to determine the status of subjects with respect to infection with common HPV types at vaccination onset. The relevance of this approach is that it approximates a population of HPV-naïve adolescents and young adults, in order to study the impact of the vaccine on purely incident disease. The population thus generated represents about half of the study population of young adult women. It is not a completely HPV-naïve population because testing for all high-risk HPV types was not conducted, but it was close.

Analyses were also conducted in the general population. For the completely naïve population, administration of Gardasil resulted in a 46 percent reduction in the incidence of CIN 2/3 or AIS caused by vaccine or non-vaccine HPV types. Subjects with prevalent HPV infection certainly had a lot of disease, and when added up, a masking of the effect of Gardasil is seen. Nevertheless, there are statistically significant results for all endpoints. The numbers in the group that received Gardasil are always lower than those in the placebo group because women who are infected at baseline are at high risk for developing a second and third infection, and Gardasil prevents a large proportion of those infections. So even among infected women, there is a difference, and the benefit of the vaccine will become more apparent over time because the proportion of incident cases will become greater in the overall mix.

The time-to-event curve in the completely naïve population shows a lag until disease becomes detected (subjects first have to acquire infection, then develop disease). There is still some prevalent disease because the study did not screen for all HPV types at enrollment. But then the curves separate and continue to do so over time. In the general population, there is such heavy burden of CIN 2/3 at baseline, so that the lines of separation are slower to diverge, but they do diverge over time. The reductions induced by the vaccine become more apparent and the difference is now statistically significant.

Prevalent cases of external genital lesions are less common than prevalent cases of CIN because detection does not require screening – women detect the lesions and get treated. Also, subjects with a history of genital warts were excluded from enrollment. What is seen is a substantial separation of the curves early on, which demonstrates what happens when vaccine is given in a setting with somewhat lower prevalence.

Cross-protection is a hot topic in this field and two analyses are being conducted to examine whether this vaccine will impact the incidence of infection and disease caused by types related to HPV 16/18. Early, preliminary results of the first analysis are quite encouraging, showing impact on a set of related HPV types. The effect is seen for cervical, vulvar, and vaginal disease. Analyses to confirm these results are still under way.

Another analysis is evaluating persistent infection, which is not a critical endpoint, per se, but it provides a good mechanistic evaluation that helps look at the disease without the need for a Pap test. Such an analysis would prevent ascertainment bias and other issues that affect the statistical analysis of cross-protection. Those results will be presented over the next few months.

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In conclusion, the new data show the continuing efficacy of the vaccine. The overall risk of cervical, vulvar, and vaginal cancer - using surrogate markers, the overall risk of CIN, the overall risk of external genital lesions, regardless of the causal HPV types - are reduced among the subjects who received Gardasil. And the benefit continues to improve over time. Other data shared with the work group show reductions in Pap test abnormalities and cervical procedures. The preliminary cross-protection data will be shared with the work group in the very near term.

Discussion

Dr. Treanor asked whether it would be correct to say that the RMITT-2 population is a subset of the per-protocol population. After Dr. Barr confirmed this assumption, Dr. Treanor asked what proportion of the per-protocol population was in the RMITT-2 population. Dr. Barr replied that the per-protocol population is a one-type-at-a-time population. However, approximately 83 percent of the population participated in at least one per-protocol population: either the 6, the 11, the 16, or the 18; whereas, for the RMITT-2 population, about 50 percent of the population participated in that analysis. It is not possible to just subtract one from the other to determine the protection against nonvaccine. However, one can subtract the completely HPV naïve population from the general population, which includes everyone in the study.

Dr. Treanor asked whether there was a suggestion that the vaccine had an impact on the development of CIN in people who were already 16/18 positive at the beginning of the study. Dr. Barr replied that this was a real phenomenon to the extent that it prevents CIN caused by types other than those found at baseline. For example, a woman who is HPV-16 infected is at a much higher risk than the general population of women for developing 6/11/18 infection, either by her behavior or her partners, or by some intrinsic factor. The reductions represent a benefit with respect to the types for which she is negative. Dr. Treanor asked whether, for a person who is Type-18 positive at the beginning of the study, vaccination has no impact on the rate with which that person might subsequently develop CIN 18. Dr. Barr responded that the data do not show such a benefit. There is a benefit among women who have already cleared their infection and remain seropositive. Their rate of reacquisition of disease is lower, and the vaccine helps prevent that reacquisition.

Dr. Morse asked whether the placebo group was offered the vaccine, given the overall benefit shown. Dr. Barr replied that the results were unblinded in November of last year and the placebo group is receiving vaccine now.

Dr. Abramson asked if there was something more than just a passive system in the Phase IV that would provide information about this vaccine in pregnancy. Dr. Barr replied that there would be follow up in the clinical trials on all pregnancy outcomes. In addition, a post-marketing study, which is going to look at exposure in 44,000 women and children at an HMO in the U.S., will look carefully at pregnancy. In Scandinavia, which has extensive vaccination and pregnancy databases, there are plans to link vaccine allocation with pregnancy status and look at pregnancy outcomes in a comprehensive fashion.

