Update From the Advisory Committee on Immunization Practices

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This year marks the 50th anniversary of the Advisory Committee on Immunization Practices (ACIP). The ACIP, composed of national medical and public health experts and 1 community representative, meets 3 times a year to develop vaccine recommendations for the civilian population in the United States. The Advisory Committee on Immunization Practices recommendations become official recommendations of the Centers for Disease Control and Prevention (CDC) when adopted by the CDC Director and published in the Morbidity and Mortality Weekly Report (http://www.cdc.gov/vaccines/hcp/acip-recs/recs-by-date.html). Members of ACIP include people with expertise in vaccines, public health, and various aspects of medicine and preventive medicine (http://annals.org/article.aspx?articleid=744177). Members of the Pediatric Infectious Diseases Society frequently serve on this committee and on ACIP work groups, and our society serves as one of 31 ex officio organizations that participate as nonvoting representatives. The American Academy of Pediatrics (AAP) Committee on Infectious Diseases (COID) also works closely with the ACIP to maximize harmonization between CDC and AAP recommendations. The Advisory Committee on Immunization Practices last met at the CDC on February 26–27, 2014. During this meeting, there were 2 votes taken, 1 on annual influenza vaccination and the other on human papillomavirus (HPV) vaccine. Several other topics were discussed as well. All ACIP vaccine recommendations have GRADE (Grading of Recommendations, Assessment, Development and Evaluation) methods applied (http://www.cdc.gov/vaccines/acip/recs/GRADING/table-ref.html), The following represent highlights from the February 2014 ACIP meeting.

Seasonal Influenza Vaccines

Influenza activity in the United States during the 2013–2014 season began approximately 4 weeks earlier than usual and occurred at moderate levels. Activity peaked in late December and early January, and influenza A(H1N1) viruses have predominated. Oseltamivir resistance, found in only 0.7% of the pH1N1 strains tested by the CDC since October 2013, has not been a major problem this season. There have been higher rates of influenza-associated hospitalization in 2013–2014 in persons 18–64 years of age than during the past several seasons. Possible contributing factors to this observation include the following: (1) this age group may lack the cross-protective immunity to pH1N1 seen in adults ≥65 years of age, likely acquired from past infection with antigenically related viruses; (2) this age group had a relatively low attack rate during the 2009 pH1N1 pandemic, which has also led to less cross-protective immunity; (3) the incidence of underlying conditions that may contribute increased risk for complications from influenza begins to increase in middle-aged adults; and (4) preliminary vaccination coverage estimates for this season indicate that this age group has substantially lower vaccination coverage than other younger and older age groups. Additional CDC data for influenza vaccination coverage are found at http://www.cdc.gov/flu/fluuvaxview/index.htm.

Between October 1, 2013 and February 15, 2014, 99.9% of the pH1N1 isolates matched the vaccine strain; 100% of the H3N2 isolates matched the vaccine strain; and 62% of the influenza B isolates matched the Yamagata lineage vaccine strain, whereas the other 38%
of the influenza B isolates matched the Victoria lineage vaccine strain. Thus, the match of the quadrivalent vaccine strains to the circulating viruses is very good this year. The mid-season interim adjusted vaccine effectiveness (VE) estimates for ≥1 dose of 2013–2014 seasonal influenza vaccine are shown in Table 1.

Since October 2013, ACIP has discussed the relative efficacy and safety of live-attenuated influenza vaccine (LAIV) and inactivated influenza vaccine (IIV) for children. This discussion has included (1) GRADE analyses as well as (2) safety surveillance data reviews from the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD). In VAERS and VSD, no new safety concerns were detected for either IIV or LAIV during the 2013–2014 influenza season in persons <18 years of age. Comparative efficacy and safety studies of LAIV and IIV were discussed, and, at present, ACIP is not recommending that LAIV be given preferentially over IIV in healthy children. This will be revisited in the June 2014 meeting. Live-attenuated influenza vaccine supply has also been monitored, and it is estimated that current and projected manufacturing capacity is sufficient for eligible US children 2–17 years of age. During this meeting, the core recommendation for annual influenza vaccination for all persons aged 6 months and older was reaffirmed by unanimous vote. It was also announced that a Novel Influenza Vaccines Work Group has formed to provide recommendations for the use of novel influenza vaccines during nonpandemic periods.

