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

Advisory Committee on Immunization Practices

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Atlanta, Georgia

Record of the Proceedings

C O N T E N T S

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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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) convened a meeting of the Advisory Committee on Immunization Practices (ACIP). The meeting was held on October 24-25, 2007 at CDC's Global Communications Center in Atlanta, Georgia

Welcome and Introductions
Dr. Tanja Popovic, Chief Science Officer, CDC
Dr. Dale Morse, Chair, ACIP
Dr. Larry Pickering, Executive Secretary, ACIP/CDC

Dr. Popovic welcomed committee members and attendees on behalf of Dr. Gerberding and the CDC. She noted that the ACIP has been in existence for over 40 years and its work has contributed to CDC's being an agency highly trusted both in this country and globally. Science is the cornerstone of what CDC and this committee do and prevention is CDC's overall focus. Prevention requires that the science and evidence base be translated into practice, which unfortunately often takes years. Measurable impact is another CDC focus. This work of this committee is highly visible and members help CDC make difficult decisions and give people what they need as quickly as possible. As such, they bring enormous credibility to the work of the committee and to CDC as a whole. Finally, committee members are people of high integrity who are able to work on sensitive issues in an open manner, for which much praise and appreciation are due.

Dr. Popovic introduced the new ACIP chair, Dr. Dale L. Morse, who has served as an ACIP member since 2005. He is the director of the Office of Science and Public Health at the New York State Department of Health. New members to the ACIP include Dr. Lance Chilton, Professor, Department of Pediatrics, University of New Mexico School of Medicine; Dr. Paul Cieslak, Medical Director, Immunization Program, Program Manager, Acute and Communicable Disease Program, Oregon Public Health; Dr. Allen Craig, State Epidemiologist, Director, Communicable and Environmental Disease Services, Tennessee Department of Health; Dr. Janet Englund, Associate Professor of Pediatrics, University of Washington, Fred Hutchinson Cancer Research Center, Children's Hospital and Regional Medical Center, Seattle, Washington; and Dr. Franklyn Judson, Professor, Departments of Medicine and Preventive Medicine and Biometrics, University of Colorado at Denver and Health Science Center.

New liaison organizations include: the American Osteopathic Association, represented by Dr. Stanley Grogg; the Society of Healthcare Epidemiology of America, represented by Dr. Harry Keyserling; the American Geriatrics Society, represented by Kenneth Schmader; and the National Association of Pediatric Nurse Practitioners, for

which a representative will be selected in 2008.

Two high-profile groups visiting the ACIP meeting were recognized. The first was a delegation from Japan, led by Dr. Koichi Yamanishi, Director General of the National Institute of Biomedical Innovation in Tokyo, Japan. He and his colleagues are establishing an advisory committee on immunization practices in Japan. The People's Republic of China national and provincial health officials were attending a two-week CDC course on vaccine-preventable diseases. The delegation was led by Dr. Xin-Sheng Gong, the Director of the Expanded Program on Immunization Division of the China Centers for Disease Control and Prevention, Ministry of Health, Beijing, China.

Dr. Pickering introduced Tonica Gleaton, the new ACIP program analyst. He noted that Dr. George Curlin from NIH was unable to attend, but Dr. Carolyn Deal will attend in his place. Dr. Norm Baylor from the FDA was also unable to attend, but Florence Houn was there on his behalf.

The ACIP charter gives the executive secretary or his or her designee the authority to temporarily designate an ex-officio member as a voting member if there are fewer than eight appointed members available or qualified to vote due to a financial conflict of interest. Their conflicts of interest, if any, will be sought before any votes are taken. Topics presented at the ACIP meeting include open discussion with time reserved for public comment. To ensure transparency, CDC encourages people to advise the committee of any financial relationships that are likely to be impacted by the topic being discussed.

The goal in appointing members to the ACIP is to achieve the greatest level of expertise while minimizing potential for actual or perceived conflicts of interest. Members of the ACIP agree to forgo participation in certain activities related to vaccines during their tenure on the committee. For certain other interests that potentially enhance a member's expertise, the CDC has issued limited conflict of interest waivers. Members who conduct clinical vaccine trials or serve on data safety monitoring boards may serve as consultants on matters related to those vaccines, but they are prohibited from participating in deliberations or votes of the committee on issues related to those specific vaccines. Regarding other vaccines of the affected company, a member may participate in discussion with the proviso that he or she abstains from voting related to the vaccines of that company.

Dr. Morse welcomed all U.S. and international guests, the new members, and liaisons. He particularly welcomed participation of the American Geriatrics Society because it reflects the expanded focus on adult preventive vaccines. ACIP recently has been involved with a number of vaccines for adults, including Tdap, pneumococcal, influenza, and zoster. The potential for adjuvants is good news for the aging baby boomer population. He then called for statements on conflicts of interests of committee members.

Dr. Morse: no conflicts.
Dr. Baker: no conflicts.
Dr. Chilton: no conflicts.
Mr. Beck: no conflicts.
Dr. Cieslak: no conflicts.
Ms. Stinchfield: no conflicts.
Dr. Lett: no conflicts.

Dr. Hull: I've had some discussions with MedImmune about a project that could become a conflict. I've also been approached by a recruiter from sanofi, and so I will not be voting vaccines manufactured by those two companies.

Dr. Englund: I get research support from MedImmune for clinical studies, including FluMist in children with cancer.

Dr. Morita: no conflicts.

Dr. Craig: no conflicts.

Dr. Lieu: I receive government funding from CDC and NIH for studies of vaccine economics and safety, and I have no conflicts.

Dr. Judson: no conflicts.

Dr. Neuzil: no conflicts.

Dr. Sumaya: no conflicts.

Influenza Vaccines
Dr. Anthony Fiore, CDC/NCIRD/ID
Dr, Greg Wallace, CDC/NCIRD/ISD
Dr. Kathleen Neuzil, ACIP WG Chair
Dr. Lisa Prosser, Harvard Medical School
Dr. Benjamin Schwartz, CDC/NVPO

Influenza Vaccine Update

After outlining the session, Dr. Fiore presented current ACIP recommendations for influenza vaccine. Those published in the *MMWR* in 2007 include every underlying condition that might give an indication for influenza vaccine. A simpler version is to vaccinate persons at high risk of complications, their contacts and those who care for them, plus anyone who wants to be vaccinated.

Before 2000, annual vaccination was recommended for persons 65 and older, persons with chronic underlying medical conditions, pregnant women in their second or third trimester, contacts of any in the first three groups, and healthcare workers. In 2000, the recommendations were extended to all adults ages 50 and older because many had chronic underlying conditions. In 2004, all children ages 6 to 23 months were recommended for annual vaccination and as well as their contacts and out-of-home caregivers. The recommendation for pregnant women was advanced to include all women who will be pregnant during the influenza season. In 2006, all children between 6 and 59 months as well as their out-of-home caregivers and their close contacts were added.

Data from the National Health Interview Survey for different adult age groups indicate that by 2006, for adults 65 and older, vaccination coverage of between 60 and 70 percent had been achieved, reaching a plateau of around 70 percent. Coverage of 50- to 64-year-olds, who are at higher risk of influenza complications, has not substantially increased in recent years, reaching a plateau of about 40 to 50 percent. Healthy adults in that age group, who also are recommended for vaccination, are at about 30 percent. Younger adults at higher risk for influenza complications are also at lower coverage levels. Healthcare workers are between 35 and 40 percent coverage annually and

pregnant women have not yet reached 20 percent coverage.

Vaccination of 6- to 23-month-olds is a high priority because their rates of hospitalization for influenza are similar to those observed in the elderly. They require two doses if it is their first year of vaccination. In the past two years, 33 and 32 percent one-dose coverage has been achieved. For two doses, coverage last year was 21 percent. More recent data are available from immunization information systems or registries, including coverage from the last influenza season. For the 6- to 23-month-olds, overall coverage for both one and two doses has not substantially increased over the last three years. For 2006-2007, 6 to 22 percent of 24- to 59-month-olds had received at least one dose and between 2 and 18 percent had been fully vaccinated.

Use of Live Attenuated Influenza Vaccine in 25-59 Month Old Children

In 2006, MedImmune submitted a supplement to their Biologic License Application, or BLA, to allow use of FluMist in 12- to 59-month-olds. Their primary data source was the CP111 study, which was presented to ACIP in detail in October 2006, and safety data were presented in February 2007. A study by Belshe *et al.* was published in the *New England Journal* in February 2007. This was a large study with about 8,000 subjects, a double-blind, randomized trial with an active control. The active control was inactivated influenza vaccine and included pre-specified analyses for the 6- to 23-month-olds and 24- to 59-month-olds. Exclusion criteria included children with medically diagnosed or treated wheezing within 42 days before enrollment or a history of severe asthma as judged by the investigator. However, many other children with a history of mild or moderate asthma or history of wheezing more than 42 days before enrollment were included in the trial.

The FDA and MedImmune discussed this application at a VRBPAC meeting in May 2007 and the FDA concluded that FluMist was safe and effective in subjects 24 months of age and older. However, among subjects less than 24 months of age, the participants who received FluMist had increased hospitalizations, severity of wheezing, and severity of respiratory events, according to the FDA analyses. The number of these adverse events was quite small and the large majority of instances of medically significant wheezing, for example, required no more than a short course of a bronchodilator and a medical evaluation. But there was a statistically significant increase in these wheezing end points compared to children who received TIV.

In May 2007, the FDA issued a warning letter to MedImmune for unrelated manufacturing concerns, and the BLA supplement decision was delayed, as well as the planned vote at the June 2007 meeting. By September, the issues had been resolved, and the BLA supplement application was approved, but it differed from the original request. FluMist was indicated for persons 2- to 49-years-old, but providers were advised to avoid administering FluMist to children less than 24 months old, individuals with asthma, and children less than five years of age with recurrent wheezing. Safety was not established in persons with underlying medical conditions predisposing them to wild-type influenza infection complications. Parents or guardians were to be asked if the vaccinee had asthma or, for children less than five years old, recurrent wheezing, since this may be an asthma equivalent in this age group.

The influenza vaccine working group concluded that LAIV efficacy was at least

equivalent to TIV efficacy for children six months and older. In the clinical trial, LAIV had a 55 percent greater relative efficacy compared to TIV. There was also good evidence for safety among healthy children 24 months and older without a history of asthma or wheezing. However, additional information on safety is needed for children more than 24 months old with a history of asthma or wheezing. Safety monitoring of FluMist use in young children will use the current reporting systems: the Vaccine Adverse Events Reporting System, or VAERS, and the Vaccine Safety Datalink.

The work group concluded that a better definition of recurrent wheezing was needed and that the ACIP should provide more guidance about which two- to four-year-olds were candidates for getting FluMist and which might be better off getting TIV because of the potential for post-vaccination wheezing after FluMist. Asking about recurrent wheezing would not exclude some children who were excluded from the study, such as those with a single, recent wheezing episode. Young children who are predisposed to reactive airways diseases might not be old enough to have had more than one episode of wheezing. A single simple question consistent with guidance from other organizations was most likely to be understood and used.

The working group suggested the following guidance: FluMist is not recommended for use in children with underlying medical conditions, including asthma, that predispose them to influenza complications. However, some two- to four-year-old children have a history of wheezing and respiratory illnesses but have not been diagnosed with asthma. Therefore, to identify children who might be at higher risk for asthma, persons administering FluMist should ask parents and guardians of 24- to 59-months-olds the following question: In the past 12 months, has a healthcare provider ever told you that your child had wheezing or asthma? LAIV, or FluMist, is not recommended for children whose parents answer yes to this question or for children with a wheezing episode noted in the medical record within the past 12 months. This guidance was developed in collaboration with representatives from the Committee on Infectious Diseases of the American Academy of Pediatrics and additional guidance might be considered as more post-marketing safety data are available.

The work group will continue to follow LAIV issues, including the use of LAIV for children with a history of wheezing and optimal vaccination strategies for use of LAIV and TIV in young children. As LAIV safety analyses from VAERS, VSD, and the various post-licensure studies become available, the work group will consider them as well. It proposes that LAIV be recommended for use in two- to four-years-olds and that either TIV or LAIV can be used for healthy persons aged 2 to 49 years, i.e., persons who do not have an underlying medical condition that predisposes them to influenza complications.

Discussion

Dr. Morse asked whether it had been possible to take the definition of wheezing and analyze the clinical trials to see how many children might have answered that case definition. Dr. Fiore replied that the current definition was more restricted than the one used in the clinical trial, which involved exclusion for severe asthma. As far as children who had wheezing in the past but were enrolled in the trial, he had no information about who might have not gotten FluMist. Dr. Neuzil noted that the fact that the current

definition of wheezing is slightly more conservative than what was used in the clinical trials was partly an effort to simplify the question asked in a clinical practice.

Dr. Cieslak wondered if anyone had tested the predictive value of asking parents this question and what sort of language was used. Dr. Fiore acknowledged that the predictive value was unknown. The question would be directed to the parents, based on what a healthcare provider had told them, since the medical record might not be available.

Dr. Whitley-Williams, National Medical Association, noted that in the Belshe trial there were only 300 African-Americans out of over 8,000 participants. She was concerned about recommending live vaccines for children between 2 and 59 months, a population susceptible to asthma and reactive airway disease or wheezing, particularly in inner cities. She asked if there was any additional information on the side effects of wheezing in this population, and added that there were also very low numbers of Asians and Hispanics. Dr. Fiore said he had no additional information about minorities, but that there was an alternative influenza vaccine in clinics with high rates of asthma and reactive airways diseases.

Dr. Lewis noted that pediatricians consider recurrent wheezing to be at least more than one episode and asked whether any episode of wheezing with an acute illness would then be a contraindication. Dr. Fiore replied that it would be, if it had occurred in the last 12 months. The reason for the 12-month time period was to avoid excluding three-year olds who had an episode of wheezing associated with a respiratory infection when they were nine months old, for example, but had not had wheezing since.

Dr. Salisbury, Department of Health, London, commented that clinical trials often exclude the very children for whom answers and protection are most needed, such as children with epilepsy. He asked what the process would be for answering questions about vaccinating children with medical conditions that put them at higher risk for influenza if they are excluded from trials. Dr. Fiore replied that the FDA indication states that safety has not been shown in those children. Dr. Englund, who had received support to study this vaccine in the recent past, added that other large studies allowed children with all kinds of underlying medical conditions, except for recurrent wheezing. Dr. Neuzil responded that there was an alternative vaccine and that a conservative approach was being taken until more information through postmarketing surveillance or other means was available. The work group has identified this group of children as a priority, along with adults 50 or more years of age and adults with other medical conditions.

Dr. Temte stated that there would probably be no problem with children seen in a medical setting. For children showing up for a standing-order type immunization, the language about the wheezing episode or asthma seems simple and elegant and would be supported by the AAFP.

Dr. Walker, MedImmune, responded to the question about race or ethnicity. The FluMist database has about 14,000 children between 24 to 59 months of age and approximately 6 percent are black. In multiple subset analyses, no age, gender, or race/ethnicity differences have been seen in terms of safety events, including wheezing. The label language negotiated with the FDA was not based on a safety signal in children with asthma, but was an effort to harmonize the label with the fact that FluMist was not felt to have been sufficiently studied in adults or children with asthma. In fact, in the head-to-head trial, FluMist versus TIV, in children 24 to 59 months of age, rates of

wheezing and hospitalizations were lower in FluMist, though the difference was not statistically significant. In the subset of children who had wheezing within the past year, which is about 13 percent of the children on the study in that age group, wheezing was numerically lower in TIV recipients versus FluMist. So there was no evidence to suggest that wheezing within the past 12 months was a proxy.

Dr. Morse asked if the committee was ready to vote. Dr. Baker moved approval of the recommendation that either TIV or LAIV can be used for healthy persons aged 2 to 49 and Ms. Stinchfield seconded the motion.

Dr. Neuzil; yes.
Dr. Judson; yes.
Dr. Lieu; yes.
Dr. Craig; yes.
Dr. Morita; yes.
Dr. Englund; abstain.
Dr. Hull; abstain.
Dr. Lett; yes.
Ms. Stinchfield; yes.
Dr. Cieslak; yes.
Mr. Beck; yes.
Dr. Chilton; yes.
Dr. Baker; yes.
Dr. Morse; yes.

VFC Vote

Dr. Wallace presented a proposal for an update of the VFC resolution for live attenuated influenza vaccine and pointed out that what had been done was to add the clarifying language of healthy children and expand the age recommendation down to two years of age, with a priority when vaccine is limited for those 2 to 59 months of age, since they are recommended to get it as a routine. When vaccine is plentiful, any child who is VFC eligible up to age 18 could get it. All the language about who should not get the vaccine was moved to the contraindication. The minimum interval between two doses has been harmonized. The LAIV contraindications and precautions are verbatim from the FDA label package insert.

Dr. Baker asked if contraindications for both vaccines would be egg allergies. Dr. Wallace confirmed that this was so.

Dr. Baker moved approval and Ms. Stinchfield seconded the motion.

Dr. Baker; yes.
Dr. Chilton; yes.
Mr. Beck; yes.
Dr. Cieslak; yes.
Ms. Stinchfield; yes.
Dr. Lett; yes.
Dr. Hull; abstain.
Dr. Englund; abstain.
Dr. Morita; yes.

Dr. Craig; yes.
Dr. Lieu; yes.
Dr. Judson: yes.
Dr. Neuzil; yes.
Dr. Morse; yes.

Influenza Vaccine Recommendations for 5-18 Year Olds: Summary of CDC-CSTE Consultants Meeting

Dr. Fiore showed the draft time frame for expanding recommendations and explained that the committee was now in the first phase, which is considering expansion to include school-aged children. Six- to 59-month-olds already have a routine annual vaccination recommendation; 2010 and 2011 is the time frame for considering expansion to contacts of school-aged children and then in 2012 to 2013, a universal vaccination recommendation will be considered. The discussion can be broken down into six critical factors: vaccine supply; vaccine effectiveness; vaccine safety; disease burden; feasibility of implementation, especially a sustained implementation; and cost-effectiveness.

In September 2007, CDC invited a diverse group of approximately 70 consultants address these issues. They included influenza researchers and epidemiologists, public health and professional organization representatives, community vaccinators, school health officials, vaccine manufacturers, and safety experts. The objectives were to review the evidence base supporting expansion of recommendations to include all school-aged children, identify key evidence gaps, identify implementation challenges and potential solutions, and discuss potential methods for assessing impact.

Plenary sessions included an update from the vaccine manufacturers, vaccine safety and effectiveness issues, disease burden in school-aged children, potential opportunities and challenges in various vaccination settings, practical experience for immunizing children of this age and evaluating impact, economic analyses, and perspectives from a variety of different organizations about resources they could bring to bear on an expansion recommendation.

Regarding the influenza vaccine supply, as many as 130 million total doses for all ages are projected over the next few seasons, with the capacity to scale up to over 200 million doses within the next five years. All estimates are subject to change, based upon the market, the selected strain-growth characteristics, and regulatory approvals.

MedImmune, which makes FluMist or LAIV, reports capacity for 20 million thimerosal-free nasal vaccine doses in 2008-2009 and 35 million doses in 2009 and 2010 or later. Thimerasol remains a barrier for some, even though there are no studies that indicate harm from this vaccine preservative. ACIP has not expressed a preference for thimerosal content in influenza vaccines.

Novartis, which makes Fluvirin, one of the TIV formulations, has the capacity for 55 million doses within five years, for all age groups. They have an increasing proportion of preservative-free, including pediatric vaccines. Sanofi, which makes Fluzone, another TIV, has the capacity for 100 million doses by 2009, all ages; an increasing proportion of these are also thimerosal-free.

GlaxoSmithKline, which makes Fluarix, FluLaval and other TIV vaccines, currently has only adult formulations on the market. However, they are planning to

introduce pediatric vaccines in the next couple of years and have the capacity for 15 to 17 million preservative-free doses for children and the potential availability of doses for 6- to 35-month-olds.

CSL had a new TIV formulation approved for adults in September 2007. The company reports approximately 2 million doses will be available this influenza season, both a multi-dose and a preservative-free, thimerosal-free, formulation. They plan to develop a pediatric vaccine and capacity for 20 million doses annually within 5 years.

Regarding effectiveness in school-aged children, most consultants thought that children develop a robust antibody response to influenza vaccine and that efficacy in this age group is good. Studies have shown it is 50 to 90 percent effective against laboratory-confirmed influenza, best in years when the antigenic characteristics of the circulating viruses are similar to the vaccine strains. Several consultants noted that yearly assessments of vaccine effectiveness would be helpful, along with studies with statistical power to show vaccine effectiveness against severe outcomes, such as hospitalization. Limited data indicate that vaccine effectiveness does not decline among children immunized over multiple years, however there are a few studies with data that extends beyond five years of immunization.

Multiple established systems monitor influenza vaccine safety in this age group, including the Vaccine Adverse Events Reporting System (VAERS); the Vaccine Safety Datalink (VSD), which now has rapid-cycle analysis capacity; and the Clinical Immunization Safety Assessment Network or CISA Network. The safety profile is expected to be good, based on current data, among children immunized over multiple years, however, the data are limited. There are also fairly limited safety data for adolescents, especially for simultaneous administration with other adolescent vaccines. Systems that capture safety data for vaccinations given outside of medical settings will have to be developed.

Regarding the burden of influenza illness among school-aged children, severe outcomes, such as hospitalization and death, are rare. There was a strikingly higher rate of hospitalization in 2003-2004 for the zero- to four-year-old age group, but overall, rates are considerably lower in 5- to 17-years-old as compared to children four and younger. There have been between 40 and 70 deaths among children reported over the past three years, average age between four and seven.

Peak influenza infection rates occur among school-aged children, most involving several days of respiratory illness with a full recovery. Data from a prospective study in a single school showed that the numbers of illness episodes, school days missed, febrile illnesses, days of work missed, and infections among household members were significantly elevated during that influenza season as compared to other parts of the winter respiratory virus season. Healthcare visits and antibiotic use did not increase significantly. However, in other studies these outcome measures increased during the influenza season compared to other parts of the winter.

Kathryn Edwards from Vanderbilt reviewed the data showing few deaths and hospitalizations among school-aged children compared to younger children, the elderly, or the chronically ill. However, there were five to seven outpatient visits per 100 children annually. In many instances, children received antibiotics, often inappropriately. There were 10 to 30 illnesses per 100 children, and they were frequently associated with school absenteeism.

Implementation questions took up a large part of the discussions , i.e., what would it take to deliver influenza vaccine to 50 and 55 million children between the ages 5 to 18 every year in the short time frame available? Several consultants noted their experiences with the current recommendations. First, approximately 50 percent of school-aged children already have an indication, because they have a chronic underlying illness or because they are contacts of persons at risk.

Second, there is inconsistent public interest in influenza vaccination and the media tend to focus on rare, severe outcomes; it is difficult to get attention for low coverage rates.

Providers and programs have been relatively slow to adopt strategies known to improve coverage, such as reminder and recall systems, enhanced access, and reducing missed opportunities. Providers and healthcare workers are not always advocates for influenza vaccination and do not necessarily get vaccinated themselves. Finally, there are formidable logistical challenges to vaccinating school-aged children. Some providers report they are near capacity to provide influenza vaccination just with the current recommendations.

Peter Szilagyi of Rochester analyzed how school-aged recommendations would impact visits to the medical home. He evaluated a strategy of vaccinating school-aged children at every well-child visit or at any clinic visit of any kind over a three-month window of time and a five-month window of time. Most 5- to 8-year-olds would require one or two additional visits since they had not been vaccinated in the past and are recommended for two vaccinations in the first year. Children ages 9 to 18 visit the medical home less often, but need only one vaccination. If all visits were used and vaccination was continued throughout a five-month-time window, about two-thirds would require an extra medical visit. While some are already indicated to get influenza vaccine, Dr. Szilagyi estimated an overall increase of 68 percent more primary care visits for 5- to 18-year-olds across the country if influenza vaccination was begun in the medical home and high coverage were to be achieved.

School-based vaccination programs are one possibility for reducing the burden on providers. Representatives from immunization programs and school health groups both noted that schools and public health share a goal of improving the lives of children, which is a basis for working together. School administrators might be intrigued by the potential benefits of reducing influenza, in that it could reduce absenteeism and would help children to be ready to learn. However, most school health infrastructures are less robust than they were 20 or 30 years ago, so considerable outside assistance would be needed. Furthermore, since schools are locally controlled, this would mean district by district uptake of acceptance of setting up vaccination programs in schools.

Knox County, Tennessee has had a school-based immunization program for the past two seasons. Most of the children received LAIV donated by MedImmune and some additional support was also provided. Each year, approximately 30,000 children were vaccinated in over 80 schools. Coverage reached approximately 50 percent in both children and faculty. This was very large and challenging undertaking but was reportedly well received by all involved.

Consultants generally felt that implementation would not be planned until recommendations were made and there would have to be low expectations for coverage during the first few years. Local solutions to implementation would vary. The medical home does not have the capacity to deliver influenza vaccinations to all school-aged

children at this point. Immunization programs and providers must maintain focus on children at higher risk for influenza complications. School systems might be interested, but they currently lack the means.

Dr. Fiore touched briefly on some of the economic issues, based on cost-effectiveness ratio estimates for the use of TIV and LAIV in school-aged children. The current strategy is to use TIV in high-risk children and the cost-effectiveness ratio measured here is dollars per QALY, or quality-adjusted life-year. For the young children who currently have a recommendation for vaccination, the ratios are fairly low. As age increases, a routine vaccination recommendation would result in cost-effectiveness ratios of over $70,000 for the 5- to 11-year-olds and over $100,000 for the 12- to 17-year-olds.

Vaccinating school-aged children also has indirect effects. The current rationale for influenza vaccination recommendations in this country is to reduce influenza and influenza complications in groups with the highest rates of severe outcomes, including hospitalizations and medical or emergency room visits and mortality, and also to provide vaccination for anyone who wants to be vaccinated. Vaccinating children to reduce transmission to contacts in the community would be a paradigm shift. There is a growing literature on reductions in illness among contacts of school-aged vaccinees in community demonstration projects. Coverage among children in these projects has typically not exceeded 50 percent. The most common model has been large-scale, school-based vaccination programs, primarily using LAIV. There has been evidence of reductions in school or work absenteeism, but reductions in severe outcomes among contacts have not been demonstrated, perhaps because of small sample sizes.

Arnold Monto, a researcher in Michigan, provided a summary of the evidence for indirect effects. Few studies are designed specifically to examine issues of indirect protection, and those have used a variety of designs, so it is difficult to use the standards applied to randomized controlled trials to interpret these results. The evidence suggests indirect protection, but it is difficult to quantify.

David Shay discussed some of the challenges to measuring direct and indirect effects after a school-aged vaccination recommendation. Historical comparisons are problematic because of season-to-season variability in influenza activity and vaccine effectiveness, patterns of circulation of specific viruses, and the timing, duration and intensity of activity for any given season. Existing community-level studies in the U.S. could be expanded and adapted to evaluate the direct impact on influenza illness in school-aged children. There is currently no easy way to estimate the community-level indirect effects; this will require multi-year studies, which are beyond current capacity. Assessments of indirect effects should include lab-confirmed outcomes, if possible, in at least a subset and data from more than one influenza season.

Several consultants noted that recommendations to vaccinate school-aged children could be justified simply by the direct benefits, even if indirect effects are unknown. Indirect effects on the contacts and community should be expected, but they might be difficult to prove. Economists noted that vaccination of school-aged children has cost-effectiveness ratios at the higher end of the range for currently recommended vaccines (in the range of $100,000 per QALY). However, current economic studies are not taking all the indirect effects into account because of difficulty getting consistent data on reductions of influenza-related illness among contacts of vaccinees.

Consultants noted that planning studies to measure impact must accompany

implementation. In Ontario, Canada, which currently has a universal recommendation, it has been hard to show impact because it was difficult to set up assessment tools at the same time the immunization program was starting up. One suggestion was that extending the interval between the recommendations vote and implementation would helpful for planning for assessments and engaging providers and the public.

In summary, school-aged children have the highest influenza attack rates and are a major source of community transmission. They respond well to the vaccine and have few adverse events. As many as 50% are already recommended for vaccination. However, school-aged children are at low risk for severe influenza complications and the cost to vaccinate per QALY saved is higher than it is for young children or for children at higher risk for influenza complications. Vaccinating school-aged children with full implementation and good coverage will be difficult to accomplish in traditional medical settings, and would require other settings. This recommendation should reduce influenza illness among contacts, but will be difficult to measure. There could be an impact on rates of influenza in the community, but these will be difficult to assess and will require multiple years of observation and careful planning of assessments.

Summary of ACIP Influenza Working Group Discussions

Dr. Neuzil said there was strong consensus within the group on the overall goal, but differences about strategies to reach that goal, which is to try to control and prevent influenza and reduce the illness and the complications from this disease. There is strong support for moving towards universal influenza vaccination, but the best strategy is still under discussion, particularly the timing of recommendation. A recommendation could drive implementation, but it could also be damaging to make a recommendation that is logistically not feasible. No one in the group felt there were critical data gaps. There was also no clear indication that more data would be available in the near term on feasibility or indirect-protection issues.

At the consultation meeting in September, practitioners said they were dealing with an unprecedented number of new vaccine recommendations: expansion of influenza, HPV, acellular pertussis, mening, and second-dose varicella. So while the working group is committed to gradually expanding the flu recommendations, practitioners and the public just see a changing strategy every year. Waiting to expand the recommendation allows time for more education and harmonization with other organizations.

The work group focused considerably on logistics. Vaccine supply was not an immediate concern. If the expanded recommendation is to go into effect next year, the time to vote would be now because providers and clinics have to order vaccine before February. Manufacturers need to know what to expect, but providers have a hard time knowing in December and January what they are will need the following fall.

A number of options have been discussed. Recommendations could be expanded incrementally to an age-limited group: 5 to 11 years. However, the group cautioned that there needed to be a consistent message about what the ultimate recommendation would be. There is already a recommendation to vaccinate anyone who wants to be vaccinated, so the “consider” option was taken off the table. The question that remains is how to make a recommendation that will drive people to prepare for implementation but still allow a more time to do that.

Discussion

Dr. Morita asked whether there were any systems beginning to respond to an eventual expanded recommendation. In Chicago some clinics are already beginning mass immunization, which sets the stage for broadening to 5- to 18-year-olds, but they will need more time. Public health is looking into working with mass immunizers in the school setting for some of adolescent vaccines.

Dr. Craig favored recommending it now and letting groups work together to catch up and implement it. Regarding school-based immunization program, he did not think schools could be counted on to provide vaccinations because of the huge amount of effort involved. Other ways such as the medical home, public health clinics, and other mass clinics would have to be used.

Dr. Baker wondered whether, if one could demonstrate a decrease in school days lost, that money could eventually support school-based immunizations and capture the adolescents and school-aged children. However, she felt the real issue was better immunization of 6- to 23-month-old children, who are at risk of hospitalization. The priority should be doing a better job of immunizing those children for whom there are good data, not a paradigm shift with a hope for indirect effects.

Dr. Lieu wanted to strongly consider making a recommendation now for implementation downstream, because current systems are still struggling to finish implementing the recommendation for the 6- to 23-month-olds and the two- to five-year-olds. While providers could be educated in the interim, it is difficult to educate people unless there is certainty that it will happen.

Dr. Judson commented that recommendations based on school-based implementation are very difficult. It takes a huge amount of effort to connect up the data systems so that the results get back to the medical home and state reporting systems. These efforts compete with No Child Left Behind and the increasing academic demands on the schools. Many school districts will not appreciate a recommendation that does not help with infrastructure and other support.

Dr. Lett added that there would not be enough publicly purchased vaccine to offer to all schoolchildren and most schools are not prepared for billing. Community vaccinators with billing systems could be a venue, either independent from school systems or perhaps in concert with them, but this is a large undertaking.

Dr. Cieslak believed that the process would never get started without an ACIP recommendation. He wondered if vaccinating schoolchildren would be just one more avenue for protecting the unvaccinated, vulnerable children. Dr. Baker said she was a believer in the indirect effects, but the committee had no data upon which to make a recommendation.

Dr. Chilton appreciated the fact that the consultants and the working group had considered logistics so heavily since the challenge of getting the immunizations to children will be major. However, it provides an opportunity to immunize those children who have medical indications and have not been getting vaccinated. He added that implementation will be largely local, not national.

Ms. Stinchfield supported the recommendation going forward as soon as possible, acknowledging the logistics are daunting. She applauded the manufacturers who had

made the great amount of doses available, but felt distribution was still inadequate.

Dr. Morse asked whether it was true that the economic estimates were made in 2002 before the publicity around deaths in children and if so, how much of an effect that could have. Dr. Fiore confirmed that the survey the models were based on was conducted before the 2003-4 season.

Mr. Beck commented that until the current plan is working properly, one cannot sign people on to a new expanded plan. The keys seem to be distribution and actual vaccination, which are not in keeping with the current amount of vaccine available and the target audience.

Dr. Schuchat appreciated the discussion about preparation and education for the programs, the providers and the public. It would be helpful for them to understand the purpose of the recommendation and the evidence upon which it is based. Dr. Neuzil agreed that there was a responsibility to report on whether goals had been met and that recommendations should be made based on the direct effects, for which there is strong evidence. If there are indirect effects, they would be a bonus.

Dr. Morita felt a recommendation could go forward with a delay in implementation, because it would help people move forward with implementing some of their current strategies. There would be value in holding off on full implementation because the systems are not yet in place.