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Dr. Davis said that because this vaccine is being given to a population that may get pregnant and other vaccines for the same age group are coming along, a pregnancy cohort within the Vaccine Safety Datalink is being created so that all pregnancies within that population will be followed, and outcomes on the developing infant can also be assessed.

Bivalent HPV Vaccine – GSK
Dr. Gary Dubin, Director, HPV Development Program, GlaxoSmithKline

Dr. Dubin gave an update on GSK's recent clinical trial results and what is likely to come in the next few ACIP sessions. The vaccine that GSK has been developing for a number of years focuses on HPV 16 and 18 as targets for prevention, and consists of HPV 16/18 virus-like particles and the AS04 adjuvant, which has been included in the formulation because early clinical studies found that it enhanced immunogenicity compared to other formulations with aluminum-hydroxide adjuvant.

HPV 16 and 18 is responsible for about 70 percent of cervical cancers globally, and is even a bit higher in the U.S. than in some of the other countries. GSK has designed its development program to focus on cervical cancer prevention in women, which is believed to be a cost-effective strategy. Based on the modeling studies, high vaccine coverage levels will be required to ensure the best cervical cancer prevention in using the most cost-effective strategy. Clinical trials have been conducted in a broad age range, including girls and women between the ages of 10 and 55 years. One study specifically focused on women in the older age range.

Dr. Dubin presented some early Phase II immunogenicity data comparing two different formulations of vaccine - a formulation that contains the AS04 adjuvant, and a formulation that contains the same VLP dose formulated with aluminum hydroxide. This is actually two studies with a pooled analysis, which follow women out through four years from the administration of the first dose of vaccine. He then showed HPV-16 results and HPV-18 results, as well as inhibition ELISAs, which measure surrogate neutralizing activity. Over the course of the four-year follow-up period, higher antibody responses were observed with the AS04 formulation compared to the alum-based formulation for both of the HPV types.

GSK has also conducted some early studies looking at whether the adjuvant made a difference in induction of memory B-cells, and those data show that the formulation of vaccine with AS04 induces a higher frequency of memory B-cells. This is at peak responses, one month after the third dose, for both HPV 16 and 18, or compared to the alum-formulated vaccine. Based on the early development work, where the decision was made to formulate the vaccine with the AS04 adjuvant, the first efficacy study, initiated in 2001, was a double-blind, randomized control trial where about 1100 women 15- 25 years of age were enrolled and randomized to receive the active vaccine or control (aluminum hydroxide) on a zero, one, six-month schedule. Prior to enrollment, women were required to be naïve for a panel of high-risk HPV types.

The first study (HP-001) evaluated vaccine safety, immunogenicity, and efficacy up to 27

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months following administration of the first dose of vaccine. Women who completed the study were then offered the option of participating in a long-term follow-up study, referred to as HPV-007. This study is planned to continue to follow women for six and a half years after administration of the first dose of vaccine. Results from an interim analysis from the HPV-007 study were published a year ago in the *Lancet*. This first interim analysis presented results following women through four and a half years of follow up. The second interim analysis extends the follow-up period and adds more statistical robustness because of events occurring over the additional year of follow up. The data presented by Dr. Dubin focused on the entire five and a half year follow-up period. A final analysis of this study with the full six and a half years of follow up will be available later this year.

Dr. Dubin showed a slide illustrating the basic design of the original efficacy study, the HPV-001 study, and then the follow up of Phase HPV-007. The follow-up phase is being conducted in a blinded fashion, so the study team conducting and responsible for the study has not been unmasked in terms of individual treatment-group assignments for subjects. The original study enrolled 1113 subjects who were randomized to receive vaccine or placebo. There was good balance between the two groups, and the women were followed for up to 27 months. There were additional activities during the blinded, long-term extension phase of the study. GSK continues collecting blood samples for serology and cervical samples for HPV and DNA testing. If a woman has an abnormal cervical cytology, she is referred to colposcopy based on a management algorithm similar to what was used in the parent study.

HPV 16 and 18 efficacy endpoints, which include virologic endpoints, were assessed. Incident infection was the primary endpoint of the original study. Efficacy against persistent infection was also assessed, using either a 6- or 12-month definition of persistence, abnormal cytology, and CIN lesions associated with the vaccine types. This study also provided an opportunity to do preliminary assessments of the ability of the vaccine to prevent incident infection with other oncogenic types that are important in cervical cancer. Types 45 and 41 are the two most common types after HPV 16 and 18.

Dr. Dubin showed HPV-16 immunogenicity data using a binding ELISA from the pool of five and a half years follow up. The peak responses are seen at Month 7, which is one month after the third dose of vaccine is given. At about the Month 18, the antibody titers begin to plateau, and both for HPV 16 and for HPV 18, and there appears to be a relatively stable plateau in the antibody titer through the last time point assessed for immunogenicity, which is 63 to 64 months. In this analysis, antibody titers are fairly similar to what were seen in the earlier phases of follow up. The majority of subjects remain seropositive, even at the latest time points. At the last time point assessed in this analysis, the geometric mean antibody titer was still about 11-fold higher than titers associated with natural infection with HPV 16. The HPV-18 results are almost identical to HPV 16. Again there is a relatively stable plateau of antibody titers throughout the entire follow-up period, with almost all subjects remaining seropositive through the later time points.