### Pneumococcal Conjugate Vaccine

An informational discussion with no specific policy recommendations was held concerning the routine infant immunization schedule for 13-valent pneumococcal conjugate vaccine (PCV13). In the United States, a 4-dose schedule of PCV13 (2, 4, 6, and 12–15 months) is recommended for healthy infants, but there is emerging evidence that suggests a 3-dose schedule might be acceptable. The European Medicines Agency has approved a 3-dose PCV13 schedule, and the World Health Organization (WHO) recognizes a 3-dose schedule as an acceptable alternative to the 4-dose schedule (recommending that it should be routine in low-income countries). With the continued expansion of the number of vaccines included in the vaccine schedule, public concerns regarding the number of simultaneous injections causing parents to delay or refuse recommended vaccinations, and rare safety issues with coadministration of routine vaccines (eg, febrile seizures with coadministration of PCV, diphtheria-tetanus-acellular pertussis, and influenza vaccines), ACIP considered the evidence for a reduced dosing schedule of PCV13 in infants. The following schedules were evaluated: (1) 4 doses of PCV13 (2, 4, 6, and 12–15 months, or 3 + 1 [current recommendation]); (2) 3 doses of PCV13 (2, 4, and 6 months, or 3 + 0); and (3) 3 doses of PCV13 (2, 4, and 12–15 months, or 2 + 1).

Controlled trials and observational studies evaluating the VE of 3-dose and 4-dose schedules against vaccine-type invasive pneumococcal disease (IPD) and pneumonia were reviewed, as was immunogenicity data and practical considerations for effectively implementing the vaccine program. Evidence suggests that all of the schedule options evaluated (3 + 1, 3 + 0, and 2 + 1) are effective at preventing IPD, pneumonia, and acquisition of nasopharyngeal colonization compared with no PCV immunization. The studies reviewed were not powered for a direct comparison of 3-dose and 4-dose schedules, but GRADE review suggests that 3-dose schedules are likely equivalent to a 4-dose schedule. Immunogenicity studies show that a 3 + 1 schedule may be better than 2 + 1 before booster, but that there are no significant differences observed postbooster for most serotypes. Strong indirect (herd) effects have been observed in countries that already use a 3-dose schedule.

Although these data concerning 3-dose schedules generally are somewhat reassuring overall, discussion during the meeting indicated that significant concerns remain among ACIP member and liaisons regarding the reduction of the PCV13-dosing schedule. The Advisory Committee on Immunization Practices is not prepared to make a specific recommendation at this time but will continue to consider policy options including which 3-dose schedule should be considered, whether certain high-risk groups should be excluded from any schedule reduction, and what impact a policy change may have on vaccine nonadherence. Out of a desire to maintain unity between the CDC and AAP, ACIP will also seek the recommendation of the AAP COID on the matter.

### Table 1. Interim Adjusted VE Estimates for ≥1 Dose of 2013–2014 Seasonal Influenza Vaccine

<table>
<thead>
<tr>
<th>Age groups (yrs)</th>
<th>VE (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>61%</td>
<td>52, 68</td>
</tr>
<tr>
<td>6 mo–17 yr</td>
<td>67%</td>
<td>51, 78</td>
</tr>
<tr>
<td>18–49</td>
<td>60%</td>
<td>44, 71</td>
</tr>
<tr>
<td>50–64</td>
<td>60%</td>
<td>39, 73</td>
</tr>
<tr>
<td>≥65</td>
<td>52%</td>
<td>2, 77</td>
</tr>
<tr>
<td>Influenza A/H1N1pdm09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>62%</td>
<td>53, 69</td>
</tr>
<tr>
<td>6 mo–17 yr</td>
<td>67%</td>
<td>51, 78</td>
</tr>
<tr>
<td>18–49</td>
<td>61%</td>
<td>45, 72</td>
</tr>
<tr>
<td>50–64</td>
<td>62%</td>
<td>42, 75</td>
</tr>
<tr>
<td>≥65</td>
<td>56%</td>
<td>7, 79</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; VE, vaccine effectiveness.

*Table provided by David Kimberlin (Advisory Committee on Immunization Practices).*
HPV Vaccines

Two HPV vaccines are currently licensed by the US Food and Drug Administration (FDA): (1) HPV4 (Gardasil, Merck & Co. Inc.), which is directed against HPV types 6, 11, 16, and 18; and (2) HPV2 (Cervarix, GlaxoSmithKline), directed against HPV types 16 and 18. A 9-valent HPV vaccine (9vHPV) containing HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 is under investigation by Merck. The CDC continues to evaluate HPV-type attribution for precancerous and cancerous lesions in the United States. Cervical intraepithelial neoplasia (CIN) grades 2 and 3 and adenocarcinoma in situ (AIS) are precancerous lesions in women that are associated with oncogenic HPV types. Surveillance of