Dr. Poland thought there were two related but separate conversations. One was about yet another incremental increase in school-aged immunizations. The other was universal immunization. Two years ago the ACIP signaled its intent to move toward a universal recommendation. There are now 16 recommendations, which is confusing for practitioners and paradoxically results in decreased immunization rates. Last year, some 12 million doses of influenza vaccine were wasted, yet manufacturers are asked every year to prepare for an increased number. The question is whether the waste will increase or whether manufacturers will scale back, creating a never ending Catch-22 cycle. There are concerns that supply will be too low to meet demand, but neither history nor the data show that to be the case. In every group for which the vaccine is currently recommended, except for those over the age of 65, immunization rates are 20 to 40 percent of those recommended to get the vaccine. The target date for a universal vaccination was 2013, but that was not based on science and logistics. He urged the ACIP to simplify the recommendation to something like, “Influenza vaccination is recommended for all eligible persons to reduce the risk of infection, subsequent complications, and transmission to others,” and then point out that there are high-risk groups for whom vaccine is particularly important. Implementation four and five years from now would have the effect of paralyzing the system, so he urged the committee to say that a universal recommendation would be in place in a year or two.

Dr. Schmader said the American Geriatrics Society supports the expanded use of flu vaccine in children as well as universal vaccination, because it may reduce the burden of influenza illness in older adults, recognizing that indirect-effect science is a bit inexact.

Dr. Tan, American Medical Association, noted that influenza is an annual vaccination and it is hard to achieve the same high coverage rates as for DTaP or a traditional pediatric immunization. It will take time to get resources in place at the local level and the ACIP recommendation is critical for moving that process forward.

Dr. Salisbury noted that the U.K. runs immunization campaigns in schools on a

one-cohort-per-year basis. These are incredibly labor-intensive activities; doing it annually is an enormous burden and hugely disruptive for schools. However it can be the best way to get high coverage. The vaccine is free, so there is no issue about who should have it or be charged. There is a great opportunity cost and local providers expect to see compelling evidence that they should redirect resources for these interventions. For primary-care providers, it is another 50 percent over the usual number of people being vaccinated over a six-week period for seasonal flu.

Dr. Grogg, American Osteopathic Association, encouraged the ACIP to move forward with a recommendation for universal vaccination, understanding all the logistics and the difficulties of administering vaccine to a large number of individuals.

Dr. Temte offered three doctrines. First, the doctrine of fair warning. Clinicians need a fair warning that this is coming. Second, simplicity. Dealing with a universal recommendation is much simpler than remembering 16 separate risk-category groups. The third component is implementation. It will be impossible to immunize everyone who should be, so just try and get as many as possible. There is probably epidemiologic evidence that getting more people immunized, regardless of who they are, has some effect on transmission.

Dr. Katz was concerned that it has not been possible to get even 35 percent of healthcare workers immunized. Education must come strongly with any recommendation.

Dr. Duchin wanted to see a national strategy that could be applied at the local level by local health agencies, in conjunction with a recommendation for a broad increase in the number of people who need to be immunized. Local health officials' support of universal immunization is based on the assumption of secondary indirect benefits and herd immunity, so there needs to be a very clear rationale focused on direct benefits to those immunized.

Dr. Gellin reminded the group that this conversation had previously been about supply and public confidence. Now it is about implementation and better measurements are needed for implementation readiness. There are plenty of outside-the-box solutions that can be considered.

Dr. Foster, American Pharmacists Association, cautioned that there were two groups driving this activity – the providers and the patients, and there has been little discussion of patients. Parents are the ones who will go out of their way to get vaccines for their children.

Dr. Tan wondered what would happen during a pandemic, if there is so much concern about implementation and logistics now.

Dr. Abramson felt it was clear that logistics was the key issue. He thought there was sufficient capacity in the medical home if vaccination clinics were set up early, before flu season.

Mr. Hosbach of sanofi pasteur pointed out that when the ACIP makes a recommendation, infrastructure, money, and action follow. Manufacturers have now produced more supply than there is demand and there will be even more next year. Whether it is universal recommendations or just the existing recommendations, they need to be better implemented Second, providers are still not paid adequately to immunize. Looking just at the VFC program, at least half the states are reimbursing physicians for administration fees of $5 or less, and CMS is involved there. This committee can have

some influence there as well. Relative to implementation, many people are still assuming100 percent uptake. Based on claims data, from September 1, 2006, through January 31, 2007, an estimated 42 million out of 58 million children ages 5 to 18, or 72%, visited physician offices. The supply is here, but it may not stay in the U.S.

Dr. Mahadevia said that MedImmune conducted an economic analysis of vaccinating school-aged children at school, in conjunction with the University of Maryland. It was a large, cluster-controlled trial that captured healthcare resource use and documented indirect effects to the family and family members. After incorporating all of these factors, it was found that vaccinating children at school may be cost-effective and even cost-saving. Several factors need to be examined that influence the economics, including mass efficiency, indirect costs associated with transmission within the home, logistical resource use, and PR campaigns.

Dr. Eisenberg, Texas Medical Association, said the recommendation has to be universal to get rid of the professional confusion. This is not a burden, it is an opportunity to change the methodology and delivery of healthcare in America, to allow medical homes to meet yearly with people and emphasize the importance of preventive measures. Regarding healthcare disparities, if the ACIP keeps making categories, the underserved and underprivileged will not get vaccinated.

Mr. Glen Moise, on behalf of Families Fighting Flu, implored that committee to move forward on the recommendation and not let logistics get in the way. It takes years for these recommendations to truly ramp up and to have effect.

Dr. Wexler, Immunization Action Coalition, pointed out that 74 percent of the population is already recommended to get influenza vaccine, so it seems like a no-brainer to move toward universal recommendation. This is a completely different vaccine. It's given every year. There's no catch-up period. We'll never get to 90 percent. We just have to do the best we can and learn by doing. There is currently a recommendation to vaccinate anybody who wants it, but reimbursement does not follow without a recommendation. More than 250 organizations support a universal recommendation for all school age children up through 18 years of age, and they want to move forward.

Dr. Baker, President of the National Foundation for Infectious Diseases, or NFID, reminded members that a little over 20 percent of children 6 to 59 months of age are getting their required two doses of influenza vaccine. NFID has organized a childhood influenza immunization coalition, which represents more than 25 professional, parent, and public health organizations. Given the low immunization rate in this highly vulnerable group, the coalition's mission is to make influenza immunization in infants, children, and adolescents a national health priority. The Web site is PreventChildhoodInfluenza.org.

Draft Guidance on Pandemic Vaccine Prioritization

Dr. Schwartz explained that in a pandemic, the goal would be to vaccinate everyone, but with current technology, it will take at least 20 weeks until the first pandemic vaccine doses become available. Even then, the U.S. vaccine-production capacity currently is not sufficient to make vaccine rapidly for the entire population. Therefore, targeting groups for earlier or later vaccination will best support national goals of reducing the health, societal, and economic impacts of the next pandemic. HHS has

invested over $1 billion to increase vaccine production capacity, develop and license new vaccine-production technologies, and evaluate adjuvanted vaccine formulations.

Mathematical modelers hypothesizing a first pandemic outbreak in Southeast Asia predict almost two months until the first U.S. case and another 80 to 120 days from the first case to the peak of the first pandemic wave, but there is substantial uncertainty with a wide range around these point estimates. It is unknown where a pandemic would begin and during which season. In 1957, the pandemic virus was first introduced into the United States in early June. Not a single community outbreak occurred until mid August, and the peak of the first pandemic wave did not occur until the end of October.

Vaccine supply depends both on U.S. based capacity at the time of the pandemic and the antigen concentration needed in each dose for good immunogenicity. For example, with candidate H5N1 vaccines, the antigen concentration in clinical trials has ranged from 3.8 to 90 micrograms, depending on the vaccine formulation, suggesting a 24-fold range in the number of doses that may be available. These uncertainties highlight the importance of a prioritization strategy.

The first effort at vaccine prioritization occurred in 2005 as a joint activity of ACIP and NVAC. This process considered vaccine supply and efficacy; the impacts of past pandemics among different age and risk groups; the potential impact on critical infrastructures, particularly on healthcare; and ethics. The priority groups were identified in four tiers with several sub-tiers. The highest priority groups included healthcare providers, high-risk individuals, and the elderly, which reflects current vaccine recommendations. Only after 100 million people had been targeted for vaccination would critical infrastructure sectors outside of healthcare and some public health responders would be targeted.

Several factors led to reconsideration of this prioritization strategy. Planning assumptions evolved from a moderate pandemic to one that was more severe, extrapolated from the 1918 pandemic, having a higher case-fatality rate and substantial absenteeism, assumed on the basis of illness as well as fear of reporting to work. In four public engagement meetings, participants indicated that it was critical to protect essential services before protecting high-risk individuals. Finally, an analysis by the National Infrastructure Advisory Council defined the critical roles and the interdependencies among critical infrastructure sectors and identified specific priority groups for vaccination.

An interagency working group was created, co-led by HHS and the Department of Homeland Security with representatives from across the federal government, recognizing that a severe pandemic would be a national emergency affecting all sectors and security and critical infrastructure issues would be a major focus. Interagency involvement in drafting the guidance helps educate those sectors and facilitates policy approval.

The working group considered prior ACIP and NVAC recommendations; scientific, public health, and ethical issues; analysis and recommendations on critical infrastructure by the National Infrastructure Advisory Council; and national and homeland security issues. Two public engagement meetings and a stakeholders meeting were held, a formal decision analysis was conducted, and comments were received in response to a Federal Register and PandemicFlu.gov notice. Other participants included representatives from CDC, ASTHO and NACCHO. There were presentations from the Department of Defense, the U.S. Secret Service, and mathematical modelers.

The working group heard from ethicists at NIH and the Minnesota Center for Health Care Ethics, who had considered vaccine prioritization issues previously. Ethical discussions included the importance of transparency and inclusiveness as well as reasonableness, which means listening to the values and priorities of the community and the public when there is no single scientific best answer. Preserving society was considered of greater importance than protecting individuals in a severe pandemic. Other key issues were fairness, valuing all life equally and treating everyone in a priority group the same way; reciprocity, defined as protecting those who assume occupational risks in order to benefit society; and flexibility, reconsidering the strategy periodically and again at the time of the pandemic.

An analysis was done of the essential functions of critical infrastructure and key resource sectors, their interdependencies, and the specific work forces needed to maintain essential functions. This would include the utilities, healthcare, and emergency services, as well as such sectors as banking and finance, chemical, food and agriculture, transportation, oil and natural gas. Results suggested that of the 85 million workers in these sectors, about 12.4 million, almost 15 percent, would be critical for maintenance of essential functions. Almost half are in healthcare; the next largest number is in the emergency service sectors, which include EMS, law enforcement, and fire protection.

Public engagement and stakeholder meetings were held to consider the potential goals of pandemic vaccination. After background presentations and discussion, participants indicated how they valued each of ten potential objectives. The public engagement meeting held in Las Cruces, New Mexico had 108 persons, many of whom were Hispanic, ranging from college students to older adults. In Nassau County, New York, about 130 persons participated, and many were older adults. The stakeholders' meeting in Washington, D.C., had over 90 representatives from government, critical infrastructure sectors, and community organizations.

The top four objectives for pandemic vaccination were the same at all three meetings: protecting people working to fight the pandemic and to provide care; protecting those who provide essential community services; protecting people who are most vulnerable due to their jobs; and protecting children. Over a quarter of those who attended the public meetings were over age 65. Even though it was made clear that older persons are at greater risk of severe disease and mortality, children were given higher priority. More than one stated that they would prefer that the vaccine be given to their grandchildren rather than themselves.

A decision analysis was conducted in collaboration with the University of California, Berkeley, and the California Department of Health. Fifty-seven different population groups were defined by their job, age, and health status, and rated by the extent to which each met the occupationally related objectives, such as providing essential services, being at risk due to their jobs, or protecting homeland or national security. CDC and external influenza experts then rated the extent to which each group met the science-based objectives of vaccine effectiveness, the risk of severe illness and death, and the likelihood of transmitting infection. Weights based on the public and stakeholder values were applied to obtain a single score for each population group. The highest ranked groups included public health responders, healthcare workers, EMS providers, law enforcement, and children, which was consistent with the public and stakeholder values and ethical principles.

The draft guidance recommends that vaccination be administered in tiers, each including several target groups defined according to the objectives of protecting healthcare and community support services, critical infrastructure, homeland and national security, and protecting the general population. Target groups are then clustered into levels, within which each of the groups has a similar priority for vaccination; each vaccination tier combines target groups across categories. In addition, there are three sets of recommendations, depending on the severity of the pandemic.

The top tier for vaccination is the same regardless of pandemic severity. For critical infrastructure, it includes emergency services, EMS, police, and fire, because these individuals will have an increased burden in a pandemic, a high risk of exposure, and little surge capacity. The second tier for critical infrastructure includes the utilities because every other sector of society depends on the maintenance of these services. The third group includes food and agriculture, banking and finance, other critical infrastructure sectors. The general population recommendations begin with pregnant women, infants, and toddlers, followed by household contacts of infants too young to be vaccinated, other children, and then high-risk adults and the elderly. In a severe pandemic, the final tier is healthy adults 19 to 64 years old.

Activities during the two-month comment period include a request for comments in the Federal Register and on the HHS Web site, presentations to ACIP and NVAC, public engagement and stakeholder meetings, as well as a Web-based public-engagement process. The group will work with infrastructure sectors to validate the population estimates and with infrastructure and public health officials to consider options for implementation. The final interim guidance will reflect the evolution of science and technology, but as more is learned, the guidance may change.

Discussion

Dr. Morse noted that comments from ACIP should be coordinated with NVAC. Dr. Schwartz replied that formal comments should be submitted before the next ACIP meeting in February.

Dr. Baker pointed out that pregnant women and children 6 to 23 months were a top priority in all scenarios and encouraged NIH to also consider those populations as priorities for their avian flu and influenza studies.

Dr. Neuzil commented that CDC and HHS and other partners were looking at antivirals and business and personal stockpiles, and that those efforts should be coordinated so that the same people who get the antivirals are not also getting vaccine. She added that ACIP had a clearly defined mandate relating to vaccine recommendations, but wondered how that would change during a pandemic. Dr. Schwarz responded that there was coordination of strategies, including for other response measures such as the use of personal protective equipment, respiratory protection, masks and respirators, as well as community mitigation and social distancing, and other strategies that will provide protection in business sectors and elsewhere before vaccine becomes available. During a pandemic, CDC will be collecting epidemiological information which it could present to the ACIP because of its experience in making vaccine recommendations, but this would clearly be a policy decision.

Dr. Plotkin pointed out that the lowest priority group was the 19- to 64-year-old

age group, which is the most productive age group. He suggested that more priority be given to those who are contributing to society rather than the elderly.

Cost-Effectiveness of Influenza Vaccination: Updated Estimates for Children Aged 2-4 Years

Dr. Prosser presented data from a study funded by the CDC-Harvard Joint Initiative in Vaccine Economics, carried out to update a previously published cost-effectiveness analysis of influenza vaccination in children, incorporating current cost estimates and adding wheezing episodes and hospitalization as possible adverse events following vaccination. The specific strategies in this analysis were vaccination with either inactivated vaccine or live attenuated vaccine compared with no vaccination.

A computer simulation was developed to estimate cost and effects for children aged two to four years. Children were divided into two age groups and stratified by their risk for influenza-related complications, resulting in four subgroups. Endpoints in the model were otitis media and non-hospitalized pneumonia. Cost and quality adjustments associated with each health state are included in the model, as well as vaccination-related adverse events.

The primary endpoint for the analysis was the incremental cost-effectiveness ratio, calculated by dividing the difference in cost under vaccination or no vaccination by the difference in events for vaccination and no vaccination. Net costs and net events averted for the different endpoints in the model weere also reported. A number of sensitivity analyses were conducted, including one-way sensitivity analyses on all parameters and a probabilistic sensitivity analysis in which all parameters were varied simultaneously.

Inputs were derived from both primary and secondary data sources and fell into four main categories: the natural history of influenza in children, effects of vaccination, costs, and adjustments for quality of life. A societal perspective was used for the analysis, and the time frame was one year, except that costs and quality adjustments for long-term outcomes such as death and long-term sequelae were included.

Each of the parameters in the model was represented by a distribution, not a point estimate. So for the probability of influenza, the base-case value for two-year-olds that are not at high risk for influenza-related complications was 0.155. The 95 percent confidence interval or the range over which this probability was varied, was .02 to .35. Probabilities varied by age and by risk group within the model.

One of the key endpoints in the model was the quality-adjusted life-year, or QALY. A QALY can be roughly described as being equivalent to a year in perfect health. Most of the health states in this simulation were temporary and modeled as the loss in quality-adjusted life-years due to a particular event. To derive estimates for the QALY losses, parents were asked about the amount of time they would be willing to trade off from their own lives to avoid an influenza illness in their child. For uncomplicated influenza illness, the mean amount of time parents were willing to trade from the end of their life was 68 days. To calculate the QALY loss, the discounted time traded was divided by the discounted life expectancy, in this case, a mean quality-adjusted life-years lost of .005 for an uncomplicated episode of influenza.

A follow-up study is currently being conducted in a national sample of

respondents, which will include hospitalization related to influenza. In the upcoming survey, four different age categories for children will be included -- 1, 5, 8, and 15 years -- and also four different age categories for adults. The pilot results from a sample size of 200 look very similar to uncomplicated influenza.

The previous analysis included systemic reaction, anaphylaxis, and Guillain-Barre Syndrome as possible adverse events to vaccination. For a live attenuated vaccine, wheezing episodes and hospitalization following vaccination have been added.

Vaccine-dose costs for inactivated vaccine included thimerosal-free vaccine for children under three and reflect 2006 purchase prices. The other costs have also been updated to 2006 dollars. For live attenuated vaccine, the costs of treating an episode of wheezing and for hospitalization following a wheezing event have been added. Total vaccination costs include cost of the vaccine dose, administration costs, and parent-time costs. It was estimated that it could take up to two additional visits for a previously unvaccinated child to receive both doses, but that others would require none or only one additional visit. Parent-time costs make up a substantial portion of total vaccination costs.

QALY adjustments have also been updated to include QALY losses for wheezing episodes and hospitalization following vaccination. The QALY loss for wheezing is equivalent to about one day of a quality-adjusted life-year lost due to a wheezing episode.

Results in terms of net costs and episodes averted were similar for inactivated and live attenuated influenza vaccine. Net costs were slightly higher for live attenuated vaccine, and averted events were also slightly higher. However, confidence intervals around these estimates were wide. Projecting these estimates for the U.S. population would result in additional costs of approximately $54 million if all eligible children aged two to four received live attenuated vaccine instead of inactivated vaccine, with an additional savings of about 250,000 influenza events averted. This assumes, however, 100 percent vaccination coverage in these groups and would be lower at the current rate.

Cost-effectiveness ratios were also similar for inactivated and live attenuated vaccine. Using QALYs as a measure of health benefit allows one to combine all the benefits from the averted episodes included in the other ratios into one number. The cost-effectiveness ratio in dollars per QALY gained is $25,000 for inactivated vaccine and $23,000 per QALY for live attenuated vaccine among 2-4 year olds, similar to results from the previous analysis. For all of the age-risk groups considered in this updated analysis, ratios were most cost-effective in the high-risk subgroups and increased with increasing age, consistent with previous analyses.

The probability of influenza illness had the greatest effect on cost-effectiveness ratios. For years in which there is little influenza illness, cost-effectiveness ratios are substantially higher. Cost-effectiveness ratios were not sensitive to the probability of wheezing or hospitalization following vaccination over the range included in the base-case analysis, so a wider sensitivity analysis was conducted to look at a very large range of probabilities of hospitalization following vaccination. The base-case rate is less than .001, and as the probability of hospitalization increases beyond .006, inactivated vaccine becomes the preferred strategy, because it becomes less costly and provides greater health benefits.

To summarize, results were similar to previously published cost-effectiveness analysis in that live attenuated vaccine had similar or better cost-effectiveness ratios than inactivated vaccine for eligible age-risk groups. The inclusion of possible new adverse

events had varying effects. Results were not sensitive to an outpatient wheezing episode, but were sensitive to a possible increase in all-cause hospitalization.

There are several limitations to this analysis. Effects of herd immunity were not considered and would likely make the cost-effectiveness ratios more favorable. Data are limited on some key assumptions, such as the probability of an outpatient visit for influenza, and results were somewhat sensitive to this parameter. Importantly, quality adjustments used for adverse events may not fully reflect the negative value some parents may ascribe to these risks, and it is hard to fully capture this in the cost-effectiveness framework.

When looking at updated cost-effectiveness ratios for all age and risk groups, cost-effectiveness varies primarily by risk status and increases with increasing age. Vaccination for non-high-risk two- to four-year-olds, therefore, yields ratios that are higher than high-risk children of all ages, but lower than those for school-aged children.

In the context of recently recommended vaccines by ACIP, cost-effectiveness ratios range from cost-saving to more than $100,000 per QALY gained, and influenza vaccination of non-high-risk two- to four-year-olds with LAIV falls within this range.

In summary, the inclusion of new adverse events has little impact on the cost-effectiveness of live attenuated vaccine, except if the probability of all-cause hospitalization is higher than reported in the trials. Consistent with previous results, LAIV was more costly but also more effective, yielding slightly better cost-effectiveness ratios than inactivated vaccines.

Pediatric Use of Pneumococcal Vaccines
Dr. Julie Morita, ACIP, WG Chair
Dr. Pekka Nuorti, CDC/NCIRD/DBD

Dr. Morita explained that the working group had reviewed the use of the pneumococcal polysaccharide vaccine in persons aged 50 to 64, the preventability of invasive disease based on current or expanded recommendations, and optimal timing and frequency of revaccination with the pneumococcal polysaccharide vaccine. For the pediatric population, the working group reviewed pneumococcal immunization in HIV-infected school-aged children and the use of the pneumococcal conjugate vaccine in incompletely vaccinated children 24 to 59 months of age. Some overlapping topics included the use of the pneumococcal vaccines during an influenza pandemic, whether or not hypo-responsiveness is an issue with multiple doses of the pneumococcal polysaccharide vaccine, and asthma without high dose corticosteriod use as a potential indication for pneumococcal vaccination.

In the coming months, the group will finalize recommendations for the use of the polysaccharide vaccine in high-risk children aged two and older who have already received the conjugate vaccine and review potential time lines for the new pneumococcal vaccines. Recommendations for changes with the conjugate and the polysaccharide vaccine will be presented in February or June.

Use of Pneumococcal Conjugate Vaccine (PCV4) in 24-59-month-old Children who are Incompletely Vaccinated

Dr. Nuorti reviewed the current ACIP language for use of PCV7 in older children as stated in the *MMWR* 2000: *"PCV7 is recommended for children aged 24 to 59 months who have certain underlying diseases or immunocompromising conditions."* A list of these underlying medical conditions is given and no revisions were to be proposed to that list itself. The ACIP statement also indicates that PCV7 should be considered for all other children aged 24 to 59 months, with priority given to children who are Alaskan Native, American-Indian or African-American descent and for children who attend group day-care centers. For children who have underlying medical conditions, the recommendation is to give a subsequent dose of the pneumococcal polysaccharide vaccine, administered two or more months after the last dose of PCV7. No changes are currently proposed for the polysaccharide vaccine recommendation.

Some immunization providers have found the current permissive recommendation confusing and frequently call the NIP Info Hotline for clarification. In addition, historically, the routine catch-up recommendation was limited to those with underlying medical conditions, partly because of concerns about vaccine supply, cost issues, and lack of data on vaccine effectiveness. The work group felt that simplifying and expanding the catch-up recommendation may improve PCV7 coverage among healthy unvaccinated or incompletely vaccinated children aged 24 to 59 months, including immigrants and adoptees from countries not using PCV7.

Data from the CDC Active Bacterial Core surveillance system on the remaining disease burden of overall and PCV7-type invasive pneumococcal disease show differences between two age groups. The rates of vaccine-type disease in two- to four-year-olds are very low. In the last couple of years, they have been in the order of 1 to 2 cases per 100,000 per year, compared to about 2 to 3 cases in the under-twos. Among 150 cases of invasive pneumococcal disease identified in 2006, only 9.3 percent had any of the underlying medical conditions that are a PCV indication. Rates of PCV7-type invasive pneumococcal disease are very low in this age group because of almost eight years of routine conjugate vaccine immunization and indirect effects. However, the working group feels there is a potential additional benefit from increased individual protection and induction of immunologic memory, and possible prolonged protection for those children who are incompletely vaccinated.

PCV7 generally is safe and immunogenic in children aged 24 to 59 months, although local reactions are more common in older than younger children. In the post-licensure population-based case-control study, vaccine effectiveness was good even for one dose of PCV given at 24 months or older; the point estimate was 94 percent with a 95 percent confidence interval from 49 to 99. In that same study, a four-dose schedule, given as three primary doses and a booster, was significantly more effective than just a primary three-dose schedule. In the 2006 National Immunization Survey, the four-dose vaccine coverage among 19- to 35-month-olds was 68.4 percent and 87 percent received three or more doses. Thus the expanded catch-up recommendation could apply to up to one-third of the children in this age group.

The working group's proposal for a revised recommendation for healthy children reads, *"At ages 24 to 59 months, administer one dose of PCV7 to healthy children with any incomplete schedule."* The revised recommendation for children with underlying medical conditions only specifies the number of previously received doses, otherwise it is

similar to what was given in the *MMWR* 2000. *"At ages 24 to 59 months, administer two doses of PCV7 at least two months apart to incompletely vaccinated children with underlying medical conditions. Those who have previously received three PCV7 doses need only one dose."*

Discussion

Dr. Baker asked what the reason was for saying two doses at least two months apart for the children with underlying medical conditions incompletely immunized. Dr. Whitney from Respiratory Diseases Branch explained that it was based on immunogenicity study data.

Dr. Pickering asked what the group's plans were for updating the 2000 *MMWR* pneumococcal publication. Dr. Nuorti replied that the plan was to merge the 1997 and 2000 *MMWR*s that related to the polysaccharide vaccine or the conjugate vaccine. Since the time line for the extended valent pneumococcal conjugate vaccines was still unclear, the plan was to revise that statement in 2008.

Dr. Cieslak noted that the incidence of disease from the seven serotypes was around 1 per 100,000 for healthy children 24-59 months and wondered if there were any cost-effectiveness data on preventing a case of illness in that population. Dr. Nuorti replied that no formal cost-effectiveness analysis had been done on this expanded recommendation. Dr. Judson added that one approach was to ask how much disease a fourth or additional dose of vaccine would prevent on a population basis and what it would cost. He suspected it might not be a favorable ratio. Dr. Nuorti responded that the recommendation would potentially apply to a rather large group of children, where the rates of vaccine-type disease are very low. The working group is making this recommendation because of the potential added benefit at the individual level and the induction of immunologic memory that may result in prolonged protection for unvaccinated or incompletely vaccinated children. The current language states that PCV7 should be considered for all children in this age group with priority given to the groups mentioned. The proposal is to move from a confusing permissive recommendation to a straightforward recommendation that would apply to all children.

Dr. Hull asked if the proposed recommendation was dropping the supplementary dose of PCV23 for the high-risk children. Dr. Nuorti clarified that the proposed recommendation about the subsequent pneumococcal polysaccharide vaccine dose for children with underlying medical conditions remained unchanged.

Dr. Lieu said she had led the original analysis of pneumococcal conjugate vaccine in 1999-2000, at which time the group looked at the cost-effectiveness of catch-up vaccination. Catch-up programs never appear to be as cost-effective as a basic recommendation. The proposed recommendation does add some vaccination, but cost should not be a huge barrier because it is one dose for children who actually are incomplete at the time. Dr. Schuchat commented that catch-up campaigns often do not seem cost- effective because the disease rates decrease. However, there is the additional factor of a phenomenal herd effect. The two- to four-year-old pre-vaccine era rates were lower than the under-two rates, and now they are almost zero.

Dr. Judson asked how many children who had received three doses and not adequately responded would do so with a fourth dose. Dr. Nuorti replied that some of the

effectiveness data from the CDC case-control study suggest that children who have received the primary three-dose series plus a booster dose show better efficacy compared with those who have only received three doses. For the conjugate vaccine booster, one of the issues is the reduction of nasopharyngeal carriage and transmission that leads to herd effects. Dr. Baker added that there is also the issue of duration of protection, because a two-four-six is done and conjugate vaccines need a booster. Dr. Paradiso commented that it matters when the three doses are given. If they are given in the first year of life without the booster dose, it is more of an issue. If the third dose is given later in life, the booster is needed less. It is about carriage in particular and long-term durability of protection.

Dr. Chilton suggested that the cost per invasive disease prevented would be about $160,000, assuming 1 case per 10,000 and that the vaccine costs $50.

Dr. Nuorti reviewed the proposed recommendation for healthy children: *"At ages 24 to 59 months, administer one dose of PCV7 to healthy children with any incomplete schedule. And for children with underlying medical conditions, at ages 24 to 59 months, administer two doses of PCV7 at least two months apart to incompletely vaccinated children with underlying medical conditions. Those who have previously received three PCV7 doses need only one dose."*

Ms. Stinchfield suggested that the first sentence begin with the words, "For healthy children," which would help providers.

Dr. Campos-Outcalt asked whether "incompletely vaccinated" meant less than four doses. Dr. Nuorti replied that it means zero to three doses. Dr. Judson pointed out that zero doses would not be incompletely immunized. Dr. Nuorti said the statement could say unimmunized or incompletely immunized.

Dr. Whitney clarified that there could be children who just received two doses, for example, after one year of age, and they would be fully vaccinated. Dr. Campos-Outcalt said that was his confusion, whether children who start late but then receive the recommended number of doses are considered incompletely vaccinated for this recommendation. Dr. Nuorti replied that when the vaccine was introduced and the recommendation initially made, there were many different schedules and children may have received the polysaccharide vaccine dose before in this category. Based on data from the National Immunization Survey, the likelihood is that most of the incompletely vaccinated children have received at least three doses, but this would also apply to those who had received fewer than three doses. Dr. Lett asked if the recommendation would still say "who are unimmunized or incompletely vaccinated for age". Dr. Wallace responded that it was not only about the number of doses, but when children get them. In the catch-up schedule, all those caveats are covered by age.

Dr. Bocchini asked whether this wording would now be consistent with the Red Book and the AAP. The Red Book currently says that for 24- to 59-month-old children who are healthy with any incomplete schedule, consider one dose at two or greater months after the most recent dose. For children at high risk, for any incomplete schedule of less than three doses, one dose greater than two months after the most recent dose and another dose two months later. For any incomplete schedule of three doses, give one dose greater than two months after the most recent dose. Dr. Morse noted that this editorial clarification should be made.

Dr. Baker moved approval of the recommendation and Dr. Craig seconded the

motion.

Dr. Hull; yes.
Dr. Lett; yes.
Ms. Stinchfield; yes.
Dr. Cieslak; no.
Mr. Beck; yes.
Dr. Chilton; no.
Dr. Baker; yes.
Dr. Morse; yes.
Dr. Neuzil; yes.
Dr. Judson; no.
Dr. Lieu ; yes.
Dr. Craig; yes.
Dr. Morita; yes.
Dr. Englund; yes.
Dr. Morse: The motion carried.

Meningococcal Conjugate Vaccine (MCV4)
Dr. Carol Baker, ACIP WG Chair
Dr. Thomas Clark, CDC/NCIRD/DBD
Dr. Greg Gilmet, sanofi pasteur
Dr. Amanda Cohn, CDC/NCIRD/DBD
Dr. Greg Wallace, CDC/NCIRD/ISD

Introduction

Dr. Baker reviewed MCV4, or Menactra quadrivalent meningococcal conjugate A/C/Y/W-135 vaccine, which was licensed in 2005 for use in those 11 through 55 years of age. There was an ACIP recommendation for use in these age groups, a routine recommendation for adolescents in certain cohorts, and a recommendation that MCV4 would be preferred in those at increased risk of disease. College freshmen who will be living in dormitories and patients with functional anatomic asplenia are considered at increased risk. The first cohort was routine use in 11- to 12-year-old adolescents. This was the first vaccine for the "adolescent platform." The second cohort was at high-school entry or age 15, based on the epidemiology suggesting an increased attack rate in this group. Because of a number of factors, it was changed in June 2007 to all adolescents not previously immunized with MCV4. The meningococcal polysaccharide vaccine is currently recommended for children two to ten years old at increased risk of disease.

Since the recommendation was published, there have been three *MMWR* publications on Guillain-Barré syndrome and MCV4, one *MMWR* on inadvertent administration where vaccine was given subcutaneously rather than intramuscularly, two notices to readers on supply, and one notice to readers on the revised recommendation (all adolescents 11 through 18 years of age). On October 18, the FDA licensed MCV4 or Menactra in two- to ten-year-olds.

Update: Meningococcal Vaccine Safety

Dr. Clark reminded the committee that Guillain-Barré syndrome (GBS) is a subacute onset demyelinating neuropathy characterized by bilateral flaccid paralysis. It is thought to have an autoimmune etiology. In about 50 percent of cases, a precipitating cause can be identified. In 15 to 40 percent of those, the cause is usually Campylobacter with other post-infectious etiologies in decreasing frequency. Some cases in the past have been vaccine associated. No clear seasonality has been observed in Western countries, but incidence increases with age and there is a suggestion recently of a decreasing secular trend in the United States. Relative to adults, children have an improved prognosis with roughly half ambulatory at six months, 70 percent ambulatory at one year, and 3 to 4 percent mortality.

During the 1976/A/New Jersey/Swine Flu mass-vaccination campaign, vaccine was provided for most of the U.S. adult population and at-risk children, but the program was halted following a number of reports of GBS following vaccination. Later studies confirmed an association between this vaccine and GBS, with an attributable risk estimate in six weeks following vaccination ranging from 4.9 to 11.7 cases per million vaccine recipients. Subsequently, the Institute of Medicine reviewed data and determined that the evidence favored a causal relationship. The epi curve of the association shows a clustering in the two to three weeks following vaccination and peaking at a relative risk of about 15.