Dr. Dubin summarized results from the combined analysis (HPV001/007) and the follow up study. The endpoints assessed include incident infection, 6- and 12-month persistent infection, and abnormal cytology and CIN lesions. For all endpoints associated with HPV 16

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or 18, very high levels of efficacy are observed throughout the five and a half years of follow up. The results from the extended follow-up phase show no evidence of waning protection against any of these endpoints.

Dr. Dubin then broke down data from the extended follow-up phase only, which is essentially Years 3 through 5-1/2, from the end of the HPV-001 study through the second interim analysis. For each of the five endpoints, a very high level of efficacy was observed with evidence of complete protection against the most biologically relevant endpoints: persistent infection, abnormal cytology, or CIN lesions. In the extended follow-up phase only, the number of CIN lesions is somewhat limited, although the pooled analysis increases the numbers a bit. Most of the confidence intervals around the efficacy estimate excluded zero, so the lower limits are relatively high for most of the endpoints.

Dr. Dubin next focused on HPV 16/18-related CIN 2-plus and showed the initial results in the HP-001 study, where there were a very limited number of cases, and then a progression as cases of CIN 2-plus associated with vaccine types continue to accrue. The combined analysis now spans the five and a half year period, with additional cases of CIN 2-plus. The number of endpoints is still limited, as this is a Phase II study but the study provides good evidence of vaccine efficacy against very clinically relevant endpoints. The data will be supplemented with data from GSK's large ongoing Phase III program.

Results were presenting showing the overall efficacy of the vaccine on lesions, either cytology abnormalities that are graded ASCUS or worse, CIN 1 or worse lesions, and CIN 2 or worse lesions when considering lesions independent of HPV-DNA status. These are cumulative data over the five-and-a-half-year period. Similar data were previously reported, but with increased numbers the results are more robust. The point estimate of vaccine efficacy for each of these endpoints is greater than what might be expected if estimating the proportion of cases caused by HPV 16 and 18 alone, based on available data from natural history studies. For CIN 2-plus, for example, the point estimate is about 67 percent, with an expectation that 50 percent of CIN 2-plus lesions would likely be caused by HPV 16 and 18.

To further understand whether the vaccine is actually inducing protection against non-vaccine types that might be responsible for the observation of an effect broader than expected with HPV 16 and 18 alone, GSK conducted analyses to evaluate efficacy against virologic endpoints for other oncogenic types. Data were previously published through four and a half years showing efficacy against incident infection with HPV 45 and 31. These are the third and the fourth most common types globally, and the most important types associated with cervical cancer after HPV 16 and 18.

A five-and-a-half-year follow-up view of the data using Kaplan-Meier curves shows that even during the latter part of the follow-up period, there is continued accrual of cases at a higher rate in the placebo arm than in the vaccine arm, especially for HPV 45. Point estimates of efficacy remain similar to what they were with shorter-term follow-up, suggesting that, for these endpoints, there's no waning of the effect previously reported. These data will be supplemented with additional data from the Phase III results.

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Global ranking of HPV types in terms of their importance in cervical cancer indicates that HPV 45 and 31 are responsible for about 10 percent of cancers after HPV 16 and 18. Together, these four types are responsible globally for about 80 percent of cancers.

Dr. Dubin then discussed GSK's overall, ongoing clinical development program, focusing on immunogenicity studies that allow age bridging using immunological criteria. HPV-009 is a collaborative study conducted in Costa Rica with the National Cancer Institute. It has enrolled about 7500 women and is in ongoing follow up. The largest single HPV efficacy study conducted to date is HPV-008, with over 18,000 subjects enrolled. GSK hopes to present those results at the next open meeting.

HPV-015 is an efficacy study in women over 25 years of age. GSK believes that the vaccine is ultimately going to be important in this age category. It is already relatively clear that new incident infections can occur in women in the age range of 25 years and up. Even though the rates are lower than in younger women, they're still substantial. There are also some data to suggest that new infections are more likely to become persistent with increasing age. GSK's target is that HPV vaccination be accessible to women who are over the age of 25 years; right now, using HPV vaccination in an older age range would be considered off label.

HPV-014 bridges antibody responses in girls 15 to 25 years to antibody responses in women over the age of 25 years. It was conducted in Germany and Poland, and enrolled over 600 subjects. Immunobridging was conducted in an age-stratified manner. The same three-dose schedule was used and data are now available through the Month 18 time point, which represents the inflection in the kinetic curve of antibody responses where responses begin to plateau. GKS believes that what is seen in Month 18 is predictive of what will likely come in longer-term follow up.

Geometric mean antibody titers for HPV 16 and 18 differ in each of the age strata, with a tendency to decrease in women in the older age strata. This is expected based on an understanding of other vaccines and probably represents, to a limited extent, senescence of the immune system over time. Nonetheless, high antibody titers are seen in all age strata evaluated for both serotypes. Virtually all vaccinated women were seropositive regardless of the age strata for both types in this study. In fact, all women were seropositive after the second dose.

An issue is how to interpret immunogenicity data in the context of this study since there is no established correlate of protection. Even though a minimum protective threshold has not yet been defined, it seems relevant to look at data generated in the efficacy study just shown because there is now evidence that when antibody levels are maintained in this plateau phase, a high level of protection is observed. This appears to provide a biologically relevant threshold with which to compare antibody responses, and responses that are similar or greater to responses seen in the long-term phase of the efficacy study appear likely to predict protection.

Data on antibody levels from the five-and-a-half-year follow-up period of the efficacy study show the same plateau phase through the latter time points. When the geometric mean

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antibody titers from the immunobridging study are superimposed over those from the follow-up efficacy study, they appear quite similar, despite small differences in the responses in each of the age strata. These titers very likely correlate with protective titers, at least at this time point, and because of the kinetics of the response after Month 18, the pattern should be predictable for some of the latter time points. Results for HPV 18 look almost identical.

Regarding the safety profile in women in this study, there are no significant differences in reactogenicity observed in the older age strata compared with the 15-25 year age stratum. In fact, for many of the symptoms, there appears to be lower reactogenicity as the age strata advances.

In conclusion, the candidate vaccine appears to be generally well tolerated in all age ranges evaluated. There is evidence of a high level of efficacy against HPV-16 and -18 endpoints with complete protection against CIN lesions over the five-and-a-half year period, which uses all of the data generated to date in this study. When comparing the efficacy levels in the latter part of the follow-up period with the earlier part of the follow-up period, there is no evidence of waning protection. This study provides preliminary evidence that the vaccine is able to protect against incident infection with the most relevant non-vaccine types, and the hope is that these data can be extended in the Phase III studies. Finally, the immunobridging objectives for the 014 study were met, and antibody titers in women over the age of 25 appeared to be in the same range as titers that correlate with protection in the efficacy study.

Dr. Dubin briefly described the large, pivotal Phase III efficacy study mentioned at the beginning of the session. This is a large, double-blind, randomized trial. The subjects were randomized to receive the GSK vaccine or hepatitis A vaccine, which is used as a control. The same zero-, one-, and six-month schedule is used, and subjects are followed virologically and for histopathologic endpoints. Over 18,000 women between the ages of 15 and 25 were enrolled between May 2004 and June 2005. Fourteen countries participated in four regions of the world, and there was an event-triggered interim analysis, which will evaluate efficacy against CIN 2-plus endpoints associated with vaccine types. The required number of events was accrued toward the end of last year. The analysis is near completion, and GSK hopes to present data in the near future.

Before closing, Dr. Dubin mentioned that regulatory files have been submitted for this vaccine in a number of countries, including the E.U. GSK plans to submit a U.S. BLA by April of this year. It has already initiated a fairly large Phase IIIb program. Some of the most important studies include the efficacy study conducted in women over the age of 25 years, some studies evaluating co-administration with commonly used vaccines in this age range, the safety and immunogenicity trial in HIV-positive women, which will begin later this year, and other trials being conducted in countries for registration purposes. GSK plans to do a Phase IV study in Finland, which will actually involve long-term follow up of a large cohort of women enrolled in the Phase III program. It has a community randomized trial, which is well advanced in the planning stages, to evaluate induction of herd immunity and population impact of HPV vaccination, and other Phase IV studies are under development.

Discussion

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Dr. Baker asked whether there were plans for pregnancy follow up. Dr. Dubin replied that there is active surveillance for pregnancy outcomes in a number of the planned Phase IV studies. GSK will also be doing passive surveillance in the U.S., using a pregnancy registry.

Dr. Kathy Neuzil noted that the cross-protection data will be important from a population-impact standpoint and asked how related these viruses might be and if GSK was proposing an antigenic-relatedness hypothesis. Dr. Dubin responded that HPV 45 is one of the closest-related viruses to HPV 18, and HPV 31 is closely related to HPV 16. So if one were to analyze the L-1 protein sequences and try to predict, based on understanding of neutralizing epitopes, which types might actually be expected to be protected against because they're phylogenetically related, these two types would probably be near the top of the list. However, the mechanism of cross-protection is not known, whether it is mediated by neutralizing antibody responses that have the ability to cross-neutralize related types or whether it is related to T-cell responses. Studies are under way to try to better understand the mechanism.

Dr. Eliav Barr from Merck added that an amino acid sequence is just the linear sequence of the amino acids of the protein, and the antibodies generated by vaccines really relate to quaternary structures or the way they're folded up. Although the amino acid sequence is a convenient way to look at how things relate, one cannot say which type is closest on an epitope basis or on the face of the VLP or the face of the virion. The way to evaluate this is efficacy-based because the immunology of HPV is not very well understood.