In the 1978-'79, '79-'80, and '80-'81 seasons, there was no observed association of influenza vaccination with GBS. During the '93-'94 vaccination season, GBS case reports increased, and a case-control study was conducted, looking at the '92-'93 and '93-'94 seasons. Individually, there was no statistically significant association of GBS with vaccines, but for both seasons combined, there was a relative risk of 1.7 and the 95 percent confidence interval just crossed 1, which translates to about one excess case per million vaccinees. The IOM subsequently concluded that the evidence in these cases was inadequate to accept or reject a causal relationship. The ACIP has chosen to manage this risk by saying that, while there may be an association in some seasons, the measured magnitude of the risk is small and the potential benefits of influenza vaccination in preventing serious illness, hospitalization, and death substantially outweigh estimates of risk for vaccine-associated GBS.

In the U.K. all 1- to 20-year-olds were vaccinated with Serogroup C meningococcal vaccines, with no substantially increased incidence of Guillain-Barré syndrome. In ten years of reviewed experience with MPSV4 in the U.S., there was one case.

As of October 2997, 24 vaccine-associated cases have been reported to VAERS, reviewed and categorized according to Brighton criteria; 22 of those were among 11- to 19-year-olds. From the VSD Rapid Cycle Analysis, which includes over 213,000 doses of conjugate vaccine administered, there were zero observed cases among 11- to 19-year-olds within six weeks of receipt of vaccine; the expected number ranges from zero to one.

The Brighton GBS classification criteria use increasing evidence for Guillain-Barré syndrome to classify cases in increasing levels of certainty. The clinical case definition just includes the subacute flaccid paralysis or cranially nerve innervated muscles effected. The third or lowest level includes some other clinical characteristics. The second level includes the illness pattern as well as cyto-albuminologic dissociation

on CSF, and the most definitive or Level 1criteria include EMG findings.

When medical records of the 22 cases were reviewed, 32 percent met Level 1 criteria; 64 percent, Level 2; and 4 percent, Level 3. Among the 22 cases, 45 percent were male, 55 percent had received conjugate vaccine alone, and 86 percent were hospitalized. Among the 21 with evidence in the charts, nine had been hospitalized in intensive care. One patient was intubated, three were plasmapheresed, and 18 received IVIG as treatment. Among the 19 that were hospitalized, 15 were ambulatory at the time of discharge. eight had disability affecting activities of daily living, and 5 were discharged to inpatient rehab treatment. Looking at cases by month of onset, there was no significant increase in reports after licensure in January 2005, but the October 2006 *MMWR* reported on 17 cases and since then there have been more five cases.

The epi curve of doses of vaccine distributed shows that in October 2006 there were 17 cases out of about 6.5 million doses. Since then, distribution of doses has increased significantly, so that 22 cases in 11.5 million doses have been reported. Looking at timing of onset, there is a statistically significant cluster between Days 9 and 16, with 13 cases in that interval. Currently, among 11- to 19-year-olds, 22 reported cases results in an incidence ratio of 1.3, with a confidence limit that crosses 1. That is roughly 0.4 excess cases per million doses of vaccine. Twenty of the cases are in 15- to 19-year-olds, where the incidence rate ratio is 1.7 with a confidence interval just above 1. That is 1.3 excess cases per million doses of vaccine.

To do a sensitivity analysis, the study varied the incidence rate ratio by cases underreported and by doses not administered. The 1.7 incidence rate ratio assumes 100 percent reporting and 100 percent doses administered. Varying either of those to 70 percent results in an incidence rate ratio of 2.4, while varying either to 50 percent results in an incidence rate ratio of 3.4. Dropping both to 50 percent results in an incidence rate ratio of 6.7. The worst-case scenario would result in 11 excess cases per million vaccinees.

Next a probabilistic decision analysis was conducted, using a cohort-simulation model that compared health outcomes in a full meningococcal vaccination program to no meningococcal vaccination, including an associated risk of Guillain-Barré syndrome. An 11-year-birth cohort of 4.1 million persons was modeled over an eight-year period, using the patient perspective. Health outcomes included cases of meningococcal disease and GBS; deaths; life-years lost; and quality-adjusted life-years lost, or QALYs. Parameters and assumptions included 5 percent long-term morbidity associated with GBS among adolescents and a GBS incidence in unvaccinated persons of 1.4 per 100,000. These were taken from Vaccine Safety Datalink and Healthcare Utilization Project, and an incidence of GBS in vaccinated persons estimated by VAERS reports, which was roughly 1.8 per 100,000 at the time. For meningococcal disease, vaccine efficacy was estimated at 93 percent, based on the U.K.experience and a disease rate in unvaccinated persons of 0.77 per 100,000. A disease incidence in unvaccinated persons of 0.05 was used, calculated using the vaccine efficacy. An age-specific case fatality ratio was applied per year of life, averaging out to 10.34 percent.

In a probabilistic model, the range of values for the parameters varies, each with an associated probability. The lower bound of the GBS incidence in this case in vaccinated persons was 1.4 and the upper bound was three times 4.2 cases per 100,000, which results in five excess cases of GBS over the cohort or an attributable risk of

roughly 1.25 per million. Full vaccination compared to no vaccination prevented 359 cases of meningococcal disease and 35 deaths, and overall, full vaccination prevented 2,254 QALYs lost.

In a sensitivity analysis on the decision analysis, the variability of GBS incidence in vaccinated persons was increased to include a relative risk of 6.7. The 6.7 was taken as the 75th percentile, and so the risk actually was varied above that. That risk ratio is equivalent to an incidence of 9.5 per 100,000. Full vaccination resulted in ten additional cases of GBS in the cohort, compared to no vaccination, pointing to roughly ten excess cases out of a million doses. This change in GBS incidence resulted only in a small reduction in prevention of QALYs lost: from 2,254 to 2,247. In other words, changes in the attributable risk of GBS from vaccine result only in small changes in the outcomes,and the model, as a whole, continues to strongly favor vaccination.

In summary, the estimated excess risk from VAERS remains unchanged in analyses and so publication of these data are ongoing. The clinical outcomes observed were typical, not substantially worse than reported in the literature. Excess risk was comparable to that seen in some prior seasonal influenza vaccines, and vaccination is favored, even with larger magnitude of risk from the decision analysis. A large controlled study being conducted by the Harvard Pilgrim Medical System to assess a potential causal relationship between GBS and Menactra.

Immunogenicity and Safety of Menactra (MCV4) in 2- to 10-Year Old Children

Dr. Gilmet presented the results of four large Menactra clinical trials in children: a pivotal safety and immunogenicity single-dose comparative study of Menactra versus Menomune; an immune-memory response study two to three years after Menactra priming in young children ages two to three years; an evaluation of boosting with Menactra in infants in the U.K. who were previously primed with men-C conjugate vaccine; and a large-scale safety study performed in the U.S. and Chile.

The overall safety profile of Menactra compared to Menomune for immediate, local, and solicited systemic reactions was very comparable. Unlike adolescents, in whom local reactions were somewhat higher with Menactra than Menomune, this was not the case in these two- to ten-year-olds. No vaccine-associated serious adverse events were reported in either study group. Most events reported were mild to moderate in intensity. The percentage of vaccinees with localized pain was nearly identical in the two groups, most solicited systemic reactions were mild, with comparable percentages of fussiness, drowsiness, and fever, and all events were reported to be transient in nature.

Regarding immunogenicity, when the geometric mean titers at Day 28 post vaccination for Serogroup C were broken down by age, there was an apparent increase in the immune response with increasing age, a characteristic shared with other conjugate vaccines. Menactra responses exceeded those of Menomune at all ages, often to a considerable degree.

Comparing the seroconversion rates of Menactra versus Menomune in two- to ten-year-olds (seroconversion defined as individuals with titers less than 1 to 8 at baseline who achieve a titer greater than or equal to 1 to 32 at Day 28 post vaccination), Menactra was statistically superior to Menomune across all four vaccine-containing serogroups. There were high seroconversion rates for both vaccines across the two-to-ten age

spectrum, but the performance of Menactra was better than that of Menomune in the youngest age groups, and seroconversion rates were high in the youngest children.

Looking at geometric mean titers for Serogroup C at baseline, Day 28, and six months post vaccination with Menactra versus Menomune, a superior response is observed in Menactra at one month post vaccination, which persists at six months.

In summary, the Menactra safety profile was comparable to the Menomune standard of care. Seroconversion rates were 86 to 99 percent in children vaccinated with Menactra at Day 28. For all four serogroups, Menactra produced significantly higher serum bactericidal antibody geometric mean titers than did Menomune at Day 28, and the superior immune response persisted out six months post vaccination.

The recent broadened ACIP recommendation in 11- to 18-year-olds led to an increased uptake of Menactra this past summer. However, supply has been able to keep up with increased demand, and there is now a modest surplus, which will continue to grow and permit consideration of further program expansion in 2008 and beyond. The company is actively studying Menactra in infants and toddlers, which presents a future opportunity to more broadly immunize the population and replicate the recent success seen in the U.K. and the Netherlands with men-C conjugate vaccination programs.

Proposed Recommendations for Use of MCV4 in 2-10 Year Old Children at Increased risk of Meningococcal Disease

Dr. Cohn noted that meningococcal disease causes 1400 to 2800 cases of meningitis or sepsis per year in the United States. The case-fatality rate is 10 to 15 percent, even with proper treatment. Ten to 20 percent of survivors have permanent sequelae, such as limb loss, neurologic disability, or hearing loss.

Certain groups at increased risk for meningococcal disease have been recommended to be routinely vaccinated with meningococcal vaccine. Among two- to ten-year-olds, this includes children with functional or anatomic asplenia, terminal complement deficiencies, and travelers to areas where N. meningitidis is hyperendemic or epidemic. HIV-positive children are likely at increased risk for meningococcal disease although not to the extent that they are at risk for streptococcal infections. Two- to ten-year-olds may be at increased risk for disease due to organizational or communitywide outbreaks. There are about 70,000 persons with sickle cell anemia in the U.S., one of the primary causes of functional asplenia. Only a fraction of these individuals are two to ten years old. The incidence of asplenia is unknown. During 2001 to 2004, there were an estimated 1,000 children under 13 with HIV in the U.S. So it is likely that no more than 20,000 doses of meningococcal vaccine given to high-risk children in this age group in a given year.

Meningococcal polysaccharide vaccine is currently recommended for persons two to ten years old and over 55, who are at increased risk of meningococcal disease. This vaccine has been used since the 1970s and is safe and effective in persons two years or older. However, bactericidal antibodies titers drop two to three years after vaccination, especially in young children.

The quadrivalent meningococcal conjugate vaccine, MCV4. includes polysaccharides for Serogroups A/C/Y/W-135, conjugated to 48 micrograms of diphtheria toxoid. Conjugate vaccines elicit a T-cell dependent response, which produces

memory B-cells. Conjugate vaccines should provide longer duration of protection than polysaccharide vaccines.

In the prelicensure clinical trial comparing MCV4 to MPSV4, all subjects received four doses of DTaP prior to vaccination, and the mean subject age was 3.7 years. Over 80 percent of subjects were between two and five years old. For all serogroups at 28 days and six months, the serum bactericidal antibodies titers, which are considered a correlate of protection, were higher in the MCV4 group compared to MPSV4.

Looking again at geometric mean titers at Day 28 post vaccination in two- to ten-year-olds, the number of children in each single age year is small, especially in the older age group. MCV4 is comparable or superior to MPSV4 for each single age year. However, similar to MPSV4, SBA titers increase with increasing age in MCV4-vaccinated children, with maturation of the immune system. No single measure correlates to long-term protection, but using boostability, there is not a substantial difference in the magnitude of the immune response in two- to three-year-olds between these two vaccines.

The clinical trial also compared safety. There were no serious adverse events in either group. Of the MCV4 reactions, 91.4 were mild or moderate, and 98.8 percent of the reactions in MPSV4 recipients were mild or moderate. All reactions resolved without sequelae, and MCV4 recipients experienced more severe local reactions than MPSV4 recipients.

One additional study looked at booster responses of four- to five-year-olds who were vaccinated at two to three years old with MCV4 and compared them to vaccine-naive children two or three years later. All subjects received a challenge dose to one-tenth of a dose of MPSV4 to simulate exposure. SBA titers were tested at baseline and eight days after MPSV4 challenge in the MCV4-primed and the MCV4-naive group. While the numbers are small, for all serogroups, the MCV4-primed subjects had significantly higher geometric mean titers than the vaccine-naive group. A booster response was exhibited two to three years after vaccination with MCV4. However, the titers at baseline two to three years after MCV4 vaccination are low, especially for Serogroup C.

In summary, immunogenicity from MCV4 is noninferior in two- to ten-year-olds compared to MPSV4. Safety profiles are similar. Two- to three-year-olds have a booster response on challenge two to three years after vaccination. The titers prior to the challenge are low. Most children at increased risk for meningococcal disease are at lifelong increased risk, which will make revaccination necessary.

The meningococcal working group proposes recommendations for the use of MCV4 in high-risk two- to ten-year-olds, with draft wording as follows: *"For children two to ten years with increased risk of meningococcal disease, MCV4 is preferable to MPSV4."* The following line would address revaccination of children previously vaccinated with MPSV4. *"For children two to ten years old who previously received MPSV4 and remain at increased risk for meningococcal disease, ACIP recommends vaccination with MCV4 three to five years after receipt of MPSV4."* Background rates of Guillain-Barré syndrome are lower in two- to ten-year-olds compared to older adolescents. The following precaution would be included in the notice to readers. *"Persons with a history of GBS may be at increased risk of GBS after MCV4. Therefore, a history of GBS is a precaution to receiving MCV4."*

Discussion

Dr. Cieslak asked whether the immunogenicity studies were done in the population with functional or anatomic asplenia or other high-risk groups. Dr. Cohn said they were not.

Dr. Craig asked whether neurologists were comfortable with the diagnosis levels of Guillain-Barré syndrome. Dr. Clark responded that the case definitions were still evolving, but the fact that the great majority of cases were Level 2 or 1 seemed to be significant. Dr. Craig said that if Level 2 were uncertain, then some cases might be Level 3, and then there would be fewer GBS cases associated with this vaccine.

Dr. Iskander commented that in discussions of the use of the Brighton collaboration case definition for the controlled study, the consulting neurologist had the opposite concern and feared that requiring any level might, in fact, exclude certain atypical presentations. Dr Baker thought that the use of plasmapheresis and IVIG suggests that the people taking care of these children are convinced that they have Guillain-Barré, even though there may be misdiagnosed variants.

Dr. Judson asked how the phrase "not substantially increased" should be interpreted by clinicians or providers. Dr. Clark clarified that the risk of GBS is not substantially increased. The current influenza statement, for example, says that current estimates of the risks of vaccine are not outweighed by the effects of disease. Dr. Baker noted that people need to clearly understand the disease burden per 100,000 vaccinees vs. per million doses. Dr. Clark added that prior GBS is listed as a precaution among all vaccine recipients, not just those at high risk for disease.

Dr. Lewis pointed out that the first statement, about children with increased risks getting MCV4 preferably, begs the question of what happens when that child turns 11. There needs to be some statement to say whether or not they need to be vaccinated with the MCV4 again. Dr. Cohn replied that it is not yet known if and when that child will need to be revaccinated. There could be language such as "ACIP will provide future recommendations." Dr. Lett felt the notice to readers should specifically mention the risks and the benefits of vaccination.

Dr. Katz asked how practioners would interpret the statment that Guillain-Barré syndrome is a "precaution to receiving MCV, " as opposed to a contraindication. Dr. Iskander clarified that precautions involve situations in which the benefits may outweigh the risks, whereas in a contraindication the risks always outweigh the benefits. The basis for saying this was a precaution was that one of the original five cases reported was a third episode of Guillain-Barré syndrome following different vaccines, all with similar intervals.

Dr. Halsley was bothered by estimates that only 50 percent of the product distributed had been administered. Ten to 20 years ago, the estimates of vaccine wastage were as low as 10 percent, maybe 20 percent for the traditional low-cost vaccines. He suggested that the data be refined before publication to avoid creating false impressions about the potential rates or risk ratios. Dr. Wallace agreed, but noted that with some of the new adolescent vaccines, there was a tendency to over-buy in the beginning and that rates improve over time. Dr. Clark added that analyses done through ISO allow at least more than the 42-week risk window for cases to occur and be reported and doses not to

sit on the shelf, so there is really a two-month delay in reporting of rates.

Dr. Plotkin asked if the working group considered induction of tolerance as another reason for preferring the conjugate vaccine. Dr. Baker replied that there had been a fairly robust review of the literature on tolerance and the polysaccharide vaccines due to mening. Dr. Stephens added that the issue was not necessarily tolerance, but rather hypo-responsiveness. There is responsiveness with multiple doses of polysaccharide, but less with repeated doses. However, the data still suggest protection with the polysaccharide. Dr. Cohn pointed out that studies have shown the polysaccharide vaccine continues to be effective in high-risk individuals with terminal complement deficiencies.

Dr. Pickering asked about the statement that bactericidal titers drop at two to three years. Dr. Gilmet's presentation showed that at six months antibodies titers were still significantly different, but very low. He wondered if the assumption was that titers after two to three years for both vaccines are fairly similar and that the real benefit in this age group would be the immunological memory or lack of tolerance. Dr. Cohn replied that titers had not yet been reviewed sufficiently for MCV4, but that the boostability data are supportive of MCV4 providing a longer duration of protection than MPSV4.

Dr. Duchin asked whether the wording for the precaution regarding administration of Menactra to persons with a history of GBS was based on a single case. Dr. Iskander replied that it had more to do with ACIP influenza vaccine wording. In the manufacturer's package insert, GBS is listed as a contraindication, but CDC wants to keep it as a precaution. Dr. Duchin asked if the committee could provide some background on what is known about immunization among people who have a prior history of GBS. Dr. Iskander replied that the Clinical Immunization Safety Assessment network was currently moving forward with a protocol to accumulate clinical information on those cases.

Dr. Cohn then reviewed the proposed recommendation*: "For children two to ten years old with increased risk of meningococcal disease, MCV4 is preferable to MPSV4. For children two to ten years old who previously received MPSV4 and remain at increased risk for disease, ACIP recommends vaccination with MCV4 three to five years after receipt of MPSV4. Persons with a history of GBS may be at increased risk of GBS after MCV4. Therefore, a history of GBS is a precaution to receiving and MCV4."*
She proposed adding "*No vaccine provides lifelong protection. Therefore, revaccination will likely be necessary. ACIP will provide recommendations for revaccination when more data on duration of protection becomes available."*

Dr. Baker suggested saying "*No conjugate vaccine provides lifelong protection."*

Dr. Neuzil moved that the committee vote on the proposed language. Dr. Baker seconded the motion.

Dr. Judson said he assumed there still was not an understanding of how to interpret the declining geometric mean titers in terms of efficacy. Because meningococcal disease has a short incubation time, there may not be the same effect as when there is time for an anamnestic response to occur with boosting. If the recommendation is re-vaccination three to five years after receipt, ACIP would be erring on the side of caution without any real supporting data.

Dr. Baker suggested it would be clearer to recommend immunization after three years, rather than three to five years. Dr. Decker noted that the current recommendations call for these children to receive polysaccharide vaccine every three to five years, but

clinicians will inevitably ask whether children who previously got the polysaccharide should now get the conjugate.

Dr. Chilton asked whether there were any data on what happens when children get multiple doses of conjugate vaccine. Dr. Cohn replied that the working group had not yet reviewed data on second doses of conjugate vaccine. Dr. Baker clarified that there are data on the polysaccharide, but that data on durability of the conjugate in a variety of situations are not yet available.

Dr. Cohn then suggested the following wording: *"No conjugate vaccine provides lifelong protection. Therefore, revaccination will likely be necessary, and ACIP will provide recommendations for revaccination when more data on duration of protection become available."*

Dr. Decker wondered if would be better to say "bacterial" rather than "conjugate", since many viral vaccines are believed to give lifelong protection. Dr. Orenstein remarked that since ACIP does not recommend revaccination for any conjugate vaccine right now, it would better to say the duration of protection is not known. The ACIP will continue to evaluate and will make recommendations for revaccination, should it be necessary. Dr. Cohn agreed, but pointed out that children at high risk will continue to be so for life and that revaccination will be different for this group than for children who are just at increased risk for a certain period of time. Dr. Cohn suggested removing the language "*No conjugate vaccine provides lifelong protection. Therefore, revaccination will likely be necessary"*.

Dr. Salisbury noted that no breakthrough meningococcal disease has been seen the U.K. childhood population that was vaccinated in 1999-2000, albeit just with a meningococcal C conjugate. Meanwhile, there is probably remarkably little transmission, so they may not be exposed to risk, but the catch-up done probably displaced the meningococcal C.

Dr. Lewis expressed concern about what happens to an eleven-year-old who got MCV4 at age nine without any guidance about revaccination. Dr. Messonier said that the context for today's vote was an exceedingly small group of very specific two- to ten-year-olds who are at high risk because they do not have spleens. Discussion of the larger issues will be continued in February. Dr. Baker pointed out that the most recent adolescent statement says "All adolescents not previously vaccinated."

Dr. Decker noted that the antibody levels produced by Menactra are very comparable, age by age, to those produced by the U.K.-licensed mening C vaccines, with similar durations of antibody. The big difference is hitting the whole population at once versus doing it incrementally.

Dr. Morse asked the committee to vote on the motion on the floor to accept the proposed recommendations minus the first bullet on the revaccination.

Dr. Englund; abstain.
Dr. Morita; yes.
Dr. Craig; yes.
Dr. Lieu; yes.
Dr. Judson; yes.
Dr. Neuzil; yes.
Dr. Morse; yes.
Dr. Baker; yes.

Dr. Chilton; yes.
Mr. Beck; yes.
Dr. Cieslak; yes.
Ms. Stinchfield; yes.
Dr. Lett; yes.
Dr. Hull; abstain.
The motion passed with two abstentions.

Dr. Wallace presented the VFC recommendation for a vote. He explained that the purpose of the resolution was to add the expanded age indication just discussed. Under the polysaccharide vaccine, an eligible group was added and those who may have a precaution or a contraindication for the conjugate vaccine were included.

For the conjugate vaccine, the priority for certain ages based on supply was removed since that issue is resolving. For the high-risk groups, 'adolescents' has been changed 'children and adolescents' and age has been lowered to two years. There is still the routine recommendation for ages 11 to 12, as well as those who are 13 to 18 and have not been previously vaccinated. For the recommended schedule, it has been lowered to two years of age. In some instances, if the polysaccharide has been given previously, revaccination is recommended. Currently the conjugate vaccine is only a single-dose recommendation.

Discussion

Dr. Judson asked whether the recommendation should say N. meningitides or meningococcal disease. N. meningitidis is really endemic or hyperendemic in many populations that do not experience high rates of disease. Dr. Messennier agreed that the sentence that says "in countries where Niceria meningitidis is endemic or epidemic" should say "meningococcal disease". Dr. Wallace said the recommendation targeted people going to countries, predominantly in Africa, that have high rates of disease and that a change could be made. Dr. Decker asked whether the vaccination was given only if the country currently has an outbreak. Dr. Schuchat explained that the meningitis belt of Africa is always included. Other areas that are having outbreaks would also be added.

Dr. Craig moved approval of the recommendation and Ms. Stinchfield seconded the motion.

Dr. Neuzil; yes.
Dr. Judson; yes.
Dr. Lieu ; yes.
Dr. Craig; yes.
Dr. Morita; yes.
Dr. Englund; abstain.
Dr. Hull; abstain.
Dr. Lett; yes.
Ms. Stinchfield; yes.
Dr. Cieslak; yes.
Mr. Beck; yes.

Dr. Chilton; yes.
Dr. Baker; yes.
Dr. Morse; yes. The motion passed with two abstentions.

Considerations for Routine Use of MCV4 in 2-10 Year Old Children

Dr. Cohn presented some issues the working group has been discussing around routine use of MCV4 in two- to ten-year-olds, to prepare for an ACIP vote in February 2008. They included the burden of disease in two- to ten-year-olds, duration of protection provided by MCV4, and programmatic considerations for vaccination in the two- to ten-year-old age group.

The national passive surveillance system known as NETTS receives case reports from all 50 states. A graph of the incidence of meningococcal disease in the United States from 1970 to 2005 shows a cyclical waxing and waning pattern, with peaks typically every eight to ten years. The case-fatality rate decreased in the 1970s, but has remained stable at around 10 percent since the 1980s.

ABCS is an active laboratory and population-based surveillance system composed of ten geographically dispersed sites. Excluding Oregon, which had an ongoing Serogroup B disease outbreak and higher rates of disease than in other states, since 1996 incidence of meningococcal disease has been on a downward cycle. Serogroups B, C, and Y each cause approximately one-third of meningococcal disease in the United States. The incidence of Serogroup C and Y, which are contained in MCV4, have decreased more than Serogroup B and since 2002, Serogroup B disease has caused the highest disease incidence. There is currently no vaccine available for Serogroup B.

There are two peaks of meningococcal disease among children and adolescents: one in infancy and early childhood and the second in late adolescence. The 11- to 12-year-olds routine MCV4 recommendation targeted that adolescence rise. Disease rates in two-year-olds are around 1 per 100,000, the same as in 18- to 19-year-olds. However, rates drop quickly after age two and overall rates among two- to ten-year-olds are lower than in 11- to 19-year-olds.

Fifty-four percent of cases of meningococcal disease are vaccine preventable in two- to four-year-olds, through either Serogroup A, C, Y, or W-135, compared to 75 percent of cases among 11- to 19-year-olds. The case-fatality rate in young children, while still higher than other infectious diseases, is lower than in older age groups. The case fatality rate is five percent for two- to four-year-olds and ten percent among five- to ten-year-olds.

Excluding serogroup B and based on a small number of cases, there are an estimated 160 potentially vaccine-preventable cases among two- to ten-year-olds per year in the U.S, which is about one-third fewer than among 11- to 19-years-old. The same number occurs among a much smaller cohort of children less than two years old. The burden of disease in two- to ten-year-olds is relatively lower than in other age groups, and 25 percent of disease is in two-year-olds alone. A lower proportion of disease among two- to ten-year-olds is vaccine preventable compared to older age groups.

Unlike other causes of bacterial meningitis, meningococcal disease has a second peak in risk in late adolescence and therefore requires longer protection. Conjugate vaccines should have a longer duration of protection than polysaccharide vaccine, given

that serum bactericidal antibody titers in the younger children receiving MCV4 were not substantially higher than in children who received MPSV4. The working group fears a single dose in two-year-olds will not provide protection through late adolescence. There are no routine vaccines currently recommended at the two-year-old visit. Several vaccines are recommended in four- to six-year-olds, but the timing of this vaccination visit is after the elevated disease risk in this age group. The 2006 National Immunization Survey Teen Module showed MCV4 coverage was only 11.7 percent among 13- to 17-year-olds, which is not surprising given the short time between the recommendation and the survey.

In summary, the meningococcal working group continues to evaluate data on the use of MCV4 in two- to ten-year-olds. Vaccinating captures only the cusp of increased disease in infants and toddlers. A safe and effective vaccine given in younger infants or toddlers would have more impact on disease burden. Duration of protection is unknown. An infant or toddler vaccine that would protect through late adolescence is ideal, but more likely, revaccination will be necessary. Implementation of a vaccine recommendation in this age group may be challenging because the only established vaccination visit is at four to six years old, not the ideal time for vaccination based on burden of disease.

The working group has a wide range of opinions on the option of a permissive statement for vaccination of two- to ten-year-olds. FDA licensure is already permissive. A permissive recommendation from ACIP would have implications for insurance reimbursement and VFC coverage. It may cause confusion, but would ensure provider and parent choice. The group is planning to present recommendations on routine use of MCV4 in two- to ten-year-olds at the February 2008 ACIP meeting and ask for a vote at that time. Vaccines for infants and young toddlers may be available in the United States in the near future and Serogroup B vaccines are in development.

Discussion

Dr. Neuzil was curious to know the definition of "the near future," regarding vaccines for infants and young toddlers. Dr. Friedland reported that GlaxoSmithKline was currently in Phase III development for an infant vaccine with meningococcal Serogroups C and Y in combination with Hib vaccine. Dr. Bann said that Novartis Vaccines was also in Phase III trials with an infant A/C/Y/W-135 conjugate vaccine. Dr. Decker from sanofi pasteur commented that no manufacturers were willing to predict when FDA will license something, however, two years seems a little optimistic and five years would be sadly pessimistic. His company presented its infant-toddler clinical trial results to the working group, and expects to present more data.

Dr. Morse asked if there was information on carriage rates in the two- to ten-year-old age group versus the adolescent group, and whether they might serve as a reservoir. Dr. Cohn replied that studies suggest carriage is actually higher in adolescents than in younger children.

Dr. Lieu felt that a decision might revolve around the projected benefits vs. projected costs. When the committee voted on meningococcal conjugate vaccine for adolescents, it already was one of the vaccines with the highest cost-effectiveness ratios, i.e., the most costly for quality-adjusted life-year saved. If the incidence of disease is

lower in two- to ten-year-olds and a booster will probably be required downstream, it would be interesting to hear about plans for analysis of that issue before coming to a vote. She added that the question of how quickly immunity wanes was really crucial and where those assumptions come from would be very important in sensitivity analyses.

Dr. Hull asked whether recommending a vaccine at age two would require an additional visit. Dr. Bocchini of the AAP said there was already a routine two-year-old visit recommended, but no routine immunizations are given at that time. Dr. Chilton said that New Mexico experienced a marked drop-off in completion of immunizations after one year of age. However, of those who continue to be seen, a large proportion is seen at age two and there are recommendations for other preventive care at age two. Dr. Grogg added that people tend to come in if there is a vaccine to be given, so he encouraged the use of vaccination for screening purposes. A lot of important things, such as speech, are picked up at age two.

Dr. Lewis said that a study of health-plan patients, specifically around 15-month vaccine recommendations, found that about 70 to 80 percent attended the one-year visit and nine percent came to a 15-month visit.

Childhood and Adolescent Immunization Schedule
Dr. Angela Calugar, CDC/CNIRD/ISD

Dr. Calugar presented the final draft immunization schedule for persons aged zero through 18 years for the year 2008. The process for updating the schedule included collecting data from immunization providers, summarizing data from NIP Info, presenting the working group's comments and suggestions to subject-matter experts, and presentation of a preliminary draft to ACIP in June, with a vote in October. There might be some additional work on the immunization schedules' charts and footnote pending the ACIP vote on updated and/or new recommendations presented by other ACIP WGs during the October meeting. On the schedule, yellow bars denote the range of recommended ages, green bars represent catch-up immunization and purple bars are designated for high-risk groups.

Changes to the schedule for ages zero through six years include the following: There will be no green catch-up bars for hepatitis B and Hib vaccines, because providers found it confusing having catch-up recommendation in the routine schedules. However, a new line was incorporated at the top of the page: *"For those who fall behind or start late, see the catch-up schedule."* There is no PCV purple bar for two- to five-year-olds and only the PPV purple bar remained; this should eliminate confusion expressed by providers about pneumococcal vaccination in high-risk groups. In anticipation of the new MCV4 recommendations, MPSV4 was changed to mening-conjugate vaccine, MCV4, for the two- to six-year-olds, with a purple bar for high risk. Finally, there is additional wording under the chart: *"Providers should consult the respective ACIP statement for detailed recommendations including for high-risk conditions."* The referenced URL takes readers to the ACIP Web page with all the resources.

Regarding the footnotes for this age group, for the hepatitis B birth-dose paragraph, the last bullet reads, *"If mother is HBs-AG negative, the birth dose can be delayed in rare cases with provider's order and a copy of the mother's negative HBs-AG*

laboratory reports in the infant's medical record." PCV now reads, *"At ages 24 through 59 months, administer one dose of PCV to incompletely vaccinated healthy children and two doses of PCV at least eight weeks apart to incompletely vaccinated children with certain high-risk conditions. Administer PPV for children age two years and older with certain high-risk conditions."* For the mening vaccine, the footnote says, *"Administer MCV4 to children aged two to ten years with terminal complement deficiencies or anatomic or functional asplenia and to certain other high-risk groups. Use of MPSV4 is also acceptable."*

The influenza footnote required extensive revision related mainly to FluMist. Minimum age now starts with two-year-olds, and the minimum interval between the doses is four weeks; previously, it was six weeks. Overall, there are five bullets on the influenza vaccine for ages zero through six years. First, "*Administer annually for children aged 6 through 59 months and to close contacts of children aged zero through 59 months*. Second, "*Administer annually to children five years of age and older with certain risk factors and to other persons, including household members in close contact with persons in groups at higher risk, and to any child whose parents request vaccination."* Third, "*For healthy persons, those who do not have underlying medical conditions that predispose them to influenza complications, ages 2 through 49 years, either LAIV or TIV may be used."* Fourth, "*Children receiving TIV should receive 0.25 mL if aged 6 through 35 months or 0.5 ml if age three years or older."* And finally, *"Administer two doses separated by four weeks or longer to children younger than nine years who are receiving influenza vaccine for the first time or who were vaccinated for the first time last season, but only received one dose."*

The proposed schedule for ages 7 through 18 years also has the new sentence in the title, *"For those who fall behind or start late, see the catch-up schedule."* Ages 13 through 18 are combined in one column. For mening vaccine, 11- to 12-year-olds are covered by the routine immunization (yellow bars) and 15 through 18 years by catch-up green bars. This makes Menactra's presentation in the schedule similar to Tdap and HPV series. In addition, the purple bar for seven- to ten-year-olds now has MCV instead of MPSV4. And finally, under the immunization chart, the ACIP URL has been incorporated.