Dr. Winston Price, National Medical Association, asked how many older women were going to be involved in the immunobridging study. He also expressed concern about the lack of long-term studies being carried out on the continent of Africa or in the Caribbean. It's very critical in the U.S. to understand the importance of the vaccine in minority populations. Dr. Dubin responded that the Phase III studies have been conducted in a very broad range of countries. For example, in the largest efficacy study, HPV-008, about a third of the enrolled subjects were in Asia. Some of the other Phase III studies enrolled large numbers in Central America and South America. GSK is planning to initiate a relatively large immunobridging study in at least two and possibly three countries in Africa, if the logistics can be set up. Having broad geographic representation is important because countries that have a large burden of cervical cancer disease must have rapid access to the vaccine and it is important to understand whether or not the vaccine will behave similarly in these populations. Regarding the proportion of women over the age of 25 in GSK's development program, the immunobridging study described is relatively small with about 600 subjects enrolled. The efficacy program has focused on 15- to 25-year-old women. The strategy has been to first generate immunobridging data in younger and older women. However, there is an ongoing efficacy study that includes women over the age of 25, and that study has enrolled over 5700 women. Based on some of that data, the picture is becoming clearer about whether the vaccine is likely to provide protection to women in this age range.

Quadrivalent HPV Vaccine Update

Dr. Lauri Markowitz gave an overview of various aspects of HPV vaccine, including

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recommendations, the Vaccines for Children (VFC) program, vaccine distribution, post-licensure safety data, plans for monitoring vaccine impact, and school mandates. The ACIP voted in June 2006to recommend the HPV vaccine, and provisional recommendations were posted on the Web in July of that year. The ACIP statement will be published in April 2007, and it will be available online probably in mid-March.

The VFC resolution was adopted at the June 2006 ACIP meeting. A federal contract was established for the vaccine in October 2006. An excise tax was added after the vaccine was included in the National Vaccine Injury Compensation program, and the current contract price for the vaccine is $96.76 a dose. Quadrivalent HPV vaccine doses distributed in the U.S. were estimated at about 2.1 million doses through the end of December 2006, and about 40 percent of these doses were purchased with public-sector funds.

With regard to post-licensure safety, the first data are from the Vaccine Adverse Events Reporting System, or VAERS. These data were provided by the Immunization Safety Office at CDC, and they are through the end of January 2007. VAERS is one of the cornerstones of post-licensure surveillance activity. This is a national, spontaneous reporting system operated jointly by CDC and FDA, and although VAERS has well-described limitations, including underreporting and inability to determine a causal relationship, it does allow hypothesis generation.

Through the end of January 2007, 542 events for HPV vaccine were reported to VAERS. The overall reporting rate was about 25 per 100,000 doses, which is slightly higher than the overall average for most vaccines, but it's not unexpected for a new vaccine that providers are not familiar with. As expected, 99 percent of the reports were in females, and 47 percent were in individuals 13 to 18 years of age. About 5 percent of all the reports were designated as serious, and no deaths were reported. The most common symptoms reported to VAERS after quadrivalent HPV vaccine were injection-site pain, dizziness, syncope, fever, and nausea. Among the cases of syncope, there were three nose fractures, and one girl, who had a history of a seizure disorder, fainted, hit her head, and had a seizure.

There are many previous published reports of syncope after vaccination of adolescents, and the ACIP general recommendations statement does say that syncope can occur after vaccination, most commonly in adolescents and young adults. A precaution about this has been included in the ACIP HPV-vaccine statement, as well as a recommendation that providers should consider observing patients for 15 minutes after vaccination.

There were three cases of Guillain Barré Syndrome reported and three cases of facial palsy. For the Guillain Barré cases, one case occurred after administration of HPV vaccine alone, and the onset date postvaccination was not reported. Two cases occurred after HPV vaccine and MCV4 administration. Because of the small number of cases, a formal observed versus expected calculation has not been done, and the Immunization Safety Office will continue to monitor this on an ongoing basis. The three cases of facial palsy all occurred within one day of vaccination and after different vaccine administrations. Only one occurred after HPV vaccination alone. The background incidence of facial palsy is about 30 per 100,000 people per year, much higher than GBS, so the observed is much less than expected. This will also be

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monitored with both active and passive systems.

Data from the Vaccine in Pregnancy registry, managed by Merck, shows 44 exposures to vaccine reported through January 10th, 2007, and 38 were enrolled in the registry. Two women had elective abortions and two had spontaneous abortions. CDC also plans to monitor HPV vaccine during pregnancy in the Vaccine Safety Datalink, and those data will be presented at future meetings.

Systems are in place or being developed at CDC to monitor a variety of outcomes, including cervical cancer and other HPV-related cancers, HPV prevalence, and cervical cancer precursor lesions, such as cervical intraepithelial neoplasia and genital warts. Other monitoring systems are also being discussed. The U.S. has an excellent system of cancer registries that would be able to track trends in cervical cancer and other cancers related to HPV. SEER, the Surveillance Epidemiology and End Results study has been in place since 1973, and the National Program of Cancer Registries has been in place since 1995. Together they cover about 96 percent of the U.S. population.

Monitoring the impact of HPV vaccine will include a variety of outcomes. In addition to or in conjunction with cervical cancer registries, HPV typing will be initiated at several sites in the U.S. to allow determination of specific HPV types related to cervical cancers. It will take several decades to see any impact of HPV vaccine on cervical vaccine, so some of the more proximal outcomes are going to be monitored. Type-specific HPV prevalence is currently being monitored in the National Health and Nutrition Examination Survey, or NHANES. Self-collected vaginal swabs were added to the survey in 2002, which has allowed determination of a population-based prevalence of HPV types.

Plans are currently in progress to monitor CIN 2/3 through supplemental data collection in VSD. CDC also plans to monitor CIN 2/3 through administrative databases, such as MedStat, and through new sentinel projects to be initiated to collect population-based data on overall and type-specific CIN 2/3. Genital warts will be monitored through a network of STD clinics, administrative databases and other sources being developed.

The issue of school immunization mandates has been well covered in the news media. Currently, over 18 states have introduced some type of legislation for school-entry requirements for HPV vaccine. Additional states have introduced other types of legislation related to education or insurance coverage. No state legislature has passed a bill for school immunization mandates at the present time. In Texas, there was an executive order for a middle school HPV-vaccination requirement.

A variety of positions regarding school mandates have been adopted by different professional organizations. The Association of Immunization Managers (AIM), whose members include representatives from all 64 state, territorial, and local and national immunization program grantees, posted the following statement on their Web site in June 2006. *"School and childcare immunization requirements must be used sparingly, approached cautiously, and considered only after an appropriate vaccine implementation period. This vaccine implementation period is critical to ensure that the necessary elements are in place to support*

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a school childcare requirement, including:

- *Coverage for the vaccine in private health insurance plans*
- *Sufficient funding to purchase the vaccine*
- *Physician/provider support for the vaccine*
- *Public acceptance of the vaccine*
- *Stable and adequate vaccine supply*
- *Addition of vaccine to immunization information systems (registries)*
- *Adequate data to assure vaccine safety*
- *Significant uptake in the recommended population to reduce the compliance burden on the school/child care system."*

The work group will continue to review data on both vaccines and HPV epidemiology that will be necessary to formulate new recommendations and cost effectiveness, and then develop recommendations for options and to revise the ACIP statement as needed.

Discussion

Dr. Abramson asked whether there would be enough money in the system to cover the cohort of girls and women who will get the vaccine, about half of whom are covered by VFC, and whether AIM's problems in prioritizing different groups would be avoided. Dr. Schuchat addressed the VFC part of the question. There is a contract and financing in place for the VFC population. The money is provided per request based on estimates of the population that needs it, so financing should not be an issue for the 9- to 18-year-old girls who are VFC eligible (approximately 45% of each birth cohort). VFC covers uninsured children, people who are Medicaid eligible, native Americans, Alaska natives, and underinsured persons seeking care at a federally qualified health center or rural health center, but a large population is not VFC eligible. Dr. Markowitz added that AIM repeated the survey presented at the October meeting, so there may be some additional changes in those findings. Ms. Hannan added that out of 53 survey responses, only four have not implemented VFC in 9- to 18-year-olds. But this is not all public financing, and there are still the under-insured to consider.

Dr. Schuchat commented that the VFC program has been a tremendous resource for children, also helping states and providers provide appropriate care. A challenge has been the focus on young children and strengthening provider-program relationships. However, VFC funding has recently been obtained for states to hire adolescent coordinators to help enroll providers who care for adolescents. This will help with quality control, enrollment, and management and storage of vaccines and administration of vaccines in this new provider group.

Dr. Susan Lett noted that because of the lack of adequate reimbursement in the private sector, some doctors are not able to offer the vaccine to under-insured patients. Many are referred to clinics and public health centers, but not all those children are VFC eligible, which puts stress on the public health system. However, states have been able to increase their allocation of doses to VFC-eligible girls. Dr. Baker requested clarification about the difference between VFC-eligible and VFC-enrolled. Dr. Schuchat responded that when the VFC program was established, the provider was supposed to determine who was eligible. However, many children who were eligible for Medicaid were not enrolled. VFC makes it very simple for the

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provider to not miss an opportunity to vaccinate.

Dr. Treanor wondered if there were other vaccines for diseases that would not specifically be transmitted within the classroom and for which there are school mandates, such as hepatitis B. In other words, is using a mandate to increase vaccination rates rather than prevent transmission of diseases within the classroom a new concept? Dr. Schuchat replied that hepatitis B vaccine has had many school mandates, and that both mandates aim to reduce transmission within the classroom and assure herd protection with high coverage rates. Dr. Treanor felt this philosophy seemed to extend to boundaries of the original intent of mandates.

Dr. Rick Haupt from Merck expressed his pleasure with ACIP and others' support and the remarkable uptake of Gardasil. Merck's goal has been to have the broadest potential impact and use of this vaccine in the appropriate populations, especially underserved and poor populations, those missed in screening. As such, Merck supported school requirements initially at the state level, which increased funding and access to the vaccine. However, based on ongoing discussions with many different stakeholders and the perception this may be a distraction from getting women vaccinated, Merck is suspending its lobbying efforts for school requirements at this time. It will continue to provide information about HPV and the vaccines and advocate for public health programs that provide education about cervical cancer as well as screening and funding for vaccines at the state level. Lastly, Merck would oppose any legislation that would restrict access to Gardasil.