Proposed footnotes for ages 7 through 18 years included changes to mening and influenza vaccines. Meningococcal vaccine says: *"Administer MCV4 at ages 11 to 12 years and age 13 through 18 years if not previously vaccinated. Administer MCV4 to previously unvaccinated college freshmen living in dormitories. MPSV4 is an acceptable alternative."* For influenza vaccine, the footnote was reworded for clarity and consistency with the updated recommendations for zero through six-year-olds.

The current catch-up schedule is split in two age groups, ages four months through six years at the top and 7 to 18 years at the bottom. There was an error for the TD/TDaP ages 7 to 18 years. Under Column Dose 2 to Dose 3, it should say four weeks.

Changes to the catch-up footnotes are consistent with the routine schedule for ages zero through six and 7 through 18 years, such as updates for pneumococcal conjugate vaccine, PCV. The new wording is: *"At ages 24 through 59 months, administer one dose of PCV to incompletely vaccinated healthy children and two doses of PCV at least eight weeks apart to incompletely vaccinated children with certain high-risk conditions."* The following sentence was deleted: *"PCV is not generally recommended*

for children aged five years and older," after consulting with the subject-matter experts. For inactivated polio virus vaccine, IPV, a new sentence was added as a stand-alone bullet: *"IPV is not generally recommended for persons aged 18 years and older."*

Discussion

Dr. Chilton noted that the draft still did not say what to do with a child who has received two doses of influenza vaccine previously in separate years. Dr. Neuzil responded that ACIP voted last year to harmonize with the AAP recommendation that if a child had a single dose, then the following year, he or she should get two doses. Dr. Wallace added that if a child only gets one dose the first year and one dose the second year, ACIP is not recommending two doses the third year. Dr. Atkinson provided additional clarification, in that he had been saying publicly that if a child got one dose, skipped a year and then came back the following year, that two doses were indicated, but that is not true. The two-dose rule is only applicable in either the first or the chronologic subsequent year. So if a child got one dose one year and one dose the next year, it is still only one dose from the third year forward.

Dr. Campos-Outcalt thought it was simpler to say that any child under age nine who has not had two previous doses needs two doses. Dr. Wallace explained that these recommendations had been made by the influenza working group and that any changes in wording would have to be done by that group.

Dr. Judson pointed out that a number of situations had no long-term immunogenicity and efficacy data for different dosing regimens. He asked whether the immunogenicity and efficacy data were supportive of the last statement. Dr. Neuzil explained that the main point made in the working group was that if children are younger than nine, they need two doses the first year they receive vaccine. Seventy percent of young children are not getting any flu vaccine. If people are still confused, the working group can work on it.

Dr. Cieslak asked whether a 12-month-old was supposed to be given DTaP, and whether there was any reason that the bar does not go back to 12 months. Dr. Wallace explained that the wording reflected the ACIP recommendations, which say the time to give it is 15 to 18 months, but then adds the compromise language. Dr. Calugar added that providers should be reading the footnotes when they have additional questions. When working on the immunization schedule, the ACIP WG was considering only published recommendations or preliminary ones that were voted by the ACIP and posted on the ACIP Web site but not yet published in the MMWR.

Dr. Campos-Outcalt asked what the potential consequences might be of disseminating ACIP recommendations that have not yet appeared in an *MMWR*. Dr. Calugar replied that publication of all ACIP recommendations in the *MMWR* is a lengthy process and some are followed by the vote on the VFC resolution as well. Dr. Campos-Outcalt suggested noting that these were preliminary recommendations on the schedule. Dr. Schuchat noted that the more important issue was that the child, adolescent, and adult schedules are updated every year. In general, timing of final publication in *MMWR* is slow and unpredictable, but the provisional recommendations need to correspond with VFC votes and complete information needs to get out as quickly as possible to programs, practitioners, and insurance plans.

Dr. Whitley-Williams suggested adding a statement in the schedule about revaccination, particularly under MCV4. There is now a cohort that has been immunized and is approaching college years.

Dr. Duchin asked if it was possible to say recommendations were "approved and voted on but not yet published", because "provisional" gives the impression that they are liable to be changed prior to publication. Dr. Pickering explained that approval of recommendations is a four-stage process, involving a lot of clearance. Now it takes nine months or more, but a method for shortening the process is being investigated. However, the provisional recommendations are posted and are rarely changed, except for minor wording. The ACIP is an advisory committee and CDC has to give the acceptance, which requires clearance. Dr. Schuchat added that the ACIP is the sole authority for inclusion of a vaccine in the Vaccines for Children program and the decision is active the day of the vote.

Dr. Tan noted that the difference in timing between the provisional recommendations from ACIP and the publication in *MMWR* causes payment delays for private physicians.

Dr. Lewis noted that the DTaP fourth dose had a specific recommendation for 15 months, but that the fourth dose on all of the CPT or HEDUS rates is consistently the one that drops off. One of the biggest issues is not having it at 12 months and making that not look permissive.

Dr. Wexler expressed concern about the hepatitis B catch-up bar dropping off for the 19-month to six-year-olds, because there is no longer an indication that zero to 18-year-olds should be vaccinated. That used to be in the footnotes, but there's no green bar that serves as a reminder. The catch-up table often isn't reproduced when the schedule is reproduced. Dr. Calugar explained that immunization providers in the field had found the green bars confusing and that the fewer colors there were on the schedule, the more they could focus on routine immunization. However, there is a permanent reminder at the top of the page for those who fall behind or start late to see the catch-up schedule.

Dr. Wexler's second concern was about the permissive recommendation for influenza and hepatitis A. Hepatitis A vaccine can be given to any child up the age 18, and it should be considered, and influenza can be given to any child up through age 18. However, there is no indication on the table that these are permissive recommendations. It looks like it is only for high-risk people and many people might be advised that it is not recommended for them. Dr. Calugar pointed out that the current schedule's footnote says that hepatitis A is recommended for all children aged one year. The two doses in the series should be administered at least six months apart. Children not fully vaccinated by age two can be vaccinated at subsequent visits. Hepatitis A is recommended for other groups of children, including in areas where vaccination programs target all the children. It is as inclusive as possible and it corresponds with the current published recommendation. It is not possible to override the existing *MMWR*, but it can be discussed in the working group for next year's schedule.

Dr. Plotkin asked about the import and basis of the statement that IPV is not generally recommended after the age of 18 in the catch-up schedule. Dr. Calugar explained that it reflected the package insert. Dr. Plotkin noted that it was probably an historical remnant from the Red Book that may still apply to OPV, but does not apply to IPV. He asked whether a 19-year-old going to Northern Nigeria should have IPV. Dr.

Wallace replied that this was not a travel recommendation. Dr. Plotkin then asked whether an Amish person who hasn't had polio vaccine before could have IPV. Dr. Wallace clarified that there was not a routine recommendation that all 18-year-olds and older should be getting IPV. Dr. Hull suggested saying that it is not routinely recommended, but would be permitted in infrequent cases. Dr. Wallace said that extensive word-smithing could eventually be a problem in terms of harmonizing with AAP and AAFP. He said he would be fine with getting rid of the IPV statement all together. Dr. Pickering clarified that in The Red Book, the AAP only deals with those up to 18 years of age, but there is a section on vaccine recommendations for adults that says IPV can be given.

Ms. Johammer from the California Department of Health Services Immunization Branch said the Web site links on the schedules were not terribly helpful. Most people just refer to the schedule displayed on their walls, so it would be more helpful to have a simple Web site address like www.cdc.nip, which people could remember.

Dr. Morse asked if there was a motion to approve the schedule. Dr. Baker so moved and Dr. Chilton seconded the motion, as did Dr. Morita.

Dr. Baker; yes.
Dr. Chilton; yes.
Mr. Beck; yes.
Dr. Cieslak; yes.
Ms. Stinchfield; yes.
Dr. Lett: yes.
Dr. Hull: If I can vote, yes. Otherwise, abstain.
Dr. Englund; yes.
Dr. Morita; yes.
Dr. Craig; yes.
Dr. Lieu; yes.
Dr. Judson; yes.
Dr. Neuzil; yes.
Dr. Morse; yes.

Combination Vaccines
Ms. Patsy Stinchfield, ACIP WG Chair
Dr. Greg Wallace, CDC/NCIRD/ISD
Dr. Wayde M. Weston, GSK

Update: Combination Vaccines Working Group

Ms. Stinchfield explained that the working group had reviewed two new products. The BLA for Sanofi Pasteur's Pentacel four-dose primary series has been done, but FDA requested additional information, which resulted in an extension of the review clock. Kinrix, the GlaxoSmithKline biological, was reviewed in anticipation FDA licensure.

The group plans to revise the 1999 *MMWR* statement on the use of combination vaccines for discussion and approval by the ACIP. One of the statements under review says, "*Combination vaccines should be used to minimize the number of injections children receive, and are practical for starting immunization series for children who are*

behind schedule." Other issues include when extra doses would be justified, the benefits and risks of administering the combination vaccine with an unneeded antigen, including the reactogenicity of the inactivated vaccine, the interchangeability of formulations and of vaccines from different manufacturers and the impact on reimbursement policies. There are also monitoring issues, such as safety, efficacy, and coverage.

The group will look at the impact of using combination vaccines on the immunization schedule and potential programmatic, administrative, and financial burdens on private providers in the current vaccine market. It will review the issue of expressing the level of preference of combination vaccines versus single-antigen ones and identify any circumstances when single-antigen vaccines should be strongly considered, considered, or preferred.

Impact of Combination Vaccines

Dr. Wallace said that a child gets 34 to 36 injections through age five or six years of age and then showed the CDC series costs and the private-sector costs, which is really a catalog cost. Comvax decreases the number of injections by two, but not the price, and when adhering to the birth dose of hepatitis B, there is an extra dose of this antigen. Using TriHibit for the fourth dose reduces the number of shots in the series by one. For Pediarix, DTaP/HepB/IPV, there is a greater reduction in the number of shots and a modest increase in price. ProQuad, which currently is not available on the market, but is a licensed vaccine, also decreases the number of shots by two with the new recommendation for varicella vaccine, and the price is comparable. If approved, Pentacel will provide the greatest decrease in the number of shots, but there is an additional IPV dose; price is not yet known. Pediarix and Kinrix would also decrease the number of shots and this combination has the same additional HepB that Pediarix has on its own.

Dr. Wallace then discussed the distribution of doses since 2000 and the market impact. Some shortages were not captured by the annual data presented. When the new combination vaccine, Pediarix, was introduced, the total DTaP market increased, but then as the new combination vaccine gradually increased its market share, the others decreased. There was quite a bit of sequential catch-up with hepatitis B, but as the Pediarix market increased, the Comvax market went down. The same trend was seen in the IPV market. The monovalent Hib vaccine market share actually went up when Pediarix was introduced. Even though Pediarix does not have Hib, it displaced some of Comvax market. MMRV was introduced in 2006, coinciding with the new two-dose recommendation; there is currently a shortage, but it is expected to come back. MMR, having more of a market share than just the pediatric indication, initially went down with MMRV, while varicella stayed stable.

In conclusion, combination vaccines decrease the number of required shots, but do not markedly increase the total vaccine cost. Other costs may occur, such as storage, reimbursement or administration, however there may also be opportunity costs. Changing markets are dynamic and somewhat unpredictable and can be influenced by a number of factors. Combination vaccines may complicate schedules, particularly for catch-up; registries can be very useful for that. On the other hand, combination vaccines may improve coverage and this needs more quantitative data. They may lead to some

extra doses, which should not be an issue. Finally, combination vaccines can complicate targeting and maintaining pediatric vaccine stockpiles.

Immunogenicity and Safety of Kinrix (Combination DTaP-IPV Vaccine) in Children 4-6 Years of Age

Dr. Weston from GlaxoSmithKline explained that Kinrix received its first global licensure in 1996 in France and is currently licensed in 31 countries worldwide. A BLA application was filed on April 6th, 2007. Kinrix is intended for use as a fifth dose of DTaP vaccine and fourth dose of IPV in children four to six years of age. Current recommendations are for up to five vaccinations to be given to children in this age group; DTaP and IPV account for two of these. Combining DTaP and IPV vaccines into a single vaccine reduces by one the number of injections required to provide the recommended immunizations to this age group and should increase overall coverage and timeliness. The DTaP antigen components of Kinrix are identical to those of GSK's Infanrix and Pediarix vaccines in the same quantities and the IPV components are identical to those of Pediarix in the same quantities.

The pivotal Phase III Study 048 was conducted in the U.S. in 2005-2006. It included more than 4,000 children, over 3,000 of whom received Kinrix as the study vaccine. Primary objectives included assessments of safety and immunogenicity as well as manufacturing lot consistency. Immunogenicity and safety were also investigated in a Phase II Study 047 in 2003 and 2004. This study provided information on the immunogenicity of a co-administered MMR vaccine. Additional safety information comes from a small Phase II study conducted in Australia, Study 046. Subjects in all studies were healthy children four to six years of age, who had had four prior doses of Infanrix and three doses of IPOL vaccine in their first two years of life. They were randomized to receive either one of three manufacturing lots of Kinrix or separately administered Infanrix and IPOL vaccines. All subjects also received concomitant MMR vaccination according to age-specific recommendation.

The study was open label with regard to combination or separate vaccine receipt. The lot assignment for Kinrix was given double-blind. Safety and reactogenicity assessments were conducted on all subjects in Study 048. Immunogenicity assessments were conducted on a subset of study subjects whose parents agreed to have their children provide blood samples. All subjects received vaccinations on designated Day 0. They were then contacted by phone four to six days after vaccination to collect reactogenicity observations. Subjects who were participating in the immunogenicity analysis had a second study visit one month after vaccination for collection of blood samples and safety information. Subjects who were not part of the immunogenicity analysis got only a phone contact to collect safety information. Finally, all subjects were contacted by phone approximately six months after vaccination to collect long-term safety information.

The primary objectives were to demonstrate non-inferiority of Kinrix to Infanrix given with IPOL with respect to booster responses to DTaP antigens and post-vaccination geometric mean titers for IPV antigens. In addition, Study 048 included a consistency comparison of the three manufacturing lots of Kinrix used. Secondary objectives were evaluation of booster responses and post-vaccination antibody concentrations or titers for all Kinrix antigens compared to Infanrix and IPOL, as well as evaluation of

immunogenicity of the MMR vaccine co-administered with Kinrix compared to co-administration with Infanrix and IPOL in the Phase II 047 study.

For safety, in the Phase III 048 trial the primary objective was to determine non-inferiority of Kinrix to the Infanrix plus IPOL combination with respect to increased circumferential swelling at the DTaP injection site. Secondary objectives in all studies were evaluation of safety and reactogenicity in terms of solicited local events, i.e., injection-site pain, swelling, redness, and increased arm circumference; solicited general events, that is, fever, drowsiness, and loss of appetite; unsolicited adverse events and SAEs.

Demographic data from the Phase III 048 study show that all treatment groups were similar to each other and to the total study population in terms of sex, racial and ethnic characteristics, and age. All study objectives with respect to lot consistency were achieved.

Data were presented on serum antibody concentrations for anti-D and anti-T antibodies and percentages of subjects with antibody concentrations greater than or equal to one, which represents a seroprotective level. Serum GMCs increased many-fold following vaccination and proportions of subjects with antibody values exceeding the cutoffs given approached 100 percent following vaccination with either Kinrix or separately administered Infanrix and IPOL. Serum GMCs for pertussis toxoid, filamentous hemagglutinin, and pertactin increased many-fold following vaccination with either vaccine.

The primary immunogenicity comparisons for the diphtheria, tetanus, and pertussis components of the vaccine were based on booster responses. Both study groups showed a high booster response rate for both D and T antigens. Both treatment groups also showed high booster response rates for all pertussis antigens.

Looking at the non-inferiority comparisons for DTaP booster responses, the between-group difference and percentage of subjects with booster responses were determined for each vaccine component. Non-inferiority was defined as the upper limit of the 95 percent confidence interval for the treatment difference being less than or equal to 10 percent. That criterion was met for all DTaP antigens.

Focusing on polio virus responses, Dr. Weston showed the increases in percentages of subjects with seroprotective levels (titers of one to eight or greater) of anti-poliovirus Types 1, 2, or 3 antibodies. Most subjects had seroprotective levels of one or more antibodies prior to vaccination. Following vaccination, all subjects were seroprotected for all three poliovirus types except for a single subject in the Kinrix group who was not seroprotected for Type 1 poliovirus. Antibody titers for anti-poliovirus were similar prior to vaccination and increased many-fold following vaccination. For the non-inferiority comparison for poliovirus GMTs, the upper limit of the 95 percent confidence interval for all three ratios was less than the predefined limit of 1.5, so the study was also able to conclude non-inferiority of Kinrix to IPOL with respect to immunogenicity of the poliovirus components.

The immunogenicity of co-administered MMR vaccine with either Kinrix or separately administered Infanrix and IPOL vaccines was examined in the Phase II Study 047. Reverse cumulative concentration curves were determined for measles, mumps, and rubella antibodies when vaccine was co-administered with either Kinrix or separate Infanrix and IPOL. For all three antibodies, the RCC curves were indistinguishable,

showing no apparent difference in MMR immunogenicity whether administered with Kinrix or separate Infanrix and IPOL vaccines.

Reactogenicity data focused on solicited local events, that is, pain, redness, swelling, and increased arm circumference occurring at the DTaP-based injection site within four days of vaccination. Injection-site pain was the most commonly reported local event, reported by 57 percent of subjects in the Kinrix group and 53 percent in the coadministered Infanrix and IPOL group. This difference was found to be statistically significant. Grade 3 pain, that is, pain sufficient to prevent normal daily activities, was reported by 1.6 percent of Kinrix recipients and 0.6 percent of Infanrix plus IPOL recipients. This was also a statistically significant difference. No difference was observed on reporting of pain resulting in a medical contact. For all other solicited local events, no clinically or statistically significant differences between groups were observed.

Limb swelling has been observed in association with the whole cell and acellular pertussis vaccines. Two categories of swelling events were defined: large injection-site swelling and increased circumferential swelling. Large injection-site swelling was defined as greater than 50 millimeters, or an increase in arm circumference greater than 30 millimeters relative to pre-vaccination measurement, or a diffuse swelling, not measurable, but interfering with normal daily activities. If a large swelling reaction was noted, the parent was instructed to notify the study site and to bring the child in for further assessment. The incidence of large swelling was relatively low and similar between the treatment groups: 8.4 percent in the Kinrix group and 9.5 percent in the Infanrix and IPOL group. In the majority of cases, intensity was considered mild to moderate, and most events resolved within 48 hours.

Increased circumferential swelling, or ICS, was defined as a measure of clinically significant or severe swelling and as the basis of a non-inferiority comparison between the vaccines. The study defined it as a swelling that involved more than 50 percent of the upper arm length and that had a greater than 30 millimeter increase in upper arm circumference relative to the baseline measurement. The incidence of ICS was determined in both groups and the treatment difference between the groups was determined with a 95 percent confidence interval. Non-inferiority was defined as the upper limit of the 95 percent confidence interval for the group difference being less than or equal to two. In the Kinrix group, 0.6 percent of the recipients displayed increased circumferential swelling, whereas one percent of those in the Infanrix plus IPOL group had swelling meeting the criteria for ICS. This gives a treatment difference of minus 0.41 percent with the upper level of the 95 percent confidence interval on the difference being 0.16. This is less than 2 percent, which enables a conclusion of non-inferiority of Kinrix to Infanrix and IPOL with respect to association with increased circumferential swelling.

Regarding the incidence of solicited general symptoms within four days of vaccination, i.e., drowsiness, fever, and loss of appetite of any or Grade 3 intensity, no clinically or statistically significant differences between the treatment groups were noted. Unsolicited adverse events and SAEs were reported by comparable proportions of subjects in both groups. There were no fatalities reported during the study, no clinically relevant differences between groups, and the reporting of unsolicited AEs was noted. No SAEs reported were considered to be causally related to vaccination.

In conclusion, the data show that immune responses and reactogenicity were comparable between the groups receiving Kinrix vaccine and receiving Infanrix co-administered with IPOL. No differential effect on immunogenicity of a co-administered MMR vaccine was noted between Kinrix and Infanrix plus IPOL groups. Kinrix is expected to provide protection comparable to Infanrix and IPOL, with one fewer injection required.

Discussion

Dr. Englund asked whether the studies had looked for pre-existing diphtheria or the impact of diphtheria antibody to explain the large amount of entire limb swelling seen. Dr. Weston replied that no comparison was made on the basis of prior diphtheria or tetanus antibodies. The study did look at subjects who had a large swelling reaction or a whole-limb swelling reaction to a prior dose of DTaP-containing vaccine, and found no association between prior reaction to a DTaP vaccine and current incidence of a larger increased circumferential swelling. The incidence of large swelling was comparable to what has been seen in previous literature.

Dr. Neuzil said she assumed that Kinrix was given in one arm, and Infanrix in the same arm and polio in the other arm, so the comparison where more pain was seen with the Kinrix was just based on the arm that DTaP was given in. Dr. Weston confirmed that this was so.

Dr. Katz asked whether any studies had been done of Kinrix as primary immunization for vaccine-naive children who might just get the DTaP and IPV as their primaries. Dr. Weston answered that no such studies had been done or were planned.

Dr. Turner asked about the charts showing the number of shots saved and what the age cut-off was. Dr. Wallace replied that it was through the four- to six-year-old preschool visit.

Dr. Englund asked whether any children had had a previous large limb swelling in the past and noted that this might be a safety question. Dr. Weston said that some children had, but he could not give exact numbers or percentages. Dr. Wallace added that CDC looked at the incidence of whole-limb swelling among those who had gotten all Infanrix or all Tripedia. No difference was found in antibody levels either. He felt the cause would probably be cell mediated rather than immune globulin levels.

Dr. Chilton commented that currently the administration fee given to practitioners is dependent on the number of shots, not the number of antigens, so many pediatricians must decide whether to spare pain or to earn more money. Dr. Wallace said that issue had already been identified and that there had also been discussions about CPT codes and the amount of education required.

Dr. Morse wondered whether combination vaccines made it easier or more complicated when patients move around frequently.

Dr. Judson asked if the studies had concluded that the IPV component had no reactogenicity. Dr. Weston replied that he had not presented those data because DTaP was generally considered the more reactogenetic vaccine. The incidence of any pain associated with the DTaP injection site was similar to the proportion of patients reporting any pain at any injection site. With Kinrix, there is no separate IPV site. In the separate Infanrix and IPOL group, about 30 percent of all patients reported pain at the IPV site.

So looking at the 53 percent of subjects reporting pain at the DTaP injection site, about half that number also reported pain at the IPV site. Dr. Judson noted that the confidence intervals largely overlap and that for all other indications of inflammation or reactogenicity, the GSK combination seemed to be less reactogenetic. Dr. Weston replied that there did not seem to be increased reactogenicity for redness, swelling, or increased arm circumference with the addition of the IPV to the DTaP. A little additional pain was reported.

Immunization Schedule for HIV-infected Adults
Dr. Gina Mootrey, CDC/NCIRD/ISD

Dr. Mootrey explained that the concept of an immunization schedule for HIV-infected adults came out of a request from the CDC-NIH- IDSA working group to revise the guidelines for prevention and treatment of opportunistic infections in HIV-infected persons. The working group started with the adult immunization schedule approved in June by this committee, and modified it with input from ACIP's HPV working group, CDC subject-matter experts for each of the specific vaccines, and the opportunistic infections guidelines workgroup.

Yellow bars mean the indication is for all persons in the category who meet the age requirements and who lack evidence of immunity; the purple bars indicate the recommendation if some other risk factor is present. The title was changed from "Recommended Immunization Schedule" to "Immunization Schedule." The order of the vaccines was changed in order to put those that have an actual indication for use first, i.e., influenza, pneumococcal, and hepatitis B. The zoster vaccine is not on this schedule.

Regarding influenza vaccine, the indication is only for the trivalent inactivated vaccine, and the bar is yellow for all of the age groups. For pneumococcal polysaccharide vaccine and hepatitis B, it is also yellow for all age groups for this schedule. There are no changes for the tetanus, diphtheria, pertussis vaccine. For the HPV vaccine, the number of doses was removed and it just says three doses for females, which allows some flexibility if there is licensure of an additional vaccine before there is a new schedule. MMR vaccine and varicella vaccines are yellow for all ages, and include the words, "Do not administer to severely immunosuppressed persons." This is consistent with the childhood schedule indications. For hepatitis A vaccine and meningococcal vaccine there were no changes. The box that describes the schedule now includes a phrase stating that it has been adapted for HIV-infected persons.

There were a number of footnote modifications. For influenza vaccination, the list of medical, occupational, and other indications was removed because there is specific language saying that it is indicated for HIV-infected individuals and the other indications really were not necessary. It mentions that LAIV is contraindicated, and wording about household contacts. The list of medical and other indications for pneumococcal vaccination was removed for the same reason. It was reworded to focus on HIV-infected persons, noting that there could be better efficacy with higher CD4 counts.

Trivalent inactivated vaccine for influenza is specifically mentioned. LAIV is contraindicated, and vaccination of persons who are household contacts or caregivers for persons with HIV is recommended. Either TIV or LAIV may be used for those individuals.

Pneumococcal polysaccharide vaccine is recommended for immunosuppressive conditions, including HIV. The phrase "Vaccination should take place as close to the time of diagnosis as possible" will be removed. For revaccination with pneumococcal vaccine, the language now just says for persons greater than or equal to 65 years, a one-time revaccination if they were vaccinated five or more years previously and were less than 65 at the time of primary vaccination. For pneumococcal vaccine, the footnote says it is recommended for HIV-infected adults and better efficacy is anticipated for persons with higher CD4 and T-lymphocyte counts.

The hepatitis B footnote has some additional language. Vaccination is recommended for all adults with HIV infection. The vaccine series consists of three doses given at zero, one to two, and four to six months. The addition is *"Humoral response to hepatitis B vaccination might be reduced in persons with HIV infection. Modified dosing regimens, including doubling the standard antigen dose or administering additional doses, have been found to increase response rates. However, limited data regarding response to these alternative vaccination schedules are available."*

There is also new language on post-vaccination testing. *"Post-vaccination testing is recommended for susceptible HIV-infected persons. Testing should be performed one to two months after administration of the last dose of the vaccine series, using a method that allows determination of a protective concentration of anti-HBS greater than ten. Persons found to have anti-HBS concentrations of less than ten after the primary vaccine series should be revaccinated. Administration of three doses on an appropriate schedule followed by anti-HBS testing one to two months after the third dose usually is more practical than serologic testing after one or more doses of vaccine."*

For Tdap there are currently no changes shown on the schedule, but there has been a suggestion to delete the text related to pregnancy because it was not sufficiently HIV focused.

In the HPV vaccination footnote, the language has been changed from "Not specifically recommended for females" with the medical conditions phrase, to "Not specifically recommended for females with HIV infection." Language was added that there are no data in HIV-infected persons. "One of the four" was changed to "one or more of the HPV-vaccine types" and a phrase was added for the quadrivalent vaccine.
The footnote now reads, *"Although HPV vaccination is not specifically recommended for females with HIV infection, it is not a live-virus vaccine and can be administered. However, the immune response in vaccine efficacy might be less than that in persons who are immunocompetent. There are no data in HIV-infected persons at this time."*

Other changes include: *"Vaccination is less beneficial for women who have already been infected with one or more of the HPV-vaccine types,"* and then in the last paragraph, *"For the quadrivalent HPV vaccine, a complete series consists of three doses. A second dose should be administered two months after the first, and the third dose should be administered six months after the first."* The only change there is the addition of the word "quadrivalent."

For the MMR footnote, an indication has been added for HIV-infected persons who have CD4 T-lymphocyte counts greater than or equal to 200 cells per microliter. In addition, there is an indication to withhold measles-containing vaccines from HIV-infected persons with severe immunosuppression and language was added regarding

vaccination of close contacts of HIV-infected persons. So the footnote now says. *"MMR vaccination is recommended for all asymptomatic HIV-infected persons with a CD4 T-lymphocyte count greater than or equal to 200 cells per microliter who do not have evidence of severe immunosuppression and for whom measles vaccination would otherwise be indicated. MMR vaccination should also be considered for all symptomatic HIV-infected persons who do not have evidence of severe immunosuppression. Withhold MMR or other measles-containing vaccines from HIV-infected persons with severe immunosuppression. All family and other close contacts of HIV-infected persons should be vaccinated with MMR vaccine unless they have acceptable evidence of measles immunity."* This language is from the ACIP-MMR statement.

For the varicella vaccination footnote, the lengthy discussion of evidence of immunity was removed, and language was added on vaccination of HIV-infected adults with CD4 T-lymphocyte counts greater than or equal to 200 cells per microliter, which were taken from the June varicella ACIP recommendations. It now reads, "*HIV-infected adults without evidence of immunity may be considered for varicella vaccination -- two doses, three months apart -- provided they are not severely immunocompromised. Limited data from HIV-infected children aged one to eight years indicated that the vaccine was well tolerated and that greater than 80 percent of subjects had detectable immune response at one year after immunization. Data on the use of varicella vaccine in HIV-infected adolescents and adults are lacking. However, on the basis of expert opinion, the safety of varicella vaccine in HIV-infected persons aged greater than eight years with similar levels of immune function, meaning CD4 T-lymphocyte count greater than or equal to 200 cells per microliter, is likely to be similar to that of children aged less than or equal to eight years. Immunogenicity might be lower in these groups compared to children one to eight years."*

For hepatitis A vaccine, the language now reads as follows: *"If the combined hepatitis A and hepatitis B vaccine is used, administer three doses at zero, one, and six months or four doses at 0, 7, 21 to 30 days, and 12 months."* The suboptimal response with lower CD4 counts is mentioned. The word 'lower' was used because there was a difference of opinion about what specific T-lymphocyte count to mention.

For meningococcal vaccine, language was added on the conjugate and polysaccharide and revaccination, now reading as follows: *"Patients with HIV infection are likely at increased risk for meningococcal disease, although not to the extent that they are at risk for invasive strep pneumonia infection. Persons with HIV infection can elect to receive the conjugate or polysaccharide. MC4 is licensed for persons aged 11 to 55 years. Persons aged greater than or equal to 56 years should receive the polysaccharide. For persons aged 11 to 55 years who have been previously vaccinated with the polysaccharide, revaccination with conjugate is not indicated unless vaccination occurred three to five years previously and the person still remains at increased risk for meningococcal disease."*

Dr. Kaplan was one of the four co-chairs of the effort to revise the guidelines for prevention and treatment of opportunistic infections (OIs) and combine them into one adult document covering 29 different diseases, under the auspices of the Office of AIDS Research at NIH. The challenge was to make that document consistent with the footnotes in this adult vaccination schedule, particularly for hepatitis A, hepatitis B and pneumococcus. He mentioned three options for solving this problem. One would be to

have all the OI working groups weigh in on the footnotes, which would obviously be a huge effort. A second possibility would be to use the adult immunization figure, which everyone likes, but drop the footnotes, with one generic footnote referring readers to the OI guidelines. For those diseases not in the OI guidelines, readers would be referred to existing ACIP recommendations. This second option would simplify things greatly, allow the figure to be used with appropriate credit, and avoid the arduous task of trying to reconcile the guidelines with these footnotes. The third option would be to drop the figure, but no one wants to do that.

Dr. Mootrey mentioned that the anticipated submission date for publication to *MMWR* for the opportunistic infections guidelines was December 15th.

Discussion

Dr. Judson said was disturbed by cognitive dissonance among CDC experts or divisions making recommendations around the same goal, such as preventing and controlling HIV, but far more important was the issue of simply vaccinating people with HIV who are at risk of further transmission, without connecting the ethical obligation to cease transmission or cease exposure of others to their HIV infection. These are critical issues from a broader public health standpoint.

Dr. Craig thought the hepatitis B footnote about doubling the dose or increasing the number of vaccine doses would be confusing to clinicians. Dr. Kaplan pointed out that this was an example of where the language in the guidelines goes into much more detail. The current recommendation is to use the double dose, and there are good data to support that, particularly with people with CD4 counts higher than 350.

Dr. Baker asked what the reasoning was behind the suggestion that pregnant HIV women to drop TD when non-pregnant people get TD every ten years. She felt it would be ethically wrong to pick out one group that would not get the benefit of prevention. Dr. Kaplan said referring people to the OI guidelines would solve that issue.

Dr. Neuzil wondered why zoster vaccine was removed from the schedule. Dr. Mootrey explained that there had been tremendous push-back at the OI meeting, immediately before the June ACIP meeting, and there is a contraindication for the use of zoster vaccine for those with CD4 counts less than 200. Dr. Neuzil's concern was that there is an increasing number of HIV-infected adults who are 60 years and over. If there is a contraindication and no recommendation, it needs to be stated on the schedule. Dr. Kaplan noted that there was a statement in the OI guidelines that there is no information on the use of the zoster vaccine in HIV-infected persons, therefore there is a recommendation against using it.

Dr. Schuchat recalled that at the October 2006 meeting there was lengthy discussion about what to do with zoster in HIV-infected persons, whether there should be a permissive off-label recommendation or whether it would be better to wait for on-going studies that might reveal any benefit or any risk to HIV-infected persons. That discussion did not focus on the 60-and-over population, but for the vast majority of the population the risks and benefits are unknown. Dr. Benson noted that Merck was finalizing the details of a protocol for an ACTG study and awaiting final sign-up from NIH.

Ms. Stinchfield referred to the contraindication for influenza LAIV and wondered whether a person who was immunocompetent and had a normal CD4 count in an

undetectable viral load would be considered a healthy individual. She suggested using the word "precaution" rather than a contraindication.

Dr. Neuzil asked whether the table would be just used in the OI document, or would it also stand independently with the footnotes for other reasons. Dr. Mootrey responded that the intent was that it just be part of that document. Dr. Lett felt that if the table were to stand alone, it would need to have the footnotes. Dr. Schuchat commented that from her perspective, the OI document would be the Bible for practitioners who treat HIV patients, rather than ACIP stand-alone immunization recommendations. So the table would best belong in the document with adequate supporting information.

Dr. England said that the statement for MMR and varicella, "Do not give to severe immunocompromised patients" appears to be saying not to give it. She suggested putting that in parentheses so make it less confusing.

Dr. Judson felt that the overwhelming priorities in HIV care were suppression of the virus, restoration of immunity, and prevention of further transmission. Those who actually have HIV will have their care carefully tailored, by people who weigh information from many experts as to whether any individual vaccine is indicated. There may be other small complicated subpopulation groups for whom the ACIP general recommendations will not be particularly helpful.

Dr. Craig found it strange to vote on this schedule without looking at all the other material. Dr. Kaplan explained that the OI document was huge, with 29 different opportunistic disease areas, and tables on prevention and treatment. The information on immunizations is under each disease-specific section. The advantage of the figure is that people like it and it also incorporates standard adult recommendations. Dr. Seward added that the ACIP approved the pediatric schedule with footnotes in June, using the same process as the adult schedule, i.e., language was abstracted from approved ACIP statements, with no new recommendations, and this had just been pulled into one document for HIV. The variations presented were from comments received following that first iteration.

Dr. Hull was inclined to turn the table over to the OI group. ACIP has made its recommendations and perhaps a new document is not needed. The committees does not have the expertise to delve into the fine points of caring for AIDS patients. Dr. Morse suggested calling the table an adaptation of existing ACIP statements and not vote on it.

Dr. Schuchat felt it was unfair to ask the ACIP to vote on text they have not been able to review. It defeats the purpose of having a deliberative process. Dr. Pickering thought it was still important to harmonize ACIP recommendations with those in the OI document. Dr. Baker noted that there seemed to be full compatibility on HIV pediatric patients. Dr. Morse concluded that since there seemed to be no consensus about voting, the alternative would be for the OI group to cite ACIP in their document. Dr. Mootrey could work with them to make sure there is harmonization. Mr. Beck said he was still uncomfortable with harmonization, because of the current difficulty coming to agreement on language. He felt the committee should at least be able to review content of another document.

Dr. Hull was curious about whether there was a requirement that ACIP pass on the recommendations and immunization made by another group. Dr. Pickering said the charter stipulates making recommendations for the civilian population, when asked. Dr. Morse said the usual procedure would be to send it back to the adult immunization

committee to review the language and bring a consensus recommendation back in February, which would slow up publication.

Mr. Beck asked who had responsibility for the accuracy of the OI document. Dr. Kaplan said it had to be approved by all the participating agencies, including all the appropriate divisions at CDC, not to mention the expertise of about a hundred panel members. In-depth review and clearance will incorporate the thoughts of ACIP.

Mr. Beck moved that the document be returned to the organization from which it came, with the direction that they harmonize the contents with ACIP recommendations. Dr. Craig seconded the motion. Dr. Schuchat stated that this did not need an official vote, so Mr. Beck withdrew his motion and Dr. Craig withdrew his second. The consensus was not to vote on this issue.

Vaccine Supply
Dr. Greg Wallace, CDC/NCIRD/ISD

Dr. Wallace started with hepatitis A vaccine and reminded the audience that Merck had reported some supply issues in July, with backorders in both their pediatric and adult preparation. Since GSK indicated at that time that they had adequate supplies, no changes were recommended in the ACIP schedule by the recurring *ad-hoc* supply group. Currently backorders are suspended for the adult and pediatric vial formulations, and possibly for the adult syringes as well, although there may be some of that preparation still left. Current projections are for a return to the market late in the first quarter of 2008, dependent upon remediation actions and approval with FDA. There continues to be adequate supply from GSK, and no change in the ACIP recommendation.

Regarding the varicella-based vaccine supply, varicella-zoster virus bulk is used to manufacture varicella vaccine (Varivax), MMRV vaccine (ProQuad) and the zoster vaccine (Zostavax). Merck experienced lower than expected yields in their process and temporarily suspended the production of their bulk product. However, they have adequate bulk to make the varicella vaccine, which takes less titer than the ProQuad, and also the zoster vaccine, which has a lower demand than the routine pediatric vaccines. Again, no changes were made to the current vaccine policy recommendations, but people were informed that ProQuad was temporarily unavailable. A notice went out in February of 2007, announcing that Merck was prioritizing the production of varicella vaccine and zoster vaccine, and expected MMRV to run out by the end of the year. This resulted in a big run on vaccine and ProQuad ran out even sooner. ProQuad orders were suspended in June. Merck still has adequate bulk supply to make Varivax and Zostavax. Also, with the new two-dose pre-school recommendation, the run on vaccine lasted longer and doses ordered increased faster than projected. Shipping delays are starting to decrease back to the four- to five-week level and should settle down over the winter. The committee and the public will be informed as updates on remediation are received.

Dr. Wallace presented some graphs showing the history of influenza vaccine production and distribution. Influenza vaccination was not a big program going through the eighties, but then there was a large increase in production and distribution during the nineties. In the past 7-10 years, there were fluctuations and some flattening out, with delays in 2000-2002. But in 2003, production and distribution were nearly equivalent, which was followed by media reports of pediatric deaths and another outcry about not

having enough vaccine. In 2004, there was a vaccine shortage due to a manufacturing failure, followed by an unprecedented increase in vaccine production. Demand is also growing, but not at the same rate as production.

Ninety-five million doses had been distributed through the third week in October 2007. Finishing distribution by October is considered the gold standard. These data represent distribution from the manufacturer, so there is another layer of distribution from the major distributors. The goal is to get out over a 100 million doses in a couple of months time, so timing becomes very critical. With the different age recommendations for different vaccine preparations, implementation can be very complicated.

A major challenge is how to project pediatric vaccine in a changing world. Dr. Wallace presented a graph showing distribution of hepatitis B pediatric vaccine, Tdap, Hib, MMR, hepatitis A, varicella and rotavirus to demonstrate his point that one cannot empirically predict market demand.

Regarding implementation of new adolescent recommendations, Menactra had some limitations the first year and the public sector did not purchase much vaccine the second year. Anecdotally, there was some vaccine left over from the previous year.
Now that the recommendations have been generalized, 2007 is already showing good uptake, in the public sector as well, and it appears to reflect real administration. There has been a flattening of Tdap in the public sector, but sanofi pasteur reported an increase in demand, based on claims data for adults. It is harder to evaluate adolescents and adults when some of the recommendations cross age groups.

For HPV, there initially were concerns about price and being able to stock it, so the public sector portion in 2006 was probably larger than normal for adolescent vaccines. While there has been an increase in the amount of HPV in the public sector in 2007, it is a smaller proportion than before. Some of this is due to the private sector catching up and some adult vaccination may be going on as well.

There are some caveats regarding the adolescent doses. Much of the 2007 demand occurred during the third quarter when adolescents were going back to school. Whether that trend sustains over time remains to be seen. The system is also undergoing a step-by-step transition to a federal or nationalized third-party distribution for the public sector, which requires some seeding of inventory. However, it is very difficult to evaluate trends, especially when doses are going to both adults and adolescents with changing recommendations. Regarding combination vaccines, manufacturers say that trying to predict seasonal demand, which can be led by funding and other issues, makes it hard to plan production.

Discussion

Dr. Lett asked whether the six- to seven-week delay in varicella, which had forced providers in her state to prioritize and sometimes only give a first dose, was occurring elsewhere and whether the ACIP would be providing any guidance about prioritization. Dr. Wallace said he had not been getting complaints. There had been some unpredicted demand, but the situation seemed to be easing.

Public Comment

Ms. Diane McGowan spoke on behalf of her son Martin, who died from the flu at age 15. He was healthy and active, but not vaccinated and not part of any recommendation. She felt the committee was on track to vote for a universal vaccination, but without a vote, families are facing another potentially deadly flu season. She read the names of a few of the numerous children who died of flu during the recent flu season, none of whom were in the current recommendation, and urged the committee to vote for a universal vaccination in February.

Mr. Gary Stein, whose family lost a daughter to influenza when she was four and half, said that board members of Family Fighting Flu were dedicated to advocating to parents the importance of flu vaccination and to spreading awareness of the importance of this disease. ACIP's ultimate recommendation to move to a universal pediatric recommendation will help immensely. He expressed appreciation for the progress and discussion so far, but urged the committee to vote as soon as possible to expand the recommendation.

Dr. Plotkin spoke about a new national lay organization being formed that would speak in favor in vaccination and counter the impact of anti-vaccination organizations on immunization coverage. Seed money was found and the Task Force for Child Survival was engaged to get this organization off the ground. Alan Hinman, formerly with CDC, is putting together documents and applications to foundations. It is believed that the organization should be led by lay people and not accept funds from manufacturers or from the government, so contributions and support from all who believe in immunization would be greatly appreciated. The Task Force for Child Survival is a 501(c)(3) organization, so contributions are tax deductible.

October 25, 2007 - Day Two

Dr. Morse welcomed Ciro Sumaya and asked whether he had any conflicts to declare. Dr. Sumaya said he had no conflicts.

Human Papillomavirus (HPV) Vaccines
Dr. Janet Englund, ACIP, WG Chair
Dr. Lauri Markowitz, CDC/NCHHSTP/DSTDP
Dr. Richard Haupt, Merck
Dr. Martine Wettendorff, GSK
Dr. Gary Dubin, GSK
Dr. Elizabeth Unger, CDC/NCZVED
Dr. Eileen Dunne, CDC/HCHHSTP/DSTDP

Introduction

Dr. Englund introduced potential issues for the February ACIP meeting, including recommendations for a bivalent HPV vaccine and issues related to having two licensed HPV vaccines. The BLA for the bivalent vaccine was submitted to the FDA in March of 2007 and a decision is anticipated in January 2008. The HPV vaccine working group has also been discussing bivalent HPV vaccine efficacy, immunogenicity, and safety; quadrivalent HPV vaccine cross-protection; VAERS data and vaccine safety; recurrent

respiratory papillomatosis and genital warts; cost effectiveness of both the bivalent and quadrivalent vaccines; vaccination of HPV-infected adults; and HPV in older women.

Overview of HPV Vaccine Trial Data

Dr. Markowitz noted that a substantial amount of data had been published and presented in the last six months. Her presentation provided background on efficacy and immunogenicity, safety issues and ongoing and planned trials by both manufacturers.

There are over 100 different HPV types, which differ by end disease association. About 40 types are mucosal and sexually transmitted; these are classified as high or low risk based on their association with cervical cancer. The high-risk, or the oncogenic, types include 16 and 18, which cause about 70 percent of cervical cancers worldwide. Low-risk types include 6 and 11, causing over 90 percent of genital warts and almost all recurrent respiratory papilomatosis or RRP. HPV also causes other anogenital cancers.

There are two L1 virus-like particle, or VLP, vaccines. The HPV L1 capsid protein is the antigen used for immunization, and expression of the L1 protein is done using recombinant technology. The L1 proteins self-assemble into virus-like particles which are noninfectious and contain no viral DNA.

The quadrivalent vaccine developed by Merck includes two low-risk type VLPs -- 6 and 11 -- and two high-risk type VLPs-- 16 and 18, while the GSK bivalent vaccine includes two high risk typeVLPs -- 16 and 18. The quadrivalent vaccine is produced in a yeast substrate and the bivalent vaccine is produced in the Baculovirus system in insect cells. Both are given intramuscularly in a three-dose schedule, but the timing of the second dose differs slightly. The quadrivalent vaccine uses an adjuvant containing aluminum hydroxyphosphate sulfate, used in other vaccines, and the bivalent contains a new adjuvant, AS04, containing alum and monophosphoryl lipid A. This adjuvant is not in any vaccine in widespread use around the world or licensed for use in the U.S. The quadrivalent vaccine was licensed by the FDA in June 2006 and is now licensed in over 80 different countries worldwide. The bivalent vaccine was submitted for licensure in March of 2007, and has been recently licensed in the European Union, Australia and Mexico, and several other countries.

Both vaccines have had large clinical development programs. After the preclinical and the Phase I trials, Phase II efficacy trials were conducted in females either 16 to 23 or 15 to 25 years of age, and these trials were powered primarily to detect virologic endpoints. Large pivotal efficacy trials were conducted in similar-aged women, powered to detect histologic endpoints such as cervical intraepithelial neoplasia.

Adolescent immunogenicity and safety studies were conducted to bridge the antibody results from the efficacy trials in the older females. On the basis of these studies, the vaccines have received indications for use down to nine or ten years of age. Smaller efficacy and immunogenicity studies have been or are being done also in older women by both companies. Merck is also conducting efficacy trials in men.

For the quadrivalent vaccine, there were two Phase II trials and two Phase III trials, called Future I and Future II, with slightly different protocols. Both were large, multinational, multisite trials. Phase III trials enrolled women from North America, Latin America, Europe, and Asia. Over 21,000 women were included in these combined Phase II and Phase III trials. Similarly large trials were conducted for the bivalent vaccine.

There was a Phase II trial conducted in North America and Latin America, and one large efficacy Phase III trial, also a multinational, multisite trial. There over 19,000 women in these two combined trials. Another ongoing efficacy trial of the bivalent vaccine is being conducted in Costa Rica by the National Cancer Institute.

Regarding efficacy, these trials had similar endpoints, such as persistent infection or cervical intraepithelial neoplasia (CIN), grade 2 or 3, but they used slightly different protocols for detecting HPV and for screening and management of the abnormal cytology results. A variety of different efficacy analysis populations were used. Most women were sexually active and enrolled without regard to their HPV-PCR antibody status. The main analyses have or will be done in the per-protocol population, which includes women without evidence of infection with the relevant vaccine type through one month after the third dose, which is Month 7; they received all three vaccinations, did not deviate from the protocol, and cases were counted after dose 3. Some of the trials also analyzed the unrestricted-susceptible population or the total vaccinated population. These women were naïve to the relevant HPV type at baseline, had received at least one vaccination, and cases were counted after the first dose. The intent-to-treat population, which included all subjects regardless of their baseline status, received at least one vaccination, and cases were counted after dose 1.

The major endpoint was CIN 2/3 or adenocarcinoma in situ (AIS) from the quadrivalent and the bivalent vaccine trials. The main analysis for the quadrivalent vaccine was done in the per-protocol population, where vaccine efficacy was 98 percent with one case in over 5,000 women. For the Future II study, results for the unrestricted population, women who received at least one dose, showed 95 percent efficacy. For the bivalent trial and unrestricted analysis, efficacy was 90 percent with only two cases in the vaccine group.

For both the quadrivalent and the bivalent vaccine trials, cases in the vaccine groups had a non-oncogenic type that was detected in a preceding specimen as well as in the CIN 2/3 lesion. When analyses were done using lesions believed to be causally associated with the vaccine type, the analyses showed even higher efficacy, with both vaccines having efficacy of 100 percent. GSK has published results showing 100 percent efficacy with this modified, revised analysis.

High efficacy was found for both HPV vaccines for prevention of CIN 2/3 or AIS due to HPV 16 and 18 separately. There were small numbers of cases due to HPV 18 in the bivalent vaccine trial. The quadrivalent vaccine trials have also evaluated other endpoints, some due to HPV 6 and 11. In the per-protocol populations, there was 100 percent efficacy for prevention of genital warts or condyloma, and vulvar or vaginal cancer precursor lesions, VIN or VaIN 2/3.

For the quadrivalent vaccine, in women who were HPV-PCR positive with or without antibody, there was no evidence of therapeutic efficacy to the respective vaccine types. Among women who were antibody positive and PCR negative, suggesting a cleared infection, there was a high point estimate of efficacy, but there were few cases in that group. In the PCR-positive group, there was no efficacy. Data published on subjects enrolled in the ongoing trial in Costa Rica show the bivalent vaccine had no impact on viral clearance among those infected at enrollment.

Overall efficacy for the quadrivalent vaccine has been published, including all women regardless of their infection status at baseline – the intent-to-treat population.

About 27 percent had evidence of prior exposure or ongoing exposure with one or more of the four vaccine types, therefore the efficacy in this total population was lower than in the HPV-naïve women. Looking at the combined data for three of the quadrivalent HPV vaccine trials, efficacy for CIN 2/3 was 41 percent; for VIN or VaIN, 71 percent; and for vulvar or vaginal lesions, including genital warts, 78 percent. Although efficacy was lower in this intent-to-treat population, it increased with time since vaccination, because most of the disease outcomes in both the vaccine and the placebo group were due to infections present at the time of enrollment.

Regarding duration of protection, the mean follow-up time published or presented is three years for the quadrivalent vaccine and 15 months for the bivalent vaccine. However, from the smaller Phase II trials for both vaccines, follow-up data through about five years demonstate excellent duration of protection. For the quadrivalent vaccine, various endpoints have been high through five years, including for persistent infection, CIN 1-3, and condyloma. For the bivalent vaccine, with follow-up through five and a half years, there is high efficacy for various endpoints, including incident infection, 12-month persistent infection, and CIN lesions.

The issue around cross-protection is whether the vaccines provide protection against related HPV types that are not in the vaccines, which would increase the impact of the vaccines on cervical cancer. While 70 percent of cervical cancers are due to HPV 16, other oncogenic types are responsible for an additional small percentages. On the phylogenetic tree for HPV, the focus has been on two groups: the A9 species, which contains HPV 16 and related types, and the A7 species, which contains HPV 18 and related types. The published Phase III trial for the bivalent vaccine looked at cross-protection using six-month persistent infection as the endpoint, and observed cross-protection for some other types, e.g., type 45 (related to 18) and types 31 and 52 (related to type 16). Significant protection was found against a combination of all tested 12 non-vaccine types using a 12-month persistent endpoint; efficacy was 27 percent.

The analysis of cross-protection for the quadrivalent vaccine grouped types by their phylogenetic relationships. There was significant protection against nonvaccine types in the A9 species and a 47 percent point estimate efficacy for the seven A7 species.

In terms of the immunogenicity data, the main basis of protection is neutralizing antibody. The minimum protective antibody threshold is not known, due to the high efficacy seen to date in the vaccine trials. Serologic tests for HPV have not been standardized. Merck has been using a competitive Luminex immunoassay, which measures antibody to neutralizing epitopes on the L1 VLP. GSK is using a type-specific ELISA. Difference in the methods of antibody detection preclude direct comparison of the type-specific antibody titers within studies and between the two vaccines.

Both vaccines have been found to be very immunogenic. For the quadrivalent vaccine, 100 percent of participants had detectable antibody to all four types one month after the first dose, and by month 36 seropositivity was still high for all types. HPV 18 had fallen to 84 percent, but there were no breakthrough infections associated with the lack of detection of antibody. Both vaccines have been found to produce antibody titers substantially higher than those after natural infection. For the quadrivalent vaccine, the vaccine-induced antibody is substantially higher than after natural infection, falling and then plateauing at about 18 months and remaining fairly stable through 60 months. Administration of a challenge dose at month 60 resulted in a potent anamnestic response

and a rapid increase in antibody titers, suggesting immune memory.

Bridging immunogenicity studies conducted by both manufacturers found that immunogenicity in adolescents was non-inferior to the older women in the Phase III trials. Seropositivity rates were similar, over 99 percent, and GMTs were twofold higher in the younger age group compared to the older women. Data from the immunogenicity study in older women (26 to 55 years) for the bivalent vaccine showed 100 percent seropositivity after three doses; there were age-related differences in peak GMTs, but they were all still very high. The quadrivalent vaccine studies are ongoing.

Multiple safety outcomes have been evaluated, including injection-site reactions; serious adverse events; new onset chronic diseases, including new onset autoimmune diseases; and pregnancy and pregnancy-related outcomes. Injection-site events occurred more commonly in the vaccine than in control subjects for both vaccines. There was no significant increase in serious adverse events or new onset chronic diseases, and no differences in overall pregnancy outcomes between the vaccine or control groups.

A large amount of data will be coming in from ongoing trials being conducted by both companies. First, there will be follow-up of the Phase II and Phase III trials, including females who were vaccinated in adolescence in the immunogenicity trials. There will be immunogenicity and efficacy data in females greater than 25 years of age and data from efficacy trials in men 16 to 26 years of age for the quadrivalent vaccine. On-going studies are looking at simultaneous administration of HPV with other routinely administered vaccines, and those data will be available from both companies. GSK is conducting a comparative immunogenicity study of the two vaccines, a head-to-head trial enrolling about 1000 women. Both companies are looking at safety and immunogenicity in HIV-infected women and, in the case of the quadrivalent vaccine, also in HIV-infected men. Finally, both companies have large Phase IV trials looking at long-term follow-up.

Quadrivalent HPV Vaccine Cross-Protection

Dr. Haupt discussed the impact of the cross-protection efficacy of Gardasil in the context of co-infection with vaccine and novaccine HPV types. Even after accounting for co-infection, administration of Gardasil to HPV-naive women resulted in a clinically important reduction in CIN 2/3 and AIS due to cross-protection.

The alpha genus of the HPV phylogenetic tree is where most of the HPV strains that cause genital infection reside. Since the alpha genus HPV types are defined by their amino acid sequence to the L1 protein, they all share at least 65 percent amino acid sequence homology to the L1 protein. Within the alpha genus, there is the A9 species, whose prototype is type 16, and there is A7, characterized by type 18. To be within a similar species, the amino acid sequence homology has to be at least 75 percent shared. Type 16 alone contributes to 55-60 percent and type 18 contributes another 10 to 15 percent; the A9 species contributes 70 percent and A7 contributes another 20 percent. So these two species account for about 90 percent of all cervical cancers. Three other minor species contribute to the rest.

In clinical trials, Merck tested for 14 different HPV types – Types 6, 11, 16, and 18 and ten additional oncogenic strains, mostly A9 or A7 family members. This was the baseline data. Women were randomized to the vaccine or placebo. About a third of the women in the clinical-trial database were already infected with at least one HPV type at

baseline and of those, about half were infected with more than one type. Type 16 is the most prevalent type in the clinical database in terms of baseline-infection rate, but many types are found at baseline. HPV infection is common and sexually active women are at risk for getting infected from all types.

Another analysis tried to attribute different HPV types to cervical disease seen in the placebo arm of the clinical trials, using women who were negative to all 14 types by PCR testing at baseline and serologically negative at baseline to the four types in the vaccine. In addition, women were required to have a normal Pap test: this served as a proxy for evidence of not being infected with other genital HPV types not tested for at baseline. The study then was able to look at new cervical-disease lesions, incident CIN 1/2/3, caused by incident infections with the genital HPV types. Over 80 percent of the incident cases of CIN 2 and CIN 3 in the clinical trials were caused by either HPV 16 or one of its related members. The data also indicated that when going from CIN 1 to CIN 3, there is an increase in the relative contribution of HPV 16 to the higher grade lesions.

The baseline data led to the conclusion that the contribution of HPV types varies depending on the type of lesion, but when looking at cancer, Types16 and 18 are by far the most important, contributing 70 to 85 percent of all cervical cancers around the world. The next five, all related to 16/18, contributed another 15 percent. When looking at high-grade lesions, type 16 is very important, but members related to 18 become less important and there is more co-infection with other types. In the lowest grade, type 16 is still the most important, but many other types also contribute.

When designing the cross-protection evaluation, the first task was to decide which types to look at. After types 16/18, types 45, 31, 33, 52, and 58 each contribute at least 2 percent of the cervical cancer burden around the world. Each of these also shares at least an 80 percent L1 amino acid sequence homology to 16/18, so there is biological plausibility that neutralizing antibody generated against 16 and 18 from the vaccine may cross-react and neutralize these other related types. In fact, there was such evidence through cross-neutralization antibody studies already done.

The next decision was which endpoint to use. In the primary vaccine efficacy deliberations with regulatory agencies, it was determined that high-grade cervical precancers -- CIN 2/3 and adenocarcinoma in situ -- should be the appropriate endpoints for defining efficacy against 16/18 related cervical cancer in the trials. No opinions from similar regulatory authorities have been rendered about the correct endpoints to use for a cross-protection analysis.

The WHO expert committee on biologic standardizations has suggested that disease endpoints would be much more rigorous in an efficacy evaluation for cross-protection. Many infections resolve spontaneously without intervention, so infections that lead to disease are the most important for demonstrating efficacy. Recognizing that the nonvaccine types are less prevalent or less often lead to high-grade cervical precancer, WHO suggested that a rigorous viral persistence endpoint could be an alternative endpoint for efficacy analysis, e.g., prevention of viral persistence at 12 months.

Merck did two analyses in its Phase III studies. The first looked at a composite endpoint of prevention of 31, 33, 45, 52, and 58 viral persistence and demonstrated cross-protection efficacy against that composite endpoint. While un-blinding the clinical studies data, researchers recognized that a lot of CIN 2/3 in the trials could not be

attributed to the vaccine types, so there was a pre-specified data analysis plan to look at the potential impact of the vaccine against non-vaccine types related to the vaccine types. A cluster endpoint of 31- and 45-related disease was used, along with a cluster endpoint of the five next most important types after 16 and 18 -- 31, 33, 45, 52, and 58. The entire database of the Phase III trials was used to look at disease endpoints for up to four years.

Based on analyses of many different populations, including per-protocol analyses, and different forms of modified intention-to-treat analyses, it was decided that the best population in which to determine cross-protection efficacy was the generally HPV-naïve population, i.e., women with normal Paps and negative to the 14 types tested. From a methodological perspective, there was a lot of co-infection and mixed infection in the clinical trials. If women are generally HPV naïve, it is more possible to ascribe cross-protection against new infections and lesions. From a clinical-prevalence perspective, this population more closely approximates the primary age group recommended to be vaccinated, the 11- to 12-year-olds.

There are several sets of results, starting with high-grade disease lesions and efficacy against CIN 2/3 and adenocarcinoma in situ caused by types not in the vaccine. For the 31 and 45 endpoint, eight cases were seen in the Gardasil group, 21 cases of CIN 2/3 and AIS in the placebo group, with an efficacy of 62 percent, which was statistically significant. For the other cluster endpoint, -- 31, 33, 45, 52, and 58 – there were 27 cases in Gardasil and 48 in the placebo, which is 43 percent efficacy, also statistically significant. Another cluster endpoint looked at the ten other oncogenic strains outside of the vaccine types. There were 38 cases in the Gardasil group and 62 in the placebo group, for a vaccine efficacy of 38 percent, which was statistically significant. For the A9 species, there were 26 cases in the Gardasil group and 48 in the placebo group, a point estimate of 45 percent. That too was statistically significant. The point estimate for the A7 species was similar, but the number of cases was too few to ascribe statistical significance.

Results for cross-protecting efficacy for any grade CIN (CIN 2/3 plus CIN 1) gives a sense of the overall potential reduction in burden of disease through cross-protection. HPV 16 causes the most cases of incident CIN of any grade, including CIN 1. A greater mixture of other HPV types contributes to lower grade lesions, but they do not necessarily progress to higher grade lesions. Here one begins to see types 6 and 11, which in addition to causing 90 percent of genital warts, cause about 10 percent of low-grade cervical pre-cancers or low-grade cervical dysplasia. In the clinical trials, about 8 percent of CIN/1 lesions were caused by Types 6 and 11.

For CIN of any grade and AIS, with the same cluster endpoints, 31 and 45, there were 23 cases in the Gardasil group and 42 in the placebo group, which is 45 percent efficacy. Using the five-cluster endpoint, there was 33 percent efficacy. Both of these were statistically significant. Using the cluster endpoint of the ten oncogenic strains after 16 and 18, once again, efficacy was at 27 percent, which is statistically significant. In the stratified analysis, there was statistically significant efficacy against the A9 species; there was a similar and positive point estimate in the A7 species, but it did not achieve statistical significance.

Dr. Haupt presented three potential clinical scenarios on how cross-protection may interface with infection from vaccine types. One would be that the benefit is completely additive. Any disease lesion caused by the vaccine type is separate and

different from the disease lesion caused by the other types, but that is not a reasonable assumption based on the data from the clinical trials. The other end of the spectrum would be to say that every lesion has a vaccine type as well as one of these others and, therefore, there is no added benefit. The reasonable choice lies somewhere in the middle. In order to truly define the clinical benefit for a woman, consider that if a woman has a CIN 2/3 lesion and HPV 16 and HPV 52 are both found in it, there is still only one disease lesion and it should not be counted twice in terms of the efficacy of the vaccine.

Merck first looked at the efficacy of the vaccine against CIN 2/3 caused by types 16 and 18. There were 51 cases in the placebo group and none in the vaccine group, for 100 percent efficacy. The vaccine prevented 51 cases of CIN 2/3. For the group of five types -- the 31, 33, 45, 52, or 58 related CIN 2/3 -- there were 48 cases in the placebo group and 27 cases in the vaccine group, a reduction of another 21 cases, which might seem to be 40 percent additional reduction based upon cross protection. However out of the total of 99 CIN 2/3 cases, 16 had co-infection with vaccine types along with the related non-vaccine types. So if 16 of those CIN 2/3 cases in the placebo group had 16 or 18 and one of the other types, the cross-protection benefit is not 72 cases – it is 56. There is, in fact, a net benefit of cross-protection in terms of serious disease lesions. The analysis showed about 10 percent additional reduction of CIN 2/3 in this population of women, which is a real clinical benefit.

In summary, Merck feels that the clinical benefit of Gardasil has three major components. The vaccine is almost 100 percent efficacious against 16/18-related disease, and that includes cervical CIN 1/2/3. It also includes vulvar, VIN 1/2/3, and vaginal VaIN 1/2/3, as well as adenocarcinoma in situ. Another major component is the 6 and 11 prevention. Again, the efficacy is virtually 100 percent, with tremendous efficacy against both genital warts and low-grade CIN, caused by 6 and 11. Lastly, there is an important additional clinical benefit from cross-protection. In fact, the 38 percent efficacy against ten oncogenic strains not in the vaccine has a significant clinical impact for women in terms of reducing disease lesions.

Discussion

Dr. Neuzil said she understood that part of the reason the study focused on clusters was power. However, it seemed to her that types 31 and 45 might be driving the efficacy shown and that it may, in fact, be significantly lower in those other types. Dr. Haupt replied that the pre-specified analysis to use composite endpoints was indeed based on power. The contribution of non-vaccine HPV types, especially to high-grade lesions like CIN 2/3, is lower, but a much larger study would be required to look at individual type efficacy with statistical power. Type-specific analyses were done, but those data have limitations based on the number of cases seen. It is true that 31 and 45 drive this composite endpoint of the five types because they cause more CIN 2/3 lesions. The efficacy in the trials was driven predominantly off of Type 31. Even though the studies were not designed to look at individual types with statistical relevancy, positive trends were seen for every type except 45, where a neutral impact was seen for CIN 2/3. Efficacy against Type 45 was seen in the persistent-infection analysis. Going from persistent infection to any CIN to CIN 2/3, the number of cases became smaller, so it was hard to show efficacy with 45 against high-grade disease endpoints.

Dr. Pickering asked if it might be more appropriate to group the findings according to the phylogenetic tree and show protection within a species. Dr. Haupt replied that that data were presented according the prespecified analytic plan, which focused on the five most important types contributing to cervical cancer after Type 16 and 18. It just turned out that four were related to 16 as an A9 species, and one of them was an A7. In the stratified analysis, where types are grouped by species, most of the efficacy was driven off of efficacy against the A9 species.

Ms. Stinchfield wondered whether anything could be done to reduce the vaccine's sting so that it is not a disincentive for Dose 2 and 3. Dr. Haupt acknowledged complaints and said that from the clinical trial database, half of the local adverse events could be attributed to the proprietary aluminum adjuvant used and another half was related to the viruslike particles, which do actually hurt. Merck is educating providers about that side effect and would be willing to support studies to help reduce pain.

Dr. Craig asked about the reports of more syncope from this vaccine. Dr. Haupt replied that syncope was seen equally in the Gardasil and the placebo group during clinical trials, and it occurred in less than 0.2 percent of all study participants. More syncope has been reported in the post-licensure time period, but there is no indication that it is anything other than the idea of getting a needle and a noxious stimulus.

Dr. Judson commented that experience over the years with hepatitis B and other protein-alum combinations indicates that the reactogenic part is predominantly the alum and that studies that use alum minus the active protein are not really placebos in terms of reactogenicity. He asked whether Merck had also looked at tenacity and acid base and other factors. Dr. Haupt replied that the pH the injection vehicle is neutral and not all aluminum adjuvants are the same. Merck's is aluminum hydroxyphosphate sulfate, which acts very differently than aluminum hydroxide and aluminum phosphate. In fact, it works best in a neutral pH, the same pH that adsorbs best with the VLPs. Dr. Judson suggested that the inflammation is partly why it works in terms of recruiting processing cells.

Dr. Jeff Duchin asked at what point after immunization these data were from and whether Merck was planning to continue to monitor the durability of cross-protection over time as it relates to the 16/18 types and the four components as compared to the cross-protecting aspects of the vaccine. Dr. Haupt replied that since they were looking for cross-protection efficacy and it was a modified intention-to-treat analysis, case counting began after one dose or after Day 1. Merck is completing the final analysis of the entire Phase III database, so there will be a four-year follow-up analysis for this group in evaluating efficacy against 16/18, efficacy against 6 and 11, and also efficacy against cross-protection. Other post-licensure studies are planned to evaluate cross-protection in a broader population level as well as vaccine efficacy at a population level.

Dr. Cieslak asked for clarification on the number of cases prevented by vaccine serotypes other than 16 and 18. Dr. Haupt confirmed that there were five additional cases prevented when there was co-infection with vaccine type 16/18 or the other five types was factored in, and that efficacy against 16 and 18 could be inflating the apparent efficacy against those other types.

Dr. Hull asked what number a clinician would use when telling a patient about reduction of the risk of cervical cancer with the vaccine. Dr. Haupt replied that 78 percent would be a reasonable estimate of the net incremental benefit of cross-protection,

although Merck has avoided giving a scientific number for overall protective efficacy.

Dr. Morse asked whether there were any data on GMT elevation for HPV 18 after a booster dose. Dr. Markowitz replied that the same anamnestic response was seen for all four types in the quadrivalent vaccine. Dr. Haupt added that their assays were type-specific, neutralizing assays, using competitive Luminex. Merck was measuring an antibody that competes with a monoclonal antibody to a known epitope that neutralizes on the vaccine. It is not a total IgG antibody. In the women that become nominally seronegative to type 18, no cases of disease have been seen beyond five years now and they do boost with a challenge dose.

Bivalent HPV Vaccine ASO4 Adjuvant System

Dr. Wettendorff explained that GSK's AS04 adjuvant had been specifically designed to enhance immunogenicity and increase duration of protection against cervical cancer. The two HPV types responsible for more than 70 percent of cervical cancer are HPV 16 and 18 and GSK deliberately chose not to include additional HPV types in its vaccines, based on concerns about potential interference. Preclinical and clinical data have shown that when there are more VLPs in the vaccine, the immune response can be impaired, especially to HPV 18. Impairing the immune response to HPV 18 could also impact protection against closely related phylogenetically HPV types, such as HPV 45. Both HPV 18 and 45 are highly present in adenocarcinoma, are very often detected in very young women and often escape detection by Pap smear. At sexual debut, young girls and women will be at risk for infection with oncogenic HPV types and long-term protection is key. Finally, natural HPV infection does not always stimulate the immune system; women can be reinfected even if they are seropositive for HPV types. The GSK vaccine has been designed to induce high and sustained immune responses of high quality.

The vaccine contains two components: L1 proteins in the form of VLP from HPV 16 and 18 (equal amounts of both types) and the proprietary adjuvant system, AS04. Early dose-range trials showed that, combined with the AS04 adjuvant system, this combination and this antigen concentration was giving the peak of antibody response. The AS04 adjuvant is composed of 500 micrograms of aluminum hydroxide and 50 micrograms of monophosphoryl lipid A, or MPL. MPL A is a derivative from lipopolysaccharide from Salmonella minnesota. Lipopolysaccharides, or LPS, are a major component of the outer membrane of gram-negative bacteria. This substance is ubiquitous in nature, with frequent population exposure. GSK has chemically modified the LPS to assure an appropriate safety and reactogenicity profile while retaining the adjuvant property of the molecule.

AS04 has been designed to enhance immunogenicity and increase duration of protection. For women over age 25, it is important to consider the age-related decline of immune response to vaccines. These women are still at risk of HPV infection. It has been shown that HPV vaccine can induce antibodies in the serum that can transudate to the genital mucosa and having higher antibodies in the serum will translate into higher levels of antibodies at the site of infection.

Following vaccination, there are two important steps, the first being the innate response, which is not antigen specific and does not have memory. The other is the

adaptive immune response, which is antigen specific and includes T and B effector responses as well as memory responses. The innate immune responses are characterized by the recruitment of immune cells at the site of infection. Antigen-presenting cells capture the vaccine antigen and migrate to the lymphoid organs, where they mature and present the antigen to T cells. Antigen presentation and T-cell activation within the lymphoid organs is followed by activation of effector and memory responses that migrate back through the blood to the tissues. The adaptive immune responses determine the quantity, quality, and memory of the antigen-specific immune responses.

The activation of the antigen-presenting cells at the site of vaccination is the most important step and this is where MPL has an effect. On the surface of the antigen-presenting cells are molecules called "toll-like receptors," which can recognize molecular patterns from specific pathogens. When the toll-like receptor of an antigen-presenting cell is activated, it triggers an intracellular pathway that leads to the production of a specific microenvironment around the antigen-presenting cells that directs the type of immune response in the context of the interaction between the T-helper cells and the antigen-presenting cells.

Toll-Like Receptor 4 (TLR4) recognizes LPS. Once activated, a cascade of intracellular events is initiated, leading to the production of ProTh1cytokines, such IL-12 and interferon gamma, as well chemokine and proinflammatory cytokines, such as TNF alpha and IL-6. This creates a specific microenvironment around the antigen-presenting cells, which has an impact on the induction of the specific antigen responses, the adaptive immune responses of B and T cells. MPL is actually a derivative from LPS, and it can act on TLR4 the same way as LPS does.

When using vaccines containing the antigen and AS04, the MPL triggers the TLR4 receptor on the antigen-presenting cells, initiating the cascade of events creating a microenvironment of cytokines around the antigen-presenting cells. These antigen-presenting cells up the regulation of costimulatory molecules, which helps present the vaccine antigen to specific T cells, resulting in an optimal T- and B-cell activation.

Antigen-presenting cells that have cosignals via TLR and the antigens will optimally activate and differentiate T cells, leading to optimal adaptive responses. Vaccine containing AS04, via the activation of TLR4, will have an impact on the quantity, quality, and longevity of the immune responses against the HPV vaccine antigen. As the MPL effect is quite local and transient, no adverse immune events relative to vaccinations with AS04 are expected.

Dr. Wettendorff then presented data on the impact of MPL and AS04 on the induction of innate immunity, based on experiments using a monocytic human cell line that can be activated through TLR4 to produce a proinflammatory cytokine. In this case, production of TNF alpha was measured. Stimulation of the cells with MPL induced a dose response to production of TNF alpha by the cells. When cells were stimulated with aluminum hydroxide, there was no stimulation of this TLR and no production of TNF alpha. When MPL was combined with aluminum hydroxide, the stimulation through TLR4 was maintained, which sets the stage for optimal adaptive responses later on.

GSK evaluated the quantity and the persistence of immune responses induced by the vaccine, the presence of antibodies at the site of infection in the genital mucosa, and confirmed that this vaccine is able to induce high antibody titers, whatever the age range.

To study the magnitude of the immune responses in the Phase II clinical trials,

two vaccines were compared that each had 20 micrograms of each L1 VLP from HPV 16 and 18, but were formulated either with aluminum hydroxide or with AS04 adjuvant. For HPV 16 and HPV 18, measuring neutralizing antibody response over a four-year period, there were statistically significantly higher titers induced by the AS04-containing vaccines as compared to the aluminum hydroxide vaccine.

In the same trials, GSK evaluated the impact of the adjuvant on the induction of memory B cells following the primary vaccination course and found that the memory B cells induced by the AS04 vaccines were much higher than those using aluminum hydroxide. This has been shown for both HPV 16 and 18. Although the role of memory B cells is not clear in the context of HPV, it is clear that induction of memory B cells at the end of the primary vaccination course will help to maintain high antibodies levels for a long period of time in the blood and the genital mucosa.

These results led to evaluation of the efficacy generated by the HPV 16/18-AS04 vaccine, and the persistence of the antibody response was confirmed in this initial efficacy trial, HPV-001/007. Looking at antibody responses, as measured by total antibodies by ELISA, for both HPV 16 and 18, there was close to 100 percent seropositivity up to five and a half years following vaccination. In terms of GMT titers, a peak was observed at Month 7 and then a decline up to Month 18, but there was a plateau from Months 18 onward both for HPV 16 and 18. At the end of the follow-up period, antibody titers were more than tenfold higher than those induced by natural infection. The graphs for HPV 16 and 18 are nearly identical, when using a total ELISA assay as well as a pseudovirion-neutralizion assay developed by NCI, where there was exactly the same persistence of seropositivity, more than 98 percent at the end of the follow-up and antibody titers for both HPV 16 and 18 that were significantly higher than those induced by natural infections.

In evaluating the presence of antibodies in the genital mucosa in different age groups, it was determined that there was a good correlation between antibody levels in the serum and those in the cervical mucosal centers for both HPV 16 and 18. This was at month 24, when antibody levels in the serum had reached a plateau and there was still protection.

The efficacy trial was performed in women age 15 to 25 or older. Two trials were conducted to bridge the younger age group, 10 to 15 years old, and the older age group, 26 to 55 years old. In the immunobridge study to the younger age group, the graphs are consistent and similar for HPV 16 and 18: 100 percent seropositivity and GMTs around two times higher in this population than in the 15-to-25 population, which suggests that the vaccine will be able to induce long-term protection in this population where it is most needed.

For the older group, the age stratification was as follows: 15 to 25, 26 to 35, 36 to 45, and 46 to 55. Exactly the same picture was seen for HPV 16 and 18: 100 percent seropositivity following vaccination course. As expected, a decline in GMTs is seen with age, but even in the oldest age range, antibody titers are still much higher than what is induced by natural infection. These antibody titers are even higher than those obtained at the plateau phase of the efficacy studies, which are considered protective levels. This suggests that GSK's vaccine will be able to counterbalance the immune decline in older age groups.

In conclusion, AS04 was designed to enhance immunogenicity and increase

duration of protection. The clinical data generated substantiate this enhanced immune profile in terms of sustained response, intensity of the response at the site of infection, and in a broad age range. Antibody responses are comparable for both HPV 16 and HPV 18. Including only 16 and 18 in the vaccine combined with AS04 has assured the best immune response to both HPV 16 and 18 and potentially to the closely related types 31 and 45, inducing long-term protection against cervical cancer.

Bivalent HPV Vaccine Clinical Overview and Safety Review

Dr. Dubin noted that the GSK vaccine development program included two efficacy studies, both of which evaluated vaccine efficacy against HPV 16 and 18 endpoints. The Phase II program, referred to as HPV-001, and its extension phase, HPV-007, evaluated vaccine efficacy in a group of women who were naïve for oncogenic HPV infections at baseline, a population that approximates those targeted for public-health vaccination: young adolescent girls who have not yet initiated sexual activity and who have not yet been exposed to HPV. This study demonstrated that the vaccine provided up to 100 percent protection against HPV 16 and 18 endpoints, and this efficacy was sustained over five and a half years of follow-up.

The Phase III program, HPV-008, evaluated efficacy in a large cohort of over 18,000 women who were not screened prior to study entry and who therefore represent the more general population of women who might be targeted for vaccination. Results confirmed that the vaccine was highly efficacious against cervical precancers (CIN 2+ lesions) caused by HPV 16 and 18.

These trials also assessed the vaccine's efficacy against other oncogenic types. After HPV 16 and 18, the next most common HPV type associated with cervical cancer is HPV 45, responsible for approximately 6.7 percent of cases. HPV 45 is phylogenetically related to HPV 18 and, like HPV 18, is responsible for a significant portion of adenocarcinoma cases, a particularly aggressive form of cervical cancer that often escapes Pap smear detection or is detected too late. HPV 16/18 and 45 appear to have some unique properties in their potential to progress from cervical precancers to cancers. These are the only three types that actually cause a greater proportion of cervical cancer cases than cases of high-grade squamous intraepithelial neoplasia. The next ten most common HPV types are associated with about 22 percent of cervical cancers. HPV 45 and HPV 18 are both members of the A7 species, along with a few others. Five other types are related phylogenetically to HPV 16, and are members of the A9 species.

In the Phase II studies, significant cross-protection was observed when evaluating vaccine efficacy against individual virus types using persistent infection as the definition. Using incident infection as the virologic endpoint, significant cross-protection was observed against HPV 45 over the entire five-and-a-half-year follow-up period. An additional year of follow-up is coming very soon.

Assessment of cross-protection can be extremely complex, due to potential confounding effects of multiple infections, so in the Phase III program, a more robust measure of efficacy for cross-protection was used. Persistent infection avoids possible confounding effects and allows direct determination of the impact of the vaccine on each of the individual types. It will still be important to look at overall aggregate effects against lesions, independent of any HPV types. Persistent infection has been recognized

by WHO as a valid endpoint for assessment of cross-protection.

GSK has found evidence of significant cross-protection against three of the four individual oncogenic types that cause cervical cancer, including HPV Types 45, 31, and 52. These evaluations were done in a very broad cohort, with subjects that were non-naïve for other oncogenic types at study entry, so it better reflects the general population. Cross-protection was also assessed against the combination of all tested 12 additional non-vaccine oncogenic types using a 12-month definition of persistent infection. This pre-specified analysis showed vaccine efficacy of 27 percent against these12 viruses. This analysis was part of the interim efficacy analysis for the primary endpoint in the study and because of the timing, over 90 percent of the infections seen were in subjects that had not yet received all three doses of vaccine. It is expected therefore that with longer follow-up time these results might increase.

GSK has recently conducted exploratory analyses to evaluate cross-protection in an HPV-naive cohort, a subset of almost 9,000 women in the HPV-008 study population who were negative at study entry for a panel of 14 oncogenic types and had normal cytology. Protection was observed against HPV 45 alone, the combination of HPV 45 and 31, in combined analyses, which included the five most common HPV types associated with cervical cancer, with efficacy of 41 percent, and in analyses that included the ten most common types stratified by their phylogenetic relationships to either HPV 16 or 18. Results indicated significant vaccine efficacy against both HPV-related viruses.

Dr. Dubin then described GSK's experience with the AS04 adjuvant in other vaccine programs. AS04 is used in Fendrix, a licensed, adjuvanted hepatitis B vaccine available in the European Union for use in hemodialysis patients. AS04 is also used in the investigational genital herpes vaccine program in large-scale Phase III clinical development. In total, there are 40 completed studies and three ongoing studies in the development programs for these vaccines, including over 26,000 subjects, 16,000 of which have received over 40,000 doses of AS04 adjuvanted vaccine.

AS04 adjuvanted vaccines have been generally well tolerated. Injection-site symptoms are commonly reported, but are usually of short duration and low-grade intensities. Rates of unsolicited symptoms were carefully assessed, including serious adverse events, throughout the entire duration of the trials and were similar in active AS04 vaccinees and controls in each of the programs.

Dr. Dubin summarized results from a large pooled safety analysis, which represents the single largest cohort reported to date for analysis of HPV vaccine safety, with data from over 29,000 women in 30 countries, 16,000 of whom have received the active HPV vaccine. The analysis included all subjects that received at least one dose of vaccine. The database represents a broad range of ages and an ethnically and geographically diverse cohort. The trials were designed to collect comprehensive safety data, especially for outcomes that might occur at low frequencies.

Information was collected on injection-site and systemic symptoms, using diary cards over a seven-day period following each dose of vaccine. Information was also collected on all unsolicited adverse events for a period of 30 days following each dose of vaccine. Serious adverse events and medically significant conditions were evaluated during the entire follow-up period, which ranged up to five and a half years. Medically significant conditions were defined as conditions that prompted either physician or emergency-room visits. Outcomes of pregnancies and the occurrence of new onset

autoimmune diseases were assessed throughout the trials.

The entire cohort was stratified by age, baseline HPV 16 and 18 serostatus and baseline 16 and 18 DNA status. Naïve individuals were defined as being seronegative and DNA negative for both of the vaccine types. Currently or previously exposed individuals were defined as those seropositive or DNA positive for at least one of the vaccine types and currently infected individuals were DNA positive for at least one of the vaccine types.

Three different control preparations were used for comparison with the HPV vaccine, depending on the phase of development and the age of the target population. They included an adult formulation of licensed hepatitis A vaccine, the pediatric formulation of the hepatitis A vaccine for the adolescent studies, and aluminum hydroxide. Local injection-site symptoms, such as pain, redness, and swelling, were more commonly reported in vaccine recipients, however most of the symptoms resolved after a few days, and the rates of Grade 3, or severe symptoms, were very low. General solicited symptoms tended to occur at lower frequencies than injection-site symptoms. Although the rates of some specific symptoms, such as myalgia, were higher in the vaccine group, the differences tended to be small and the rate of Grade 3 symptoms was low.

Similar patterns of reactogenicity were observed among subjects stratified by baseline HPV 16 and 18, initial serostatus, or DNA status. There did not appear to be any differences in the rate of local injection-site symptoms according to the history of prior HPV infection or current infection at the time of infection, either for all symptoms considered at any intensity grades or Grade 3 symptoms alone. Similar patterns of reactogenicity were seen in young adolescent girls and in women over 25 years of age. The immunobridging data for these two age groups were also similar: higher rates of local injection-site symptoms compared to control, but low rates of Grade 3 symptoms.

Regarding reporting at least one unsolicited symptom or medically significant condition during the trials, rates observed in the HPV group were very similar to the rates observed in the placebo and control groups. There was no difference in the rate of serious adverse events reported or the proportion of subjects that withdrew from the studies due to either an adverse event of any intensity grade or serious adverse event.

In the pooled analysis, a total of five fatalities were reported; none were considered related to vaccination. Although the individuals remained blinded because they came from the ongoing Phase III efficacy study, only one had received the HPV vaccine and the other four were all hepatitis A controls.

Since the majority of women targeted for vaccination will be of childbearing potential and since autoimmune diseases tend to occur more frequently in young women than in other demographic groups, GSK assessed all pregnancies very carefully during the course of the studies and prospectively solicited information on new onset of chronic diseases, including autoimmune conditions. The rate of autoimmune diseases reported in subjects that had received the HPV vaccine was very similar to placebo or control groups. There were strict protocol requirements for adequate contraception during the vaccination phase, but pregnancies were allowed during the long-term follow-up periods. Overall, a fairly large number of pregnancies was reported. However, rates of specific pregnancy outcomes, such as miscarriages, abnormal infants, or premature, were very similar in the active vaccine group compared to the control groups in this pooled analysis.

In conclusion, studies clearly demonstrate a very high level of protection against

HPV 16 and 18 endpoints, including CIN2+ lesions, as well as efficacy against nonvaccine types. The vaccine is generally well tolerated across all age groups; rates of unsolicited symptoms, serious adverse events, autoimmune diseases, and pregnancy outcomes are comparable in all of the analyses conducted to date, indicating a very favorable safety profile.

Since the HPV vaccine is now licensed in over 30 countries, GSK is planning its Phase IV activities, including a long-term efficacy follow-up for subjects enrolled in Finland in the Phase III program. Finland has cancer registries that will show cancer outcomes many years into the future. A large cohort study in adolescents and young adults is being planned, which will assess safety outcomes, including autoimmune diseases, pregnancy outcomes, and vaccine effectiveness. A large community-randomized trial was recently initiated in Finland. This trial will ultimately enroll over 70,000 subjects and will assess vaccine effectiveness, induction of herd immunity, and potential impact of vaccination on non-vaccine oncogenic HPV types, as well as safety and pregnancy outcomes. After U.S. licensure is achieved, there will be a pregnancy registry in this country. Meanwhile, GSK looks forward to presenting results of the final analysis of the ongoing efficacy and head-to-head trials.

Discussion

Dr. Sumaya asked for clarification on the different types of tests used to assess the antibody response to anti-HPV 18. Dr. Dubin explained that each company used its own assays to evaluate vaccine immunogenicity over time, so it is difficult to compare results. However, very high levels of sustained seropositivity have been observed for both types over the long-term follow-up. The head-to-head comparative trial should provide the requested data. There is some preclinical data from a study on mice that directly compared Gardasil and the GSK candidate vaccine head to head. These analyses show, for HPV 18, a three- to fivefold difference in geometric mean antibody titer several weeks following the two-dose injection schedule used in mice. These data do indicate that there are likely to be differences, especially in terms of HPV 18 immunogenicity. Utimately the duration of protection may be dictated by the ability of the vaccines to induce sustained antibody titers. Even though immune memory needs to be considered as an important element in the immune response, there are no clinical data to date that establish the role of immune memory in providing protection for this particular disease. These infections tend to occur very quickly, perhaps even before an anamnestic response can impact the course of the infections.

Dr. Schaffner asked whether there were any plans to immunize or study the vaccine in males. Dr. Dubin replied that the Phase IV community randomized trial in Finland would include evaluation of immunization of boys, particularly whether vaccinating boys induces better herd immunity than vaccinating boys and girls or females only. Results of modeling suggest that if there is high coverage level in girls, there is likely to be very little incremental benefit in cervical cancer protection by vaccinating boys. However, policy groups will be meeting to determine whether there is a role for male vaccination based on induction of herd immunity.

Dr. Judson noted that no one knows what the minimal effective neutralizing antibody titer is, but that re-infections with the same serotype seem to be extremely rare,

based on natural history studies. Dr. Dubin explained that two biological benchmarks were used in the studies -- the level of natural infection, which provides incomplete protection, and the level of antibodies seen during the plateau phase of the long-term efficacy study, which has provided complete protection. It is thought that the threshold of protection will be somewhere between those two biological benchmarks. In the long-term studies done to date and in all of age ranges evaluated, titers for both types were sustained above the higher protective threshold in the efficacy study.

Dr. Iskander commented that in future presentations on reactogenicity data, it would be helpful to use standard terminology to talk about saline placebo versus aluminum placebo. It is also helpful to be able to tease out components of reactogenicity that are attributable to the adjuvant vs. other components. Dr. Neuzil added that it would also be helpful to see one-, two-, and three-dose efficacy presentations.

Outcomes Related to HPV 6/11: Recurrent Respiratory Papillomatosis and Genital Warts

Dr. Unger summarized what is known about recurrent respiratory papillomatosis or RRP, its natural history, risk factors, and burden of disease. Respiratory papillomatosis is a descriptive name for papillomas or warts in the upper respiratory tract. It is called recurrent respiratory papillomatosis because recurrence is the rule and is required for formal classification. The larynx is the most frequent site of involvement and, within the larynx, the vocal cords. Protrusion of these growths into the airway results in hoarseness and continued growth can result in airway obstruction. Hoarseness and changes in voice quality are the most common presenting signs. Diagnosis may be delayed for several months to a year from the first symptoms, particularly in children. Rarely, sudden death due to airway obstruction may be the mode of presentation.

There are two modes of onset of disease -- in childhood, referred to as juvenile onset, and in adults. The age of demarcation varies somewhat, but age 18 is commonly used. Both juvenile and adult RRP are associated with HPV 6 and 11. Diagnosis is apparent at endoscopy, as the gross lesions have a characteristic but somewhat variable appearance. Histologically, the papillomas are characterized by projections of a thickened squamous epithelium with frequent koilocytotic changes that are characteristic of a productive viral infection. HPV 6 and 11 can be demonstrated by in situ hybridization. These lesions are histologically benign.

The goal in therapy is not to remove all lesions, but to preserve the airway. Aggressive treatment can actually increase morbidity because of damage to the vocal cords, quality of voice, and web formation. Diagnosis and treatment occur in tertiary-care centers by otolaryngologists. Obstructing lesions are removed with laser surgery, microdebriders, or biopsy forceps. A variety of additional therapies and adjuvant treatments are used. Lesions recur unpredictably and can spread throughout the respiratory tree. Children are particularly susceptible to sudden airway obstruction due to growths and intervening infections, and tracheostomy may be required to maintain airways in these situations.

Spread below the larynx into the lower respiratory tract is a rare event. In the lungs, these lesions appear as benign squamous lined cysts that slowly enlarge and compromise lung capacity and result in pneumonia. Rarely, malignant transformation

has occurred. Successful treatment of growth in the lungs has not been described.

Intrapartum exposure to maternal genital HPV infection is the implicated mode of transmission of juvenile onset RRP, despite the median age of diagnosis at three years. None of the U.S. data on risk factors are population-based, however, clinicians frequently cite the classic triad of a teenaged mother, vaginal delivery, and firstborn child. Young maternal age would be more likely to be associated with a recent infection. Vaginal delivery would be associated with infant exposure to genital secretions and firstborn associated with longer delivery times and increased time of exposure. However, there are no objective measures of the magnitude of these risks, and the rare outcome in the face of high frequency of maternal infection argue strongly that other factors are involved. Investigators are looking for genetic susceptibility factors.

Silverberg and colleagues conducted a retrospective cohort study to evaluate the association between maternal and infant characteristics and RRP, using data from Danish registries gathered between 1974 and 1983. Among 1.2 million live births, investigators identified a little over 3,000 births among women with genital warts during pregnancy and 57 cases of juvenile onset RRP. Of these, 21 cases were born to mothers with documented warts and 36 to mothers without, indicating maternal warts as a significant risk factor. The relative risk of RRP was over 200. Nevertheless, the majority of RRP cases occurred in children whose mothers did not have documented genital warts. Cesarean section was not protective, although the low rate of C-sections in this population limited the power to detect a difference.

RRP is a very rare disease and most reports in the literature are case series or anecdotal clinical experience. Juvenile-onset RRP or JORRP has been studied more extensively than the adult-onset disease. The best estimate of U.S. incidence and prevalence comes from a population-based study in Seattle and Atlanta, conducted in 1996. Based on this study, the estimated incidence of JORRP is between 0.4 and 1.1 per 100,000 person-years for children less than 18 years and prevalence is between 1.7 and 2.6 per 100,000 in children younger than 18 years. The1999 U.S. Census figures would predict 80 to 1500 incident cases and 700 to 3,000 prevalent cases of JORRP in the United States.

Based on the two-city study of incidence and prevalence, the CDC and the RRP task force conducted a record-based registry of all children less than 18 years of age treated at 22 tertiary-care centers throughout the U.S.. It collected data on incident and prevalent cases seen between 1996 and 2002 to determine disease characteristics. The registry included 603 children. There was no evidence of a male preponderance, and slightly more than half had private insurance. In agreement with case-report series, the median age at diagnosis was 3.1 years, with a range of one month to 17 years. Age of diagnosis is not the same as the age of onset, as substantial and variable delays occur between first symptoms, sometimes diagnosed as croup or asthma and final diagnosis.

Because the registry was not population based, it did not provide evidence of burden of disease in terms of incidence or prevalence, but it did reflect the numbers of surgery required to manage the illness. The mean lifetime number of surgical treatments was 13, with a range of 2 to 179. Regardless of the age of diagnosis, as the airway matured, the numbers of surgeries decreased, reflecting the increasing size of the airway. Nonetheless, age at diagnosis was a predictor of disease severity, reflected by the likelihood of disease extension below the larynx and requirement for a tracheostomy.

Based on an analysis published by Bishai and colleagues and prevalence data from the Atlanta-Seattle study, and updating the figures to 2006 costs, the estimated cost of a single case of JORRP would be almost $43,000 annually, which would correspond to about $154,000 over a lifetime. This translates to an annual cost of between $19 million and $186 million for prevalent cases in the U.S.

Even less is known about adult onset RRP (AORRP). The only reported estimate of incidence is 1.8 per 100,000 person-years among people aged greater than 15. This comes from a 1993 survey of American otolaryngologists. However, a survey response rate of 23 percent and use of analytic methods extrapolating the rates of respondents to 100% of U.S. otolaryngologists suggests that 1.8 is a significant overestimate of prevalence. There has been no attempt to estimate incidence. Risk factors for AORRP have not been well studied, but orogenital transmission during sexual activity is believed to be the mode of AORRP acquisition. The two small case-control studies that looked at risk factors suffer from limitations, but both reach the same conclusion that the traditional risk factors for juvenile onset RRP were not active in the adult form. One study did find significantly more lifetime sex partners and more frequent oral sex among cases of adult onset RRP than controls.

Dr. Dunne provided information on HPV-associated genital warts. HPV Types 6 and 11 are the primary cause of genital warts; one recent study found that HPV 6 or 11 was detected in 97 percent of 65 genital-wart specimens. HPV 6 was found in approximately 70 percent, HPV 11 in approximately 40 percent, and both types were found in 10 to 20 percent of specimens.

Clinical presentation varies and includes flat warts, papules, pedunculated, grouped warts or condylomas; clinical presentation may vary based on the type of genital mucosa involved. Many cases go unreported, as genital warts rarely cause symptoms such as pain. They are, however, associated with frequent recurrences with or without treatment, and usually recurrences cluster around the first detected episode. For HIV-infected persons, warts may be larger, more numerous, and more difficult to treat. During pregnancy, warts are more likely to proliferate.

The psychosocial burden due to genital warts is important. Diagnoses cause anxiety, discomfort, embarrassment, anger, and shame, and these emotions can adversely affect intimate relationships. One study evaluating the psychosocial impact found significant distress was associated with recurrences and treatments due to genital warts. In addition, there was commonly a delay in seeking treatment.

Treatments for genital warts are described as patient applied or provider administered. They include antiproliferatives, such as antimitotic treatment like podophyllin; destructive or excisional treatments, such as cryotherapy, excision or laser treatments; and immunomodulating treatments, such as imiquimod, a therapy that induces an immune response to warts. Treatments can result in side effects, including burning, itching, pain, and, rarely, fistulas or ulcers. Episodes of care last, on average, for three clinic visits, and 70 percent of the cases are concluded within a ten-week period.

Transmission is by sexual contact, primarily through sexual intercourse. A study conducted in 1971, before the etiology of genital warts was known to be HPV, found that as many as 64 percent of the sexual contacts of men or woman with genital warts acquired the disease. On average, the acquisition of genital warts after sexual contact

was 2.8 months. A recent study conducted in a cohort of college women in Seattle demonstrated the high acquisition of genital warts. The study evaluated women who had incident HPV 6 or 11 infection and followed them for development of warts. By 24 months, approximately 60 percent of the women with incident HPV 6 or 11 infections developed genital warts. The median time between detection of incident HPV 6 or 11 infection and detection of the genital warts was 2.9 months, and the median time to clearance with treatment was 5.9 months.

There are imprecise estimates of the burden of genital warts in the United States because there are no nationally representative data and the disease is not nationally reportable or notifiable. Previously experts estimated that 1 percent of sexually active individuals had genital warts. The best available data are from large databases on insurance claims, including Medstat and Integrated Healthcare Information Services (IHCIS); National Health and Nutrition Survey (NHANES), a nationally representative sample of the U.S. population; and clinic data from the STD Surveillance Network, a network of sentinel STD clinics in the U.S. in five geographic regions. None of these data have prevalence or incidence of disease from a nationally representative population, but all offer some insight on the burden of disease. The National Disease and Therapeutic Index (NDTI) uses physician reporting to assess prevalence and incidence, but there are wide standard errors of estimates.

An evaluation of genital warts using administrative discharge data was conducted in Medstat, a national insurance-claims database. The results showed the highest rate per 1,000 person-years occurred in the 20- to 30-year-old females and males and the peak occurred at a younger age in females than males. However, the overall rate in person-years was similar for males and females at 1.7 per 1000 person-years.

The IHCIS database is a collection of claims data from 1.7 million members from 30 health plans and it showed that the rate of new genital-wart claims was 157 per 100,000 person-years, with age-specific differences. Both Medstat and IHCIS demonstrate a similar incidence of genital warts, half a million cases per year, with a range of 200,000 to 1 million cases and clear age-specific differences in prevalence and incidence.

There are limitations to these administrative databases. Data on prevalence are among an insured population, and detection requires an office visit. Other studies have shown that many who have genital warts do not seek treatment or healthcare. In addition, the discharge codes can be nonspecific for genital warts.

During 1999 to 2004, there was an NHANES assessment of genital warts. Sexually active men and women were asked the question, "Has a doctor ever told you that you had genital warts?" Prevalence of ever having been diagnosed with genital warts was higher in women (7.2 percent) than men (4 percent) and highest among the 25- to 34-year-old women and 35- to 44-year-old men. STD clinic data suggest genital warts are one of the most common STD diagnoses, and are typically more common in men than women, which likely reflects the population attending STD clinics. The STD Surveillance Network evaluated prevalence of genital-wart diagnosis in 17 STD clinics in five geographic areas. Although it varied by geographic area, a substantial proportion of visits were for genital warts: between 1.7 and 13.6 percent of all visits.

HPV vaccination could reduce the costs associated with genital warts. The primary factors that drive cost-effectiveness evaluations are direct medical costs,

including cost of treatment; repeat visits for treatment; and quality of adjusted life years, or QALYs. The short-term reduction in QALYs associated with genital warts has been estimated to be approximately ten percent. However, there are limited studies and this estimate is primarily based on expert opinion. An important consideration for HPV vaccine cost-effectivenes is the issue of discounting, whereby benefits that accrue earlier are valued more highly than benefits that accrue later. The impact of the HPV vaccine on genital warts would be earlier than for cervical cancer and some cervical cancer precursor outcomes.

The annual direct healthcare costs of genital warts in the U.S. are estimated to be $200 to $225 million. The cost for a treated case of genital warts is $567, which includes treatment and repeat visits required due to recurrences or to complete treatment. Treatment costs using commonly prescribed therapies range between $150 and $2400, and repeat visits for office treatments are, on average, three visits over a three-month period. The percentage of total averted costs in QALYs saved by HPV vaccination attributable to reductions in genital warts is about 12 to 13 percent.

In summary, there are imprecise estimates of prevalence and incidence of genital warts in the U.S. Available data suggest an incidence on the order of half a million cases per year, with a range of 200,000 to 1 million. The incidence and prevalence varies based on ages being considered. Genital warts are common in young women and men, and the peak prevalence is in 20- to 30-year-olds. There is a substantial health and economic burden due to genital warts.

Discussion

Dr. Chilton asked whether the fact that lifetime costs for treatment of respiratory papillomatosis were less than four times the annual costs implied that the average life expectancy is less than four years. Dr. Chesson replied that the cost estimates by Dr. Bishai assumed a 4.2 year duration of the cost associated with RRP, which does not assume death at four years, just the end of the costs. Dr. Schuchat added that the need for surgery decreases with age, so the frequency of surgery is weighted early in the life.

Dr. Katz asked how measles vaccine worked in treating RRP. Dr. Unger replied that there had been no placebo-controlled comparison. It is given by one clinician, who does not know why it works and in fact there is controversy about whether it really does work. Most people posit that it is an adjuvant effect.

Issues for ACIP Consideration

Dr. Markowitz reminded the ACIP that in June 2007 there was the first update on the Phase III data from the bivalent HPV vaccine and an introduction to considerations for ACIP recommendations. Today there were presentations on background data that the committee will need for recommendations. Proposed sessions for February would include an overview of the vaccine data and other data that may become available, along with cost-effectiveness analyses of the two vaccines and then a potential vote on the bivalent HPV vaccine.

ACIP currently recommends routine vaccination of females with quadrivalent HPV vaccine at 11 to 12 years of age. Vaccination can be started as young as nine years

of age and is recommended for females 13 to 26 years of age who have not been previously vaccinated or completed a full series. There are a variety of special situations, including equivocal or abnormal Paps, positive HPV test, or genital warts. Vaccination would provide protection against vaccine types not already acquired, but will have no therapeutic effect. Immunocompromised patients can be vaccinated, although the immune response and vaccine efficacy might be less in this group. Quadrivalent vaccine can be administered at the same visit as other age-appropriate vaccines. There were no data on administration of the quadrivalent vaccine with vaccines other than hepatitis B vaccine at the time of licensure, but it is not a live vaccine. The vaccine is not recommended for use in pregnancy.

Questions under consideration are related to the bivalent vaccine itself and to having two licensed HPV vaccines. First, what recommendations should be made for bivalent vaccine use in 10- to 25-year-old females, assuming this is the age for which it is licensed? If it is licensed for use in older females, what recommendations should be made in that age group? Possible ACIP recommendations are for vaccination of 11 to 12 year olds, similar to the quadrivalent vaccine. It could be given as young as ten years of age, with catch-up recommended for 13 to 25 year-olds. For the special situations and pregnancy, the possible ACIP recommendation would be similar to the quadrivalent vaccine.

Regarding simultaneous vaccination, there will be no data on administration with any vaccine at the time of licensure, although studies are ongoing. Although it is not a live vaccine, and the general recommendations state that non-live vaccines can be given simultaneously with other vaccines, the bivalent HPV vaccine contains a new adjuvant. The options are either not recommending simultaneous administration until further data are available or stating that the vaccine can be administered simultaneously.

It is not clear whether there will be a FDA indication for use of the vaccine in older women based solely on immunobridging data. Efficacy trials are ongoing for both the quadrivalent and the bivalent vaccines. If there is an indication, the work group is discussing a variety of options, including a permissive recommendation in some specific age groups, recommendations for specific subgroups, or other recommendations.

For two licensed HPV vaccines, issues that need to be addressed are: 1) Should a preference be stated for one vaccine? Data to be considered for this issue include: Are there differences related to protection against HPV 16 and 18 outcomes, differences related to protection against outcomes related to other oncogenic types, or differences related to protection against HPV 6 and 11? Are there differences in cost- effectiveness between the two vaccines? 2) Can the vaccines be used interchangeably, i.e., can vaccination series be started with one vaccine and completed with another?

Dr. Markowitz reviewed summary data comparing the two vaccines. In terms of protection against HPV 16 or 18, CIN, or AIS endpoints, the working group feels that both vaccines are similar and have very high efficacy. For the quadrivalent vaccine, there are additional data showing it is effective against VIN and VaIN. For HPV 6- and 11-related genital lesions, quadrivalent vaccine provides protection but the bivalent vaccine does not. For cross-protection against high-risk types other than HPV 16 and 18, it is still somewhat unclear because the endpoints used are different. The work group feels that both vaccines do provide some cross-protection, although it may be limited. The overall impact of cross-protection might be similar between the two vaccines, although it could

differ slightly for specific types. At the present time, there are no data to indicate differences in duration of protection. Efficacy has been very high for both vaccines and they appear similar at the present time, but this remains a question.

The quadravalent vaccination series will cost $360; pricing for the bivalent is still unknown. Cost-effectiveness will be reviewed at the next ACIP meeting. All else being equal, the quadrivalent vaccine that provides protection against 6 and 11 would be somewhat more cost-effective, but differences in any of the other attributes could change the relative cost-effectiveness.

The work group has not crafted specific recommendations related to having two licensed HPV vaccines, but has discussed stating differences in the data available for the two vaccines to date, specifically with regard to protection against HPV 6 and 11, and noting that the quadrivalent vaccine provides protection against genital warts. This would encourage providers to understand differences between the two vaccines. For protection against 6/11/16/18-related outcomes, the quadrivalent vaccine would be recommended, and for protection against HPV 16- and 18-related outcomes, the quadrivalent or the bivalent vaccine would be recommended.

Regarding a preferential recommendation, this is a very unique situation, since one vaccine provides protection against additional outcomes. There are knowns about both vaccines, and some of the attributes may favor one vaccine over the other, but that will not be known for several years.

In terms of interchangeability of the two licensed vaccines, the work group discussed stating that, whenever feasible, the same brand of HPV vaccine should be used for all doses of the vaccination series. If the vaccine previously administered is unknown, either HPV vaccine should be used to continue or complete the vaccine series to provide protection against HPV 16 and 18.

The work group will be reviewing an enormous amount of data and discussing issues related to recommendations for the bivalent vaccine and for two licensed HPV vaccines, in preparation for a possible vote on the bivalent vaccine in February 2008.

Discussion

Dr. Neuzil suggested some additional considerations for the work group. The presentations have talked about clinical trials with highly select populations where women follow very strict schedules and the majority get three doses. It will be very important to know how these vaccines perform when not given on strict schedules and people do not get three doses and it is given to the entire population.

Dr. Judson added that it would also be helpful for clinicians and patients who need to understand the costs and benefits of the vaccines to know the age-specific prevalence rates within a certain margin of error for different age groups with different sexual histories. Dr. Markowitz said that some of these issues have been presented and discussed at previous ACIP meetings before recommendations were made for the quadrivalent HPV vaccine; the committee did not want to make recommendations based specific sexual histories.

Dr. Schaffner noted that those who are interested in adult immunization have been encouraging the committee to move away from risk-based immunizations to larger, age-based recommendations.

Immunization Safety
Dr. John Iskander, CDC/OD/OSCO
Dr. Bill Thompson, CDC/NCIRD/ID
Dr. Barbara Slade, CDC/OD/OSCO
Dr. Sandra Chaves, CDC/NCIRD/DVD

Introduction

Dr. Iskander introduced the three presenters and their topics.

Early Thimerosal Exposure and Neuropsychological Outcomes at 7-10 years

Dr. Thompson presented results from a published study on early thimerosal exposure and neuropsychological outcomes at seven to ten years. Thimerosal is a preservative used in many childhood vaccines during the 1990s. It is metabolized into ethylmercury and thiosalicylate and is 50 percent mercury by weight. Little is known about the potential harmful effects of low-dose ethylmercury exposure from vaccines and immunoglobulins. More is known about prenatal methylmercury exposure from fish consumption.

The study was designed with significant input from independent, external experts. The analysis plan was written and approved in 2002 prior to data collection. All statistical analyses were executed as specified in the analysis plan; subsequent to reviewing the first round of results, additional analyses were conducted based on input from the external experts.

This was a retrospective cohort study of children from four Vaccine Safety Datalink (VSD) sites, who were born between 1993 and 1997 and could have received thimerosal-containing vaccines. They were aged 7 to 10 years at the time of the neuropsychological testing, and were stratified by thimerosal exposure during the first seven months of life, using the automated VSD vaccine records.

Forty-two different outcomes were assessed during a three-hour testing period. Autism was not assessed; there is a separate ongoing autism case-control study. The study measured speech and language, verbal-memory, attention and executive-functioning, behavioral-regulation, fine-motor coordination, tics, general intellectual functioning and achievement, and visual spatial-ability. Measures were selected based on Tom Verstraeten's VSD screening study and the methylmercury fish studies, as well as suggestions by the external panel of consultants. Sources of information included VSD automated data, which provided data and information on postnatal vaccine exposures; medical-chart reviews of all the children and the mother's prenatal records; vaccine records brought in by parents; and a maternal interview regarding potential prenatal exposures.

For each outcome in the primary model , a prenatal thimerosal exposure variable and a thimerosal exposure from zero to seven months variable were defined. Adjustments were made for site variables, child and family characteristics, and other exposures and confounders. An expanded model included the prenatal thimerosal exposure variable and a thimerosal exposure from 0 to 28 days variable, based on concern that very early exposure was potentially problematic. That same model also included thimerosal exposure from one to seven months. The published manuscript

presents results from 378 statistical tests, representing 42 neuropsychological outcomes and three exposure periods: the prenatal period, the zero- to seven-month period; and the 0-to-28-days period. Models were run for the entire sample as well as gender-specific analyses.

A total of 1,107 children were tested in the clinics, representing a 30 percent response rate. After excluding children for conditions found during parental interviews, the final analysis sample had 1,047 children. This provided power of 90 percent to detect 0.10 of a standard-regression coefficient, which was more power than the methylmercury fish studies had.

The majority of outcomes had no association with thimerosal exposure. There were 12 outcomes where increasing thimerosal exposure was associated with better outcomes, and 7 outcomes where increasing thimerosal exposure was associated with poorer outcomes. This represents significant findings for 5 percent of the statistical tests conducted. For the prenatal exposure period, a better outcome was found for the NEPSY Speeded Naming Test and a poorer outcome for the WISC III Digit Span Backward Recall. For the birth to seven-month exposure period, better outcomes were found on Grooved Peg-Board Non-Dominant Hand and the WISC III Digit Span Backward Recall and no poorer outcomes were found. For the birth to 28-day period, better outcomes were found on Finger-Tapping Dominant-Hand and poorer outcomes for the Goldman-Fristoe Test of Articulation.

In terms of the sex-specific effects, for the prenatal period in males better outcomes were found for the Stanford Binet Copying and poorer outcomes for the WISC III Digit Span Backward Recall; there were no significant effects for the prenatal period for females. For the birth-to-seven-month period, better outcomes were found in males with the WISC III Letter-Word Identification and poorer outcomes with the BRIEF Parent Rating of Behavior Regulation, and motor tic and phonic tics, as reported by the child assessor. For females, there were better outcomes for Grooved Peg-Board Non-Dominant Hand and the WISC III Digit Span Backward Recall. For the birth-to-28-days period, better outcomes were found on three measures for the males; for females, better outcomes were found on motor tics based on the parent reporting and a poorer outcome was found on the WASI Verbal IQ measure.

Among the 42 outcomes, few significant associations with thimerosal exposure were found prenatally or during the first seven months of life. These few associations were equally divided among better and poorer outcomes and were mostly sex specific. The negative association for tics is potentially important because a similar association was found in two previous vaccine safety studies: Tom Verstraeten's 2003 VSD screening study and the Andrews study in the U.K. Further study is needed.

The other negative associations were a poorer outcome with verbal IQ among girls and the GFTA measure amongst all children, which suggest a possible association with language development. This association was also found in one HMO in the Verstraeten-VSD screening study. However, the present study found a better outcome for performance IQ for boys, which suggests that the finding cannot be generalized.

In conclusion, the weight of the evidence does not support a causal association between early ethylmercury exposure from thimerosal-containing vaccines and immunoglobulins and neuropsychological functioning at seven to ten years of age.

As part of this study, a public-use data set was created and made available on the CDC Web site the day the manuscript was published.

Discussion

Ms. Stinchfield asked for clarification on the immunoglobulin part of thimerosal exposure. Dr. Thompson explained that if a pregnant mother was rH negative she received immunoglobulins, which contained thimerosal.

Mr. Lassiter asked why this study did not compare a no-thimerosal group versus a thimerosal group, since there is no established toxicity limit for ethylmercury. Dr. Thompson replied that very few children in HMOs had received no thimerosal-containing vaccines at the time of the study. Instead the study looked at a range of exposures, from low to high. A study currently being carried out in Italy had a similar test battery and randomly assigned children to thimerosal exposure and no-thimerosal exposure. CDC also has an ongoing thimerosal-autism study, which should be completed in the next year.

Ms. Redwood observed that this was just an observational study and not designed to address causation and effect. The small sample size and few children in the highest and lowest exposure groups reduced the study's power and ability to establish statistical significance. Early interventions, which may have reduced or eliminated deficits such as speech delays by age seven to ten years, were not controlled, and there was no analysis of combined prenatal and postnatal mercury exposures. In addition, newborns weighing 5 lbs 8 ounces or less, approximately 9 percent of all U.S. births, were excluded. These infants may be more vulnerable to mercury effects due to their smaller size. The study did find associations similar to those detected in similar studies, such as an increased rate of motor and verbal tics, and poor language ability, which are also seen in autism. Replication of these same findings in two other thimerosal investigations supports arguments for causality. These findings were downplayed because several areas, including performance IQ, letter and word identification, were enhanced by thimerosal exposure. Children diagnosed with neurodevelopmental delays typically have scatter skills. The fact that there are both detrimental and beneficial findings from exposure to thimerosal does not equate with no evidence of injury.

Summary of Syncope Reports to VAERS

Dr. Slade presented a summary of postvaccination syncope events in young women after receiving the HPV vaccine, as reported to Vaccine Adverse Event Reporting System (VAERS) from January 1, 2005, through July 31, 2007. Syncope is a transient loss of postural tone and consciousness with spontaneous recovery. It is generally thought to be due to an abnormal sympathetic reflex resulting in bradycardia, peripheral vasodilation, and hypotension with decreased brain profusion. It can be elicited by a variety of stimuli and has been documented to occur after medical procedures, including vaccination. The ACIP recommends that providers strongly consider observing patients for 15 minutes after vaccination. If syncope occurs, the individual should be observed until symptoms resolve.

Post-marketing safety is monitored through the VAERS, a national passive surveillance system jointly operated by the FDA and CDC. It covers all licensed U.S. vaccines and receives about 15,000 reports each year.

The objectives of this analysis included describing trends and syncopal events reported in VAERS, characterization of the post-vaccination syncopal events, and identification of potential areas for further study. Serious reports of syncope have been reported, including death. As an example, a15-year-old male who had received hepatitis B vaccine had syncope, fell, hit his head, had cerebral hemorrhage, and subsequently died. Eighty-nine percent of previously reported syncopal events occurred within 15 minutes of vaccination. Of the 3,168 syncope reports from 1990 through 2004, 35% occurred among persons aged 10 to 18, and 14% resulted in hospitalization, primarily due to injury from the fall or for medical observation.

This study used MedDRA coding terms for "syncope" and "syncope vasovagal." Cases had to be age five years or older. Vaccines reported to be temporally associated with the syncope were identified and medical records were reviewed for selected reports.

During 2002-2004, there was a total of 23,934 reports, with 203 reports of syncope. For the study period (January 1, 2005- July, 31 2007), there were 25,861 reports to VAERS, with 463 cases of syncope, a statistically significant increase. In comparison, for serious syncope, there is no statistically significant difference of the percentage of serious cases of syncope between the two time periods.

The increase in syncope reports started in 2005, with a greater increase late in 2006, and a marked increase in 2007, particularly for females aged 11 to 18 years. This time frame parallels ACIP votes to recommend the three new adolescent vaccines: MCV4, Tdap, and HPV. Of 463 syncope reports, 49% were seen in females aged 11 to 18 years of age; the excess reports among females, especially the 11- to 18-year-old age group, were attributable to the HPV vaccine.

The top three vaccines associated with syncope reports in VAERS for the study period were HPV, MCV4, and Tdap. At least one of these vaccines was reported in 60% of the syncope reports for single vaccines and 68% of reports for multiple vaccines. HPV was the most frequently reported vaccine type. The numbers for the multiple vaccines are not exclusionary, so there was overlap in the vaccines.

There were 41 syncopal reports associated with injuries among the 463 syncope reports. Thirty-one, or 76%, were among adolescents aged 11 to 18 years of age, and 71 percent were among adolescent females. The time lag from vaccination to syncope onset was less than five minutes in 49% of the cases and less than 15 minutes in 80%. Twenty-four percent or 10 of the injuries were characterized as serious due to hospitalizations related to injuries from falls. An example is a 13-year-old girl who fainted less than ten minutes after receiving both HPV and MCV4. She fell backwards, hit her head, and was admitted to the PICU for a skull fracture and subarachnoid hemorrhage. She has fully recovered.

Among individuals over age 50, there were 20 serious reports, predominantly in females, including two deaths, one from anaphylaxis and one from a hypoxic ischemic encephalopathy with multiple organ failure. But 70% of the serious reports had pre-existing medical conditions, primarily cardiovascular, and most of the cases were related to TIV, including the two deaths associated with TIV. Of concern is that only 30% of the reported events occurred within the 15 minutes after vaccination.

There are a number of limitations to the VAERS data. Incidence rates cannot be calculated because the number of doses actually administered is unknown. There is known underreporting of adverse events. The MedDRA coding terms are used for indexing rather than for diagnosis, and miscoding or misdiagnosis are not infrequent. All of the non-serious reports were not reviewed, so it cannot be determined whether the syncope was related to the particular vaccine, the age of the recipient, or both. VAERS is not set up to do root-cause analysis, and one cannot evaluate the impact of the fact that HPV has three doses rather than a single dose.

In conclusion, there has been an increase in the number of syncope reports in VAERS since 2005. This increase was associated with females aged 11 to 18. Most were non-serious reports and were related to the new "adolescent vaccines": HPV, MCV4, and Tdap. Injuries after syncope are rare, but do occur and can be serious. These injuries may be preventable, and the time interval for syncope after vaccination may differ for different age groups.

Areas for further research include determining the age-specific incidence rates for syncope associated with vaccination; a survey of providers to evaluate adherence to the 15-minute recommended waiting period after vaccination; studies to evaluate the effectiveness of this waiting period and other measures to prevent secondary injury; and evidence-based recommendations for interventions to prevent or predict syncope after vaccination.

Discussion

Dr. Chilton noted that children under age five were excluded from the study, yet the recommendations both from the AAP and the ACIP are to have all children wait 15 minutes after an immunization. Dr. Slade explained that younger aged children do not tend to have falls after syncope.

Dr. Lett pointed out that some anecdotal evidence or published studies showed an association between under-hydration and maybe hypoglycemia, lack of food intake prior to syncope. Dr. Slade replied that that area needed study. The Red Cross has started giving people a bottle of water while standing in line to donate blood. In the non-serious reports, some people commented that they had not eaten that day, which could cause syncope. The literature reports that approximately 90% of people who have an episode of syncope have a first-degree relative who also has experienced syncope, so that could be a useful question to ask before vaccination. While approximately 50% of people report having experienced syncope at some time in their lives, people who have a history of more than two episodes are very likely to have another one, so that could be an additional question to ask before vaccination.

Dr. Baker asked if there was a study to define the missing areas, e.g., age-specific rates or potential interventions. Dr. Slade responded that an on-going Vaccine Safety Datalink Project (VSD) study with the HPV will be able to look at age-specific rates. A possibility is that CDC's Clinical Immunization Safety Assessment Network (CISA) could do a study looking at effectiveness of other interventions. Dr. Baker said that the amount of pain reported from HPV suggests the syncope is probably a vasovagal phenomenon.

Dr. Craig asked if there was any way to tease out the issue of something in the HPV versus just the pain issue, even with the numbers being relatively small. Dr. Slade replied that this would be difficult, but that allaying people's fears while they are in the waiting room would probably be helpful.

Dr. Salisbury indicated that the U.K. had resisted stating any length of time that people should stay after vaccination, since keeping people would be very inconvenient in a clinic. He suggested that reports of convulsions and seizures needed to be studied as well. The U.K. has found that what are reported as seizures occurring immediately after vaccination are often just a form of fainting, so if using only syncope as an indicator, a number of other instances may be missed. Dr. Slade added that there are guidelines on how to tell the difference between syncope and a real seizure.

Dr. Iskander noted the relative lack of an evidence base for either the currently recommended interventions or any other interventions. Postvaccination syncope falls into a patient-safety model, where the need is to develop and design and evaluate interventions rather than simply to continue to accumulate data on the problem.

Update on Varicella Vaccine Safety

Dr. Chaves reminded the committee that varicella vaccine for children has been in routine use since 1995, and has resulted in a substantial reduction in disease burden, mortality rate, and health characterization. Early post-marketing data indicated that the vaccine had a safe profile. Most of the reported adverse events were not serious: mainly fever, varicella-like rash, and injection-site reaction, which were described during pre-licensure clinical trials. The rare serious adverse events reported were described as vaccine Oka strain and included pneumonitis and hepatitis, both in immunocompromised patients, as well as herpes zoster, secondary transmission, and severe rash post vaccination. Encephalitis, ataxia, thrombocytopenia and vasculitis were also described but there was no lab confirmation.

Since 1998, there has been a fivefold increase in the amount of varicella vaccine distributed in the U.S., which could help identify more rare adverse events. In addition, many adverse events were being reported in the literature as case reports. Finally, there were concerns about the late reactivation of the latent varicella vaccine virus.

The analysis used VAERS data from May 1995, when the vaccine was licensed, to December 2005, and looked at all adverse events reported as following varicella vaccine using all COSTART codes. It also searched text fields specific for zoster and meningitis. Serious reports involve hospitalization, death, and life-threatening and disabling illness. Reporting rates were based on rates of vaccine distribution.

Results were similar to what was published in 1998 -- the overall reporting rate was 52.7 per 100,000 doses and the rate of reported serious adverse events was 2.6 per 100,000 doses, roughly 5% of the total. Fifty-eight percent of all reports followed varicella vaccine administered alone and the majority were also soon after the vaccine was licensed, dropping considerably over the next few years. There were 25,306 reports following varicella vaccine received and the most common events were rash, fever, and injection-site reactions, followed by urticaria and zoster.

Among all adverse events following varicella vaccine administration, a total of 60 deaths were reported, for a rate of 0.1 per 100,000 doses distributed. The majority of

death reports had alternative diagnoses or very little data were available to make any judgment in terms of causality or association with the vaccine. Four cases are worth mentioning. One published in 2003 was a vaccine strain VZV associated with varicella pneumonitis in a child later identified as having natural killer T-cell deficiency. The paper described the vaccine as a contributing factor in his death. Two cases of encephalopathy due to ornithine transcarbamylase (OTC) deficiency were identified in this analysis. These were previously healthy children who received the vaccine and then 14 and 30 days later developed ataxia followed by encephalopathy; they were subsequently diagnosed with OTC deficiency. OTC deficiency has a variety of triggering factors, including viral infections, so the vaccine could play a role in activating this disease. The fourth case died from hemophagocytic lymphohistiocytosis or HLH diagnosed following receipt of varicella vaccine. HLH has also been described as being triggered by a variety of viral infections. This case's brother had died two years earlier from the same disease following vaccination, but there was no record whether the vaccine was varicella. Further investigation is needed to confirm these findings and evaluate to what extent varicella vaccine could play a role in activating diseases in persons with genetic predisposition.

There were 981 reports for zoster and 47 were serious enough to be hospitalized, roughly 5% of the total. The median age was 2.5, ranging from 12 months to 12 years, and the median interval from vaccination to zoster was 7.3 months. The most frequent zoster location was the face, and 12 cases had meningitis concomitantly. Twenty-eight of the 47 hospitalized children had PCR VZV positive, with ten confirmed as vaccine strain and seven as wild type; 11 had not been genotyped. Most of these children were healthy; only seven had any kind of immunosuppressed illness described in their medical charts.

Among the 12 cases that had meningitis concomitantly, nine had VZV PCR done in cerebrospinal fluid (CSF) samples. They were all children 1 to 12 years of age and most of them were healthy. The three isolates sent for typing were all confirmed to be vaccine strain. Two were in immunosuppressed children, and one was in a healthy child. After this analysis was finished, another report was received of a healthy eight-year-old, vaccinated at age four, who had zoster followed by meningitis four days later. Both CSF and skin samples were VZV positive by PCR and confirmed to be vaccine strain.

These results should be interpreted with caution. Because VAERS is passive surveillance, underreporting is an issue, principally because adverse events are more likely to be reported soon after the vaccination (e.g., diseases related to varicella vaccine virus reactivation may take years to occur). There is large number of reports soon after a vaccine is licensed due to enthusiasm and awareness, but as soon as the vaccine becomes routine, there is a drop in adverse events reported, which may contribute to underreporting. Over-reporting can also be an issue as many reports temporally related to vaccine are actually caused by other agents. There is also the challenge of dealing with multiple vaccines administered simultaneously. Most reports are not verified and very limited clinical and lab data are available. Finally, there is no denominator on doses administered by age, which makes it difficult to estimate specific rates to compare findings with data available in the literature.

Overall the vaccine has a good safety profile. The majority of adverse events reported are non-serious. Many adverse events reported could be biologically associated with the vaccine. The rate of zoster reactivation among vaccinees is unknown, but

limited data available seem to suggest a lower rate of zoster among vaccinees compared with children that had natural varicella disease.

There is little information on rates of rare complications with zoster; recent studies, mainly in Europe, suggest this may be more common than previously thought, but may also be just a reflection of lab tools available in recent years.

In conclusion, overall serious events reported after varicella vaccination continue to be rare, which is reassuring for the program, and must be considered relative to the substantial benefits of the varicella vaccination. The vaccine strain may be a contributing factor in activating diseases in patients with genetic predispositions and may also reactivate and cause serious zoster, leading to hospitalizations and neurological complications, such as meningitis in healthy children. Healthcare providers should be constantly reminded of the importance of relying on lab results for diagnosis confirmation. CDC is planning to develop communication materials to emphasize the importance of laboratory confirmation and analytical studies to assess the risk of zoster reactivation in vaccinees using Vaccine Safety Datalink.

Discussion

Dr. Katz asked whether the adult zoster study had any cerebrospinal fluid spinal fluid findings of vaccine virus. Dr. Seward said she was not aware of any, nor was she aware of any zoster cases confirmed to be due to vaccine strain.

Dr Haber made a clarification about underreporting in new vaccine. What drops is the number of the non-serious reports, but serious reports remain steady over time in VAERS.

Dr. Iskander pointed out that one VAERS presentation used the COSTART coding system whereas another used MedDRA (Medical Dictionary for Regulatory Activities), which is actually the new international standard and was adopted by VAERS in January 2007. From now on, the vast majority of the data from VAERS should be using the MedDRA coding system.

Rotavirus Vaccines
Dr. Lance Chilton, ACIP WG Chair
Dr. Leonard Friedland, GlaxoSmithKline
Dr. Margaret Cortese, CDC/NCIRD, DVD
Ms. Penina Haber, CDC/ISO/OSCO

Working Group Update

Dr. Chilton said the group was reviewing information on two vaccines: the currently licensed RotaTeq, the human reassortant vaccine and a new GSK attenuated monovalent human rotavirus vaccine, Rotatrix, for which FDA approval is expected sometime in the spring. The working group will propose recommendations for the ACIP to consider if and when Rotarix is licensed and will continue to review post-marketing data on RotaTeq as that becomes available. Draft recommendations will be presented in February, in preparation for a final recommendation and possible vote in June.

GSK's Human Rotavirus Vaccine Rotatrix

Dr. Friedland said that GlaxoSmithKline had been developing this human rotavirus vaccine since 1998. The goal has been to develop a safe and effective vaccine for children worldwide designed to protect against rotavirus infection, the leading cause of severe dehydrating diarrhea in infants and children and the single greatest cause of diarrhea deaths in children.

In 1999 the first licensed vaccine, Rotashield, was withdrawn from the market after an association with intussusception, an uncommon but intensely life-threatening event. Despite this setback, clinical development of Rotarix continued, with the aim to license and distribute it in developing countries where 90 percent of the 600,000 annual deaths from rotavirus occur. Rotarix was first licensed in Latin America in 2004. Licensure in Africa, Asia, and Europe followed in 2005 through 2006. Licensure in Canada occurred earlier this month, and the U.S. application was submitted in June.

The basis for preventing rotavirus gastroenteritis comes from studies of natural disease. Velazquez and others have shown that rotavirus infection induces immunity against subsequent infections of gastroenteritis and that two infections confer virtually 100 percent protection against moderate to severe disease, regardless of rotavirus serotype. GSK chose to develop a human rotavirus vaccine in order to mimic human infection, protect against moderate to severe disease, prevent hospitalizations, reduce the socioeconomic burden caused by rotavirus, and provide broad cross-reactive protective immunity. There is a high degree of homology between human rotavirus proteins and human rotavirus strains.

Rotarix vaccine is derived from a G1P(8) human rotavirus strain isolated from a child in Cincinnati, Ohio. Cloning and culture passages resulted in RIX4414, a live attenuated human rotavirus vaccine. RIX4414 and the original unpassaged isolate genome differ by 12 nucleotide mutations, encoding ten amino added substitutions. It is genetically stable from seed to final vaccine.

Rotarix is a lyophilized vaccine, reconstituted with a liquid diluent that contains calcium carbonate as a buffer. Each oral dose is 1 milliliter and contains at least 10^6 cell-culture infected dose 50 of live attenuated human rotavirus strain. It is administered in two oral doses, the first beginning at six weeks of age, with an interval of at least four weeks before the second dose. The two-dose series should be completed by 24 weeks of age. A second-generation, ready-to-administer liquid formulation is currently in development.

Rotarix is now licensed in over 100 countries and recommended in national immunization programs worldwide. In February 2007, it was awarded WHO prequalification, which sets the stage for U.N. agencies such as PAHO and UNICEF to purchase and use Rotarix in mass-vaccination programs. Vaccine efficacy has been demonstrated in both developed and developing countries against severe rotavirus gastroenteritis, rotavirus gastroenteritis hospitalizations, any severity of rotavirus gastroenteritis, and gastroenteritis hospitalizations of any cause.

Dr. Friedland presented results from Rota-023, a Phase III efficacy and safety study that began in 2003 in 11 countries in Latin America and also in Finland. Over 63,000 infants were enrolled and vaccinated. Results were published in the *New England Journal of Medicine* in 2006.

Infants 6 to 13 weeks of age were randomized 1-to-1 to receive Rotarix or a placebo, and the second dose was given one to two months later. Routine immunizations, with the exception of OPV, were co-administered according to local recommendations. All 63,225 infants were followed for 30 to 90 days after receiving their second dose of study vaccine. This cohort was followed for a median of 100 days after the first dose. A subset only from the 11 Latin American countries was followed for one year for a vaccine efficacy analysis, and infants from 10 of the 11 Latin American countries were followed through a second year of vaccine efficacy analysis.

The primary study objective was to determine if two doses of Rotarix can prevent severe rotavirus gastroenteritis caused by circulating rotavirus strains, starting from two weeks after the second dose until the children were approximately one year of age. Secondary objectives included efficacy against G1 and non-G1 serotypes; intent-to-treat efficacy; efficacy using a Vesikari scaling system, a widely used scoring system that assesses severity of GE episodes according to distribution of clinical features; and efficacy through two years after vaccination.

Severe gastroenteritis was clinically defined as diarrhea, three or more loose stools in 24 hours with or without vomiting, that required hospitalization and/or rehydration therapy in a medical facility. Rotavirus was detected by ELISA in stool samples. The type of rotavirus was determined by reverse transcriptase PCR followed by reverse hybridization assay. This methodology allowed discrimination between G1 vaccine virus and wild-type G1.

Rotarix was highly efficacious in Latin America. Through the first year of life, vaccine efficacy was 85 percent against severe rotavirus gastroenteritis, using both the clinical case definition and the Vesikari scoring system. Vaccine efficacy was 85 percent against rotavirus gastroenteritis hospitalizations and 40 percent against all-cause severe gastroenteritis regardless of etiology. It was sustained at similar rates through the second year after vaccination against severe rotavirus gastroenteritis, rotavirus gastroenteritis hospitalizations, and all-cause severe gastroenteritis.

Statistically significant vaccine efficacy was demonstrated for common circulating rotavirus types: G1P(8), G3P(8), G4P(8), and G9P(8). Protection against Type G2P(4) was also demonstrated, though not statistically significant, with wide confidence intervals, given the overall small number of G2P(4) cases.

The second Phase III efficacy study, Study 036, was conducted in six countries throughout Europe. Infants 6 to 14 weeks of age were randomized 2 to 1 to receive Rotarix or a placebo, and a second dose of vaccine was given one to two months later. All infants received concomitant vaccination with the DTaP-HepB-IPV/Hib combination vaccine, and a subset received concomitant vaccination with PCV7 or with meningococcal C conjugate vaccine. All 3,994 infants were followed through the first rotavirus season after vaccination and again through the second rotavirus season after vaccination.

The primary efficacy objective in Study 036 was to determine if two doses of Rotarix can prevent any rotavirus gastroenteritis caused by circulating rotavirus strains, starting from two weeks after Dose 2 until one year of age. Secondary objectives included efficacy against severe cases of rotavirus gastroenteritis, Types G1 and non-G1 serotypes, rotavirus hospitalizations, medically attended rotavirus gastroenteritis, intent-to-treat efficacy, and efficacy through two years after vaccination.

Gastroenteritis was defined as diarrhea, greater than or equal to three loose stools in 24 hours, with or without vomiting. Severity was assigned using the Vesikari scale. A score greater than or equal to 11 was defined as severe gastroenteritis. This scoring system was also used in the Rotashield efficacy studies.

Rotarix was highly efficacious in Europe. Through the first rotavirus season after vaccination, vaccine efficacy was 87 percent against any severity of rotavirus gastroenteritis and 96 percent against severe rotavirus gastroenteritis. Rotarix was 100 percent effective in preventing rotavirus gastroenteritis hospitalizations and 92 percent effective in preventing rotavirus gastroenteritis that required medical attention. Rotarix efficacy was 75 percent against all-cause gastroenteritis hospitalizations, regardless of etiology. Vaccine efficacy was sustained through two rotavirus seasons after vaccination against any severity of rotavirus gastroenteritis, severe rotavirus gastroenteritis, rotavirus gastroenteritis hospitalizations, medically attended rotavirus gastroenteritis, and all-cause GE hospitalizations.

In this study, 82 percent of the infants received their first dose of study vaccine prior to the rotavirus season. As a result, six rotavirus cases occurred prior to the time infants received their second dose of study vaccine. Vaccine efficacy from Dose 1 up until the time the infants received Dose 2 was able to be analyzed. Vaccine efficacy from Dose 1 up to before Dose 2 against any severity and against severe rotavirus gastroenteritis was 90 percent and 100 percent respectively, with wide confidence intervals, given the small number of cases.

Statistically significant vaccine efficacy was demonstrated through two rotavirus seasons for all circulating rotavirus types. It was 96 percent against G1P(8) rotavirus, 86 percent against G2P(4) rotavirus, 94 percent against G3P(8) rotavirus, 95 percent against G4P(8) rotavirus, and 85 percent against G9P(8) rotavirus.

Study 023 in Latin America was specifically designed and powered to evaluate the risk of intussusception following administration of Rotarix as compared to placebo. The primary endpoint for safety was a case of intussusception diagnosed within 31 days of receiving the first or the second dose of vaccine. Intussusception cases were detected by independent, complementary methods. All hospitals in study areas were informed about the study, and relevant departments at hospitals were advised to contact study personnel regarding each case of intussusception evaluated. Parents of participating infants were informed about symptoms consistent with intussusception and instructed to seek medical advice at the nearest hospital if symptoms indicative of intussusception appeared and to also inform their investigator.

All potential intussusception cases were reviewed by an independent clinical events committee, composed of a pediatric gastroenterologist, a surgeon, and a radiologist, who remained blinded to treatment allocation. They characterized cases as either definitive, probable, or possible using Brighton criteria. In addition, safety was monitored by an IDMC, which had the authority to unblind.

The primary safety objective in this study would be met if the upper limit of the two-sided 95 percent confidence interval of the risk difference for intussusception within 31 days after vaccination was below 6 per 10,000. No statistically significant increase in incidence of intussusception within 31 days after vaccination was defined as the lower limit of the 95 percent confidence interval of the risk difference being below zero.

With an incidence rate of three to five cases of definite intussusception per 10,000 infants within 31 days in the placebo group, the sample size in this study had more than 86 percent power to meet the primary objective if the risk difference was truly zero. Each group, Rotarix and placebo, had 31,000 infants. Within 31 days of any dose, there were six cases of intussusception in the Rotarix group and seven cases in the placebo group, with a relative risk of 0.85. Within the safety surveillance period, which was a median of 100 days after Dose 1, there were nine cases of intussusception in the Rotarix group and 16 cases in the placebo group, with a relative risk of 0.56. The results indicate that Rotarix is not associated with an increased risk of intussusception.

Of the 13 definite intussusception cases diagnosed within 31 days after any doses, six occurred in the Rotarix group and seven in the placebo group. The relative risk for a case of intussusception within 31 days of any dose was 0.85, and the risk difference was negative 0.32. There was no temporal clustering of cases after either dose.

A secondary safety objective in Study 023 was all serious adverse events that occurred during the safety surveillance period. Significantly fewer numbers of SAEs and hospitalizations occurred in the Rotarix group compared to the placebo group. This was primarily driven by fewer serious adverse events and hospitalizations related to vomiting and diarrhea in the Rotarix group. A *post-hoc* analysis showed a 42 percent reduction in the Rotarix group in hospitalizations for gastroenteritis due to any cause.

An integrated summary of safety from all the randomized placebo-controlled clinical trials was submitted with the U.S. licensing application. The main integrated safety summary compares Rotarix at potency greater than or equal to 10^6 CCID 50, the potency intended for use in the U.S. The integrated summary of safety includes data on solicited adverse events, unsolicited adverse events, and serious adverse events. Relative risk, accounting for study effect with a 95 percent confidence interval of Rotarix compared to placebo, was estimated for each safety endpoint. Potential imbalances were defined as the 95 percent confidence interval for the relative risk across studies, excluding 1.0.

Looking at any intensity of solicited symptoms within eight days after each of the two vaccinations, the integrated summary of safety shows that similar percentages of infants in the Rotarix group and the placebo group reported any intensity of fever, cough or runny nose, diarrhea, vomiting, irritability and fussiness, or loss of appetite. Overall, reporting rates of Grade 3 or severe intensity solicited symptoms in all groups was low, mostly below 5 percent. In the eight-day period after each of the two vaccinations, similar percentages of infants in the Rotarix group and the placebo group reported Grade 3 fever, cough or runny nose, diarrhea, vomiting, irritability and fussiness, or loss of appetite.

At least one serious adverse event within the 31-day postvaccination period was reported by 1.7 percent of the infants who received Rotarix and by 1.9 percent of those who received placebo. Diarrhea, gastroenteritis, and dehydration were reported by more infants in the placebo group than in the Rotarix group, as noted by the 95 percent confidence interval for the relative risk, excluding 1.0. All other serious adverse events reported within the 31-day postvaccination period, including deaths, intussusception, bronchiolitis, pneumonia, or nervous system disorders, were reported by similar proportions of subjects in both groups, as indicated by the 95 percent confidence interval for the relative risk, overlapping 1.0.

All but one of the fatalities were reported in Study 023, conducted in Latin America. There was an imbalance of deaths related to pneumonia. An analysis of serious adverse events of events medically related to pneumonia and of hospitalizations linked to pneumonia did not confirm the imbalance in the number of cases of fatal pneumonia in Study 023. The overall SAE profile shows that Rotarix, compared to placebo, is associated with fewer serious adverse events associated with gastroenteritis disease.

Rotarix is a live attenuated human rotavirus vaccine that replicates well in the GI tract. Viral shedding following Rotarix administration was evaluated by the presence in stool of rotavirus antigen detected by ELISA and the presence of live rotavirus particles in stool detected by a titration assay. The rotavirus antigen shedding as assessed by ELISA was studied in a subset of all subjects in 7 of the 11 studies submitted in the U.S. licensing application. Rotavirus antigen shedding was predominantly observed on Day 7 after Dose 1 and decreased thereafter.

Data on live virus shedding in the clinical trials are limited. In two studies, all stool samples collected at Day 7 after the first vaccine dose were tested by ELISA for rotavirus antigen; the remaining samples were tested for the presence of live rotavirus in cell culture by indirect fluorescence. In Thailand, 56 percent of infants were shedding antigen after Dose 1 and 46 percent of the antigen shedders tested positive for live rotavirus. In Finland, 58 percent of infants were shedding antigen after Dose 1 and 46 percent of those tested positive for live rotavirus. The percentage of vaccinees with live rotavirus detected in stool was estimated by multiplying the proportion of stools that were rotavirus antigen positive by the proportion of rotavirus antigen positive stools that contained live rotavirus. Thus, it was estimated that approximately 26 percent of the infants were shedding live rotavirus at Day 7 after Dose 1 in these two studies.

Rotarix has been investigated in the U.S. when co-administered with the routine vaccinations Pediarix, Prevnar, and ActHIB. The objective of the study was to demonstrate that co-administration with Rotarix does not impair the immune response to any of the antigens contained in each of the routine infant vaccinations currently included in the ACIP infant vaccination schedule.

A similar percentage of infants in the co-administered and the separately administered groups achieved seroprotective antibody concentrations to PRP; hepatitis B surface antigen; poliovirus Types 1, 2, 3; and diphtheria and tetanus. Geometric mean concentrations of antibodies to pertussis antigens PT, FHA, and PRN were similar in the co-administered and separately administered groups, and geometric mean antibody concentrations of pneumococcal antibodies were similar in the two groups.

All 17 predefined non-inferiority criteria for comparisons between the co-administered and the separately administered group were met. The conclusion from this study is that Rotarix does not negatively impact the immune response to the antigens present in Pediarix, ActHIB, or Prevnar.

In July 2007, approximately 12 million doses of vaccine were distributed. As of the 11th of July, 140 spontaneous reports of intussusception after Rotarix vaccination had been received by GSK, 88 of which had sufficient information to allow classification as definite intussusception according to Brighton case definition; of those, 56 were reported to occur within 31 days after Rotarix vaccination. GSK estimates that 556 cases of intussusception within 31 days of Rotarix vaccination would have been expected to

occur, based on expected incident rates of intussusception in infants by region, the proportion of intussusception expected to occur each month by age in the first year of life, and the number of doses distributed. While the number of doses distributed does not necessarily equal the number of doses administered and recognizing that there is unknown surveillance quality in many countries, the post-marketing experience to date shows no indication of increased intussusception risk.

Ongoing pharmaco-vigilance and risk-management activities include surveillance for intussusception cases reported in post-licensure settings and safety studies conducted in settings of universal vaccination, designed and powered to investigate the incidence of intussusception post-rotavirus vaccination. One is a post-authorization safety study being conducted in Mexico, which has a national rotavirus immunization program. This study, involving the IMSS network throughout Mexico, includes 224 pediatric health facilities with an annual birth cohort of 575,000. GSK will be monitoring for drifts and shifts in vaccine strain after market introduction. Studies are currently being conducted to assess horizontal transmission of vaccine virus strain between twins, immunogenicity and safety in preterm infants, immunogenicity and safety in HIV-positive infants, and vaccine effectiveness.

In summary, the clinical database is sufficiently large to evaluate the safety of this vaccine. There has been no increased risk of intussusception among infants vaccinated with Rotarix compared to placebo, and the reactogenicity and safety profile of Rotarix is clinically acceptable and similar to placebo. Rotavirus antigen shedding occurs in about 50 percent of subjects, with peak excretion about the seventh day after the first dose. Live virus shedding occurs in about 26 percent of infants at seven days in two clinical trials, and Rotarix does not negatively impact the immune response to the antigens present in Pediarix, Prevnar, and ActHIB. Rotarix prevents rotavirus gastroenteritis, as demonstrated in the Phase III study in Latin America and the Phase III study in Europe; in Europe, protection against any severity of rotavirus gastroenteritis was 87 percent, and severe disease was 96 percent. Rotarix prevents rotavirus gastroenteritis caused by strains G1, G2, G3, G4, and G9, and efficacy persists through two years after vaccination.

Discussion

Dr. Hull asked if there had been any surveillance for clinical illness or infection in diaper changers. Dr. Friedland replied this had not been done, but that rates of vomiting and diarrhea and other gastroenteritis-like symptoms are comparable in placebo and those receiving the vaccine.

Ms. Stinchfield asked what the time frame was on the preemie studies and the HIV studies. Dr. Friedland replied that results for the premature infant study were expected in the third quarter of 2008 and for horizontal transmission, results were expected in the second quarter of 2008. For immunocompromised infants, results are also expected in the second quarter of 2008.

Dr. Katz asked about the range of titers of the shed virus. Dr. Friedland said the data were limited, but in the clinical studies where this was tested, of those who came down with wild-type rotavirus disease, 68.6 percent were shedding live rotavirus in their stool. The quantification, expressed as FFU per 200 milligrams per stool, was threefold

higher in those who had live rotavirus wild-type disease compared to those who shed vaccine virus.

Ms. Johammer from the California Department of Public Health Immunization Program asked if the vaccine had to be mixed and how complicated that was for storage and other issues. Dr. Friedland responded that the current presentation is a lyophilized vaccine, and the process to prepare it is no different than any other currently marketed lyophilized vaccine. GSK is planning to bring forth a liquid formulation (development plans are under review by the FDA) and has conducted four clinical studies with a liquid formulation, with a large amount of CMC data, to demonstrate that the vaccine is as immunogenic and safe with the liquid formulation.

Dr. Slade asked whether any cases of Kawasaki's were observed. Dr. Friedland replied that there were no reports of Kawasaki disease in the post-marketing experience. In the completed and ongoing clinical trials, observed rates of Kawasaki disease were on par with what would be expected.

PRV (RotaTeq) Update

Coverage and Adherence with Age Recommendations

Dr. Cortese reminded the committee that ACIP recommended the pentavalent rotavirus vaccine, RotaTeq, in February of 2006 for all infants, in a three-dose series to be given at ages two, four, and six months. The age recommendations were those studied in the large safety and efficacy trial. Vaccination should not be initiated after 12 weeks of age because of insufficient data on safety in administering the first dose to older infants. Subsequent doses are to be given four to ten weeks apart, and no doses are to be given after age 32 weeks.

To assess vaccine uptake and adherence to these recommendations for doses administered as of approximately May 31st, 2007, three information sources were used. The Sentinel Area Immunization Information System covers six areas in the United States and meets certain criteria, such as covering 10,000 children or more aged less than six years. They have approximately 90 percent provider sites participating in the registries and incorporate procedures to increase completeness and accuracy. The Vaccine Safety Datalink is a collaborative project involving CDC and several large HMOs. Data were also received from state immunization registries. Since these cover entire states, they have variable levels of provider participation and completeness.

In 36 states and the District of Columbia, 1.6 million doses were reported to have been administered through May 2007, approximately one-quarter of the 6.2 million doses reported distributed by the manufacturer through that time. Sentinel site registries provide coverage estimates for specific age groups. The number of three-month-olds in the registries ranges from 200-500 in 4 sites to 7,000 in Michigan. One-dose rotavirus vaccine coverage in these sites increased from 20 to 30 percent at the end of 2006 to 40 to 60 percent in May 2007.

Using data from the sentinel registries, Dose 1 coverage with rotavirus vaccine among three-month-olds in May 2007 was compared with Dose 1 coverage of DTaP and PCV7. Rotavirus vaccine coverage ranged from 40 to 64 percent, for an average of 49

percent, compared with an average of 86 percent for one dose of the other vaccines. This is considered a respectable uptake for a new vaccine.

There are likely some real or perceived barriers, as with any new vaccine, such as reimbursement issues. The tight age frame for starting the series could also affect coverage. A recent provider survey explores these issues, and results should be presented in February. To assess how well providers are adhering to age recommendations, the study focused on administration of Dose 1. IAS sentinel sites showed that 86% of Dose 1 was given between ages 6-12 weeks and VSD showed 93 percent. Small peaks occur at approximately four and six months of age.

A study limitation is that the date of vaccination is used to determine the dose number, so the first date of vaccine administration is automatically counted as Dose 1. It is possible that some of this late peak is actually second or third doses being administered to infants whose previous doses were not counted in the registry. This could be an even greater limitation in state registries, since they have less complete provider participation. Using sentinel sites, the study looked at infants who received three doses of vaccine, to be more confident that first doses were actually first doses. Here 95 percent of the first doses were given at 6 to 12 weeks with very small peaks at those later ages. In all three data sources, only 0.2 percent or less of doses were recorded as being given before six weeks; 2 percent or less were given after age 32 weeks.

In summary, coverage with one dose of rotavirus vaccine among three-month-olds in sentinel site areas reached approximately 50 percent by May 2007, and the data suggest that providers' adherence to the ACIP age recommendations is high.

Safety Monitoring Update

Dr. Haber talked about intussusception reports to VAERS since licensure in March 2006. From March 2006 until August 2007, about 9.1 million doses of RotaTeq were distributed. During that time period, 160 intussusception reports were confirmed based on Brighton collaboration case definition Level 1. Of these, 47 were within 1 to 21 days after vaccination and 27 of the 47 reports were within one to seven days. There is a peak in Week 1 compared to Week 2 and 3, with another peak at Weeks 4 and 5 and 6. For Dose 1 there were 50 reports, with 68 reports for Dose 2 and 42 reports for Dose 3.

In comparing the observed number of reports with what would be expected by chance alone, age stratified analysis is important since the baseline of intussusception rate varies tenfold during the first six months of life and during this time three doses are administered. There are also two important data assumptions: reporting completeness to VAERS and the number of doses administered.

Looking at the observed versus the expected within 1 to 21 days after any dose, for all the three age groups, the cases observed in VAERS are lower than expected by chance alone. The rate ratio is 0.3 and the confidence interval does not include 1. This assumed 100 percent reporting and 100 percent of doses distributed. Looking at one to seven days for any dose, stratified by age group, again the reports to VAERS are lower than expected. The rate ratio is 0.51, the confidence interval does not include 1, and 100 percent is assumed for reporting and administration.

The sensitivity analysis is closer to what is assumed to be reality: 75 percent reporting and 75 percent doses distributed. At 1 to 21 days, there were 62 cases in

VAERS, whereas 113 would be expected by chance alone, and at one to seven days, there were 36 cases, with 38 expected. The rate ratio still does not include 1. Calculations were also done for the 50 percent assumptions, even though that is an unlikely scenario. The VAERS cases were higher than expected by chance alone and the rate ratio increased by 1 and 2 for the two onset intervals.

The Vaccine Safety Datalink from May 21 to October 6, 2006 has a total of 111,521 vaccinations. Three cases of IS were identified based on ICD9 code within 30 days of vaccination. Chart review to confirm the cases is currently under way - one case after Dose 1 with an onset interval of 20 days, and two cases after Dose 2, with onset intervals of 17 and 10 days. There would be 3.4 reports of intussusception expected by chance alone. The data are based on VSD Rapid Cycle Analysis background rates. Uptake at six VSD Rapid Cycle sites was about 43 percent in Dose 1, and 33 and 22 percent in Doses 2 and 3, respectively.

In conclusion, the observed intussusception rates following RotaTeq are no greater than expected. Data from VAERS should be interpreted as being from passive surveillance. VSD data after over 100,000 vaccinations saw no evidence of increased risk. The company continues to follow the VSD and Merck post-licensure cohort studies.

Discussion

Dr. Morse asked when the committee might see an evaluation of reduction in disease burden. Dr. Cortese replied that systems had already been set up to look at both burden and vaccine effectiveness. Dr. Parashar added that these included the NVSN active surveillance platform, an evaluation linking hospitalization data with immunization registries of Texas children, perhaps an evaluation with New York State through EIP sites, and using the Vaccine Safety Datalink to look at the disease impact in addition to monitoring safety. It is hoped that the data will be ready for presentation in summer or fall of 2008.

Dr. Neuzil asked whether the coverage for children getting PCV and DTap would be the highest percentage that could be reached for rotavirus, if the 3-month age restriction is followed. She thought the numbers seemed very low and wondered if they reflected incomplete reporting to the registries. Dr. Cortese reminded her that the data presented were for infants aged 3 months. The Montana sentinel site did have a low estimate. Nationally about 88 to 90 percent of infants had one dose of DTaP by age 3 months (NIS data, infants born 2002-4).

Dr. Morse asked if there were any reports of variability in coverage of vaccine by state for the underinsured. Dr. Cortese responded that there were no specific data by state and insurance data from the sentinel registries were incomplete. Dr. Schuchat added that the annual ongoing National Immunization Survey of 19- to 35-month-olds now has an annual module about individual insurance as well as the state and location, and coverage will be tracked by particular vaccines and by individual and state insurance status.

Dr. Katz asked if Merck or GSK had any studies in sub-Saharan Africa or southeast Asia. Dr. Friedland responded that there were ongoing efficacy studies currently in South Africa and in southeast Asia. Dr. Goveia reported that Merck has active studies looking at efficacy, safety, and immunogenicity in sub-Sahara Africa and

southeast Asia, in partnership with PATH, and a robust demonstration project ongoing in Nicaragua.

Dr. Neuzil wondered what the best baseline would be for reporting intussusception to VAERS and the number of vaccines distributed, as well as the best baseline for the sensitivity analysis, because clearly it is not 100 percent. Dr. Iskander responded that the committee may want to think in terms of modeling rather than sensitivity analysis. A lot of inferential data indicate reporting is actually pretty high, but unless and until there is a national immunization registry, there is no direct way to measure coverage or underreporting. The 75/75 figure seems to be the consensus.

Dr. Parashar noted that if one knew the rate of completeness and proportion of doses distributed that were given, there could be more specificity about the level of risk. Those numbers are likely change over time and reporting fluctuates depending on publicity, the media and events. It is very hard to determine the best assumptions for those two parameters. The VSD is the gold standard, with good-quality data, through a cohort analysis and about 111,000 vaccinations.

Dr. Verstraeten from GlaxoSmithKline suggested thaat without national coverage figures, one could use existing numbers to estimate the actual amount of doses distributed and administered. Dr. Iskander responded that this would mean sub-modeling within one of the already modeled variables and no one wants that.

Update of Hepatitis B
Dr. Cindy Weinbaum, CDC/NCHHSTP/DVH

Hepatitis B Vaccination of Adults

Dr. Weinbaum explained that in 1991 the ACIP and other professional medical organizations endorsed a national strategy with four main components: screening pregnant women and immunizing infants of infected mothers to prevent perinatal transmission; universal vaccination of infants to prevent infections during childhood and at later ages; catch-up vaccination of children and adolescents not vaccinated previously; and vaccination of adolescents and adults in groups at increased risk for infection. The incidence of acute hepatitis B has declined overall by 78% from the 1991 recommendations through 2006, most dramatically in children. Even in adults ages 25-44 years, in which incidence is highest, there has been a 75 percent decline.

There is still room for improvement in preventing disease among adults, including prior opportunities for vaccination among patients who are diagnosed with acute hepatitis B. In a sentinel county study between 2001 and 2004, 61 percent of individuals with reported acute hepatitis B had previously had an opportunity for immunization, through incarceration, STD treatment, or drug treatment. A survey of states found that 9.5 million people were seen annually in STD clinics, HIV counseling and testing sites, substance abuse and correctional settings, which represents only about 7 percent of people between the ages of 18 and 45.

In October of 2005, the ACIP approved updated hepatitis B vaccination recommendations for adults, which were published in the *MMWR* in December 2006. Hepatitis B vaccine for all unvaccinated adults at risk had been a standing recommendation since the vaccine was first approved. In the new recommendations, it

was also recommended for all adults seeking protection, without acknowledgment of a specific risk factor.

Practice-based vaccination strategies were offered in settings with access to a high proportion of at-risk adults, including STD and HIV testing and treatment facilities, substance abuse treatment facilities, correctional facilities, healthcare providers who serve injection-drug users or men who have sex with men, hemodialysis centers, and adult institutions for the developmentally disabled. CDC encouraged states to use Section 317 funds to purchase adult hepatitis B vaccine, stressing the need to hasten elimination of HBV transmission and implement ACIP recommendations. States were encouraged to convene managers from cooperating STD/HIV immunization and hepatitis programs to determine vaccine resources, target populations, potential venues for vaccination, numbers of doses needed, and roles of the participating programs and to develop an implementation and evaluation strategy.

More recently, about $20 million in Section 317 immunization funds were made available to purchase hepatitis B-containing vaccines for programs that serve adults at risk for viral hepatitis. These funds represented a one-time savings during the transition to a centralized vaccine distribution system, and were distributed to 51 project areas. Evaluation is planned to assure that these doses were distributed and administered in the venues recommended.

CDC has also been working with additional organizational partners, including the National Association of State and Territorial AIDS Directors, the National Council of STD Directors, and the National Association of City and County Health Officials, in addition to the Association of Immunization Managers. The adult hepatitis coordinators, immunization program managers, and HIV and STD program managers have all been working together, and CDC is developing cross-cutting strategic plans for its divisions to work together at the central level as well. After the updated recommendations were published, CDC offered Web-based education and training that focused on setting-based implementation strategies.

In summary, progress has been made in eliminating HBV transmission since 1991. Hepatitis B incidence in adults has declined by over 70 percent, but there is currently a time-limited opportunity to accelerate elimination of HBV transmission by increasing vaccine coverage among at-risk adults. The recent recommendations and additional funding are expected to accelerate this progress.

Discussion

Dr. Morita commented that the 317 funding to purchase vaccine for this initiative will make it much easier to achieve the Healthy People 2010 objective and suggested that the funding should be made available for other adult vaccine initiatives. Dr. Lett added that the funding helps with forming and strengthening partnerships.

Identification and Public Management of Persons Chronically Infected with Hepatitis B Virus

Dr. Weinbaum explained that the CDC was in the process of developing recommendations for the identification and public health management of persons

chronically infected with HBV. There are 1 million to 1.4 million persons in the U.S. who are hepatitis B surface-antigen (HBsAg) positive. Hepatitis B is the underlying cause of some 2,000 to 5,000 deaths a year. In recent years, the epidemiology of prevalent hepatitis B has changed in the U.S., and more prevalent disease is currently found among people born in countries with high endemicity than people who acquired the infection in this country. Identifying individuals who are chronically infected with hepatitis B virus provides an opportunity for the prevention of transmission by vaccination of contacts, as well as for treating the infected individuals. With improving treatment options, identifying infected persons increasingly provides opportunities to improve the health of the public.

These recommendations are intended to complement NIH's consensus development conference on the management of hepatitis B scheduled for October, 2008. The many existing recommendations will be compiled into a single document that will also recommend testing for additional populations and outline components of a testing and public health management program. Certain components of public health management programs were outlined in the appendices of two ACIP recommendations in 2005 and 2006: educating patients in order to prevent transmission to others and protect the infected individual's liver from further harm; managing contacts in order to identify tests; vaccinating household, sex, and needle-sharing contacts; referral for evaluation by physicians experienced in management of chronic liver disease; and reporting to health departments. A draft of the recommendations was reviewed by a consultants meeting in February 2007; additional input is also being sought so that they might be published in 2008.

Existing recommendations say that to prevent nosocomial transmission, donors of blood, plasma, organs, tissue, and semen are mandated to be tested. Hemodialysis patients are recommended for testing. To manage exposures, pregnant women, infants born to surface-antigen-positive women, contacts of surface-antigen-positive persons, and sources of blood and body fluid exposures in the case needle sticks or sexual assault are also recommended for testing.

Testing individuals with increased prevalence of infection has been recommended before. To the previous recommendation to test foreign-born persons from countries with a prevalence of 8 percent or higher, CDC is proposing adding persons from countries of intermediate prevalence: 2 to 7 percent. It is also proposing adding recommendations for testing injection-drug users and men who have sex with men, although for persons with ongoing risk, the emphasis is still on vaccination. HIV-positive persons are already recommended for testing. As a matter of medical management, persons on immunosuppressive therapy or about to start immunosuppressive therapy and persons with elevated ALTs and ASTs have been added.

Challenges to implementing these recommendations are expected. Some will be patient related, including lack of awareness of the need for testing and returning to obtain test results or communicating with contacts. Awareness of the need for testing will also need to be raised among providers. Insurance reimbursement for testing needs to be investigated and improved methods for risk ascertainment and contact tracing and management will be necessary.

Regarding infrastructure, there is currently no specific funding for counseling and testing for chronic hepatitis B or for follow-up of HBsAg-positive persons in a public

health setting. Health department registries exist in many states for chronic hepatitis B, but there is minimal federal support. The lack of availability of medical care for HBsAg-positive persons who are newly identified will be a challenge, along with point-of-care tests that enable people to receive their results immediately.

In summary, these new recommendations are intended to compile existing recommendations for testing in a single document, target new populations for testing, and outline components of a testing program with some guidance for implementation.

Agency Updates

CDC

Dr. Schuchat reported that a CDC working group had been developing recommendations for post-exposure interventions to prevent HBV, HCV, or HIV infection and tetanus for persons wounded during bombings and other mass casualty events in the U.S. This group was led by the immunization and injury staff, but included representatives from across CDC, as well as from NACCHO, CSTE, and the Terrorism Injury, Information, Dissemination, and Education Partnership. The guidance adapted the existing recommendation specific to the mass-casualty setting and represented a consensus judgment of U.S. public health authorities. It also benefited from the experience of the U.K. and Israel. The guidance is undergoing CDC clearance, and a prepublication copy will be provided to ACIP members, although they are not expected to vote on it.

CMS

Ms. Murphy of CMS added to the above that the immunization program has completed the VFC revision of their operations guide, which is now on the Web site, so there will be more emphasis on quality and on collaboration between CMS and CDC in fraud and abuse. Three more states have revised their VFC administration rates and one of those has actually gone to the max.

DOD

Colonel Cieslak had no new information to present, although there are many current vaccine issues that interest the military, starting with anthrax and both the licensed and some new generation anthrax vaccines. ACIP has constituted an anthrax working group, as well as one for the Japanese encephalitis new generation vaccine. The military continues to immunize against smallpox. Well over a million doses have been given and about one case of contact vaccinia or transfer vaccinia per month continues to be seen on average. Most have been trivial, but monitoring continues, albeit passive reporting.

The DoD is in late-stage trials with a new bivalent adenovirus Type 4/7 vaccine, since there has been some significant adenovirus Type 14 disease in the military as well as in some civilian locales, such as Oregon. There is interest in cross-protection and whether more serotypes need to be added.

Dr. Hachey added that the DoD had started its seasonal influenza program. It continues to have a policy of universal influenza immunization for everyone in uniform, with both live attenuated and inactivated vaccine.

HRSA

Dr. Evans said that an update on the autism hearings had been put on the Court's Web site. The Court held a major hearing last June on the first of three theories that are going to be pursued. The first theory was the combined hypothesis of MMR vaccine-caused autism as well as mercury-caused autism. A combined theory was what the petitioners chose to do first, and that lasted almost three weeks. At petitioners' request, the Court has adopted a test cases approach with three claims, families, and children for each theory. The first hearing involved the Cidello family, and two other test cases are being held. Decisions will be rendered in approximately six months.

The second major hearing for the thimerosal theory will be held with three test cases during the last three weeks of May, and the decision will not be for another six months after that. The third theory and hearings are not yet clear, but the final decisions, starting with the special masters and the appeals that follow probably will not be in much before 2011. Only when it reaches the level of the Federal Circuit Court of Appeals are precedents set and that would be final unless appealed to the Supreme Court. The Court made available the entire transcript for the June hearing, as well as audio files for each of the witnesses that testified.

NVPO

Dr. Strikas reported that the National Vaccine Advisory Committee had just met on October 23rd and 24th. Highlights included a discussion about trying to develop and enhance NVAC recommendation for improvement in vaccine coverage among adults. There was an update on revising the national vaccine plan, which was last written in 1994. The Institute of Medicine will convene an expert committee to review priorities and a series of meetings with stakeholders beginning in January 2008. The ACIP will be informed and invited to participate in that process.

There was a discussion at the NVAC meeting about influenza vaccine prioritization in a pandemic, and there will be a process with ACIP and NVAC to review that information. The NVAC adopted a draft report on mandates for adolescent vaccination. There was a report from the committee's financing working group about financing pediatric vaccines, as well as plans for stakeholders meetings in January to review their white paper on this topic. The vaccine safety subcommittee is completing an inventory of vaccine-safety activities across the government. Finally, the NVAC had earlier recommended that NVPO host a meeting of stakeholders on immunization information systems or registries, to develop recommendations on how provider participation can be improved and systems can be better funded. That meeting will occur in February 2008 in Washington.

Public Comment

Dr. Williamson, a hematologist and oncologist practicing in Muncie, Indiana, spoke on behalf of his son Philip, who is now five years old. At about one year of age, he had various thimerosal-containing vaccines and also other heavy immunogenic load, which his father was convinced caused a precipitous decline in his development. He had difficulty with chronic diarrhea, screaming, and extreme sound sensitivity.

Assuming that the incidence of autism, 1 to 166 currently, is going to increase, Dr. Williamson said he had an alternative strategy that the committee perhaps might consider. Based on Internet research regarding his son's symptoms, he discovered PDD and parent groups whose children had similar symptoms. One parent suggested trying a gluten-free and casein-free diet. When this diet was implemented, Philip almost immediately began using words and phrases, something he had not done for a year and a half. During week two, despite continued speech improvement, he developed florid sweats, redness and agitation, similar to drug withdrawal. Dr. Williamson learned that gluten and casein do transform into gluteomorphin and caseomorphin; research from 1996 shows the guts of children can abnormally absorb mannitol and lactulose and could go to the brain, thereby causing a cyclical drug effect. By removing that, he felt his son was going through withdrawal, sleeping multiple hours a day.

As a medically trained physician, Dr. Williamson felt he was straddling two worlds, but they continued with various other treatments regarding diet, antifungals, antibiotics, supplements and vitamins. The son has also been receiving chelation therapy, and he is now fully able to express himself, is mainstreamed in school, playing with his peers, and doing normal activities.

He implored the committee to consider alternative strategies, similar to screening for autoimmune diseases and PKU, and called for a rigorous, long-term prospective study of children who do receive the vaccines, and consider removal of thimerosal and other unnecessary preservatives. Most children and adults have normal levels of glutathione to help detoxify, but some do not have the ability to get rid of the metals and other toxins. This is an opportunity to build partnerships with physicians and parents and fulfill the motto of CDC for safer, healthier people.

Mr. Scott Lassiter with Safe Minds said he had spoken at the June ACIP meeting of the need to analyze thimerosal risks and referred to the expert NIH panel report to Congress that said CDC studies on thimerosal were seriously flawed. Contrary to CDC press releases, there has been no interruption in thimerosal this decade. In fact the committee began encouraging thimerosal-based flu vaccine for pregnant women in 2001, causing the rate of vaccination in that group to increase from 7 to 30 percent, which means almost one-third of recent newborns are receiving mercury in utero. There is no established toxicity limit for thimerosal and there has never been a thimerosal group versus a no-thimerosal group study. He urged committee members to reach out to experts outside of CDC and to contact Safe Minds or other autism organizations. This committee, in his opinion, was far overdue in stating a preference for mercury-free vaccines.

Ms. Beauvais said that parents were the consumers of vaccines and the ones who had to deal with the imposed mandates. As the mother of four children, she was a staunch proponent of vaccines, but was asking ACIP to state a preference for thimerosal-free vaccines. All four of her children were screened for HG toxicity with a developmental doctor and one has autism. The family has spent hundreds of thousands

of dollars restoring their children, whom she believes do not have the ability to detox thimerosal. She was not informed or given the choice of thimerosal-free vaccines. Her autistic daughter has been found to have a mercury toxicity equivalent to somebody who works in the mining industry. She has to be IV-chelated every month and health insurance doesn't cover it. She urged the ACIP to take the moral high ground and take the thimerosal out of the vaccines.

As there was no further public comment, the meeting was adjourned.

I hereby certify that to the best of my knowledge, the foregoing Minutes of the October 24-25, 2007 ACIP Meeting are accurate and complete.

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December 17, 2007
Date

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Chair,
Advisory Committee on
Immunization Practices

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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

This document can be found on the CDC website at:
http://www.cdc.gov/vaccines/recs/acip/downloads/min-oct07.pdf