Dr. Morita added that the original intent of school-entry laws was to decrease transmission in the school setting, but in places with disparities issues, they also serve as a safety net, catching children who might slip through the cracks and not get their immunizations. Evidence from a small study suggested that by the time of school entry, African-American and Hispanic kids do catch up, possibly because of the school mandates. So there is a role for HPV mandates, but not necessarily right now.

Dr. Susan Lett agreed that states need to go through their normal processes. The AIM position statement talks about how do a school mandate carefully and correctly, making sure there's an adequate supply; a good post-licensure safety track record; working with insurers on reimbursement; and convening public hearings with stakeholders to assure buy-in.

Ms. Stinchfield said that the issues around mandates were confusing and inconsistent. The traditional reason was reducing the infections that are spread in the classroom, but now people are talking about equity. Why is there no mandate for TDaP when there is pertussis all over the country? Why is there no influenza mandate? Another issue is that these are unfunded mandates. If they are so important, the resources need to be there. Dr. Amy Middleman, Society for Adolescent Medicine, added that school mandates are important currently in the absence of strong immunization platforms. Evidence from the March study indicates that in states that had school mandates for hepatitis B, adolescent completion rates are approximately 75 percent versus 39 percent in states without mandates.

Dr. Rick Zimmerman stated that he supports mandates for measles and pertussis vaccines because of the risk that one child could expose another who either didn't respond to vaccine or

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had a legitimate contraindication. Smallpox and measles were examples where that was a real risk. There has been transmission of hepatitis B among wrestlers, through dialysis, and among preschoolers. However using the argument that the end justifies the means is undesirable, given the history of issues related to government rules and eugenics in this country and others.

Dr. Sam Katz suggested looking at the state of Washington's program, which has an immunization action committee. They consider every new vaccine individually, and have nine points under which they consider whether there should be a mandate. Dr. Georges Peter, from Brown Medical School, added that the National Vaccine Advisory Committee had developed a paper entitled, "Public Health Options for Implementing Vaccine Recommendations." He felt it would be helpful in terms of providing a national framework. In addition, Dr. Peter expressed concerns about global use of this vaccine. This country is committed to a three-dose schedule, but the vaccine is expensive and also highly immunogenic. He asked if there had been consideration of alternative schedules, such as two-dose schedules, which would obviously greatly reduce the cost globally, and expressed his hope that companies would be open to that option. Dr. Abramson said he thought the two-dose schedule had already been considered by the committee. Dr. Markowitz responded that the two-dose recommendation had not been seriously considered for the U.S., but that there had been considerable interest globally, including the World Health Organization.

Dr. Schuchat commented that one of the many things that can be looked at post licensure in the surveillance and effectiveness activities is partial schedules. The pneumococcal conjugate vaccine effectiveness paper recently reported high efficacy of partial schedules, given that there was a shortage and a lot of people didn't get the full schedule.

Ms. Claire Hannan expressed her hope that the committee would further the discussion and bring groups together to talk about how school mandates can be used in the best way. She also mentioned the philosophical exemption, which many school laws are allowing. When considering how to mandate new vaccines, allowing an exemption where one doesn't exist could compromise the existing mandate.

Dr. Mark Feinberg, Merck Vaccine Division, was concerned that access and equity issues were getting lost in the discussion about school requirements. The ACIP issued its unanimous universal recommendation last June, which basically set the parameters of the public health goal. Presumably, the best public health achievement would be having those recommended to receive this vaccine get it as soon as possible to have the maximum public-health benefit, because there are millions of cases of HPV infection each year and 10,000 cases of cervical cancer. But it is more likely that certain segments of the population will get access to the vaccine and others will lag far behind. Unfortunately, the ones most likely to lag behind are those in racial and ethnic minority groups and economically disadvantaged individuals.

Dr. Feinberg said Merck has actively advocated at the state level for increases in state general funds and for Medicaid coverage of this vaccine for eligible populations. It has been an active member of the 317 coalition, which has lobbied at the state level to fight against the $100 million cut in the 317 project that was proposed by the President's budget last year and has

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been increased, fortunately, by $32 million this year. Merck has also instituted a patient-assistance program, providing the vaccine free of charge to all low-income individuals less than 200 percent of the federal poverty limit, who cannot afford this vaccine and don't have insurance.

With respect to access on the global scale, Merck is committed to providing its vaccine in an affordable and sustainable manner, working with partners such as PATH to look at alternative immunization approaches in developing countries. It has committed over $15 million worth of Gardasil specifically for projects in collaboration with PATH. Merck is very interested in working with ACIP to address access and equity issues. Dr. Duchin pointed out that the Merck program to provide vaccine to the people below 200 percent of the poverty level is not available to local or state health departments where many of these women seek care.

AGENCY UPDATES

CDC/CCID/NCIRD

Dr. Schuchat informed the group that in January this agency announced, in conjunction with the WHO, U.N. Foundation, UNICEF, and the American Red Cross, the global goal to reduce worldwide measles deaths by 50 percent by 2005 was not only achieved, it was exceeded, and deaths were reduced by 60 percent. In Africa, 217 million children in 41 priority countries were vaccinated against measles. A new goal, 90 percent worldwide reduction of measles deaths by 2010, has been established.

CMS

Ms. Linda Murphy reported that CMS continues to work with CDC and other agencies on pandemic influenza, with a particular emphasis on work between Medicare and Medicaid.

FDA

Dr. Norm Baylor stated that FDA would convene a meeting of the Vaccines and Related Biological Projects (VRBPAC) coming up February 27th and 28th, in Gaithersburg, Maryland. Evaluation of a new vaccine against H5N1, a potential pandemic influenza strain, will be presented. A discussion on the clinical development of influenza vaccines for pre-pandemic use will be held to decide on a strain selection for the 2007-2008 influenza season, including whether to include a second B strain in the vaccine.

At the January 25 meeting of VRBPAC, licensure of Pentacel was discussed. Results for a Hib component were inconsistent. In one trial, a reduction of Hib in the group that received Pentacel was seen. In the second study, similar responses to the Hib component in Hib versus the Pentacel were seen, but there was a rarer response than seen in the first study, so there are some concerns about the response to Hib with the vaccine. The statistical criteria for the

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response to the protective antigen in the pertussis component seemed shallow.

HRSA

Dr. Indira Jevaji presented an update on thimerosal and autism and another update on congressional activity. As of January 3, 2007, there were 5100 thimerosal-autism claims filed with the National Vaccine Injury Compensation Program. In 2001 or 2002, the Chief Special Master of the U.S. Court of Federal Claims ordered the process for adjudicating these claims, called the Omnibus Autism Proceedings. This process involves adjudicating petitions filed by the ACIP, the VICP and others from either MMR vaccine or thimerosal-containing vaccines. Phase I of the Omnibus Proceedings is coming to an end. It involves an extensive discovery process, however, petitioners have recently submitted a motion for additional discovery, which has been approved by the courts. The deadline for submission of the petitioners' experts was February 16, 2007. The next step is a hearing on entitlement to compensation, which is scheduled for June 2007.

Recently, the petitioners declared a desire to modify the hearing on entitlement and schedule of rates. First, instead of conducting a hearing in an omnibus fashion, the petitioners indicated their intent to establish causation in test cases. Rather than bringing evidence on all theories in June 2007, the petitioners now want to limit the first hearing to the sole issue of MMR/thimerosal as the cause of autism. Finally, the Chief Special Master issued a notice on January 11, 2007, indicating that two additional Special Masters will be assigned to hear and decide the issues presented in the test cases.

Regarding congressional activity, on December 20, 2006, the President signed the Tax Relief and Healthcare Act of 2006, which added meningococcal vaccines -- both conjugate and polysaccharide -- and the HPV vaccines to the list of taxable vaccines. There are two prerequisites for vaccine coverage by the VICP: the imposition of the excise tax and *MMWR* publication of a CDC recommendation for routine use in children. Both requirements have been satisfied for the meningococcal vaccines. However, the HPV vaccine will be covered once the CDC publishes the ACIP statement in the *MMWR* publication. Finally, some meningococcal vaccines will be added to the vaccine injury table under the general category.

NIH

Dr. Curlin apologized for not having the Jordan Report, as expected, but promised to see that all liaison members and members of the ACIP receive a copy. Anyone else can request a copy by email. The Jordan Report is an occasional document from NIH about vaccine research and development activities, largely funded by NIH. There's a considerable amount of good vaccine research and development in the pipeline and NIH's perspective is just a small pass at the total picture. The Report will probably be reformatted in the future.

NVPO and NVAC

Dr. Bruce Gellin reported that at NVAC, there's discussion of HPV vaccine and highlights of the work of the Adolescent Working Group, which has been asked by the Assistant Secretary

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of Health to define the problem statement. A paper is working its way through before solutions are sought. There's also an active Vaccine Financing workgroup, which will feed into a discussion in Chicago. Results of that meeting will be presented because financing is relevant and comes up frequently.

At NVAC, the recommendation on registries has been approved and publication is forthcoming. Work on pandemic vaccine prioritization has already been reported. When the draft guidance is available, it is hoped that this committee in its full capacity, as well as individuals and the organizations they represent, will provide feedback. There will also be a public-comment period. Finally, a long-overdue effort is to update the 1994 national vaccine plan.

Closing Session

Dr. Abramson thanked the participants for attending the meeting. With no further discussion or business brought before ACIP, Dr. Abramson adjourned the meeting at 12:03 p.m. on February 22, 2007.

I hereby certify that to the best of my knowledge, the foregoing Minutes of the February 21-22, 2007 ACIP Meeting are accurate and complete.

_____
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_____
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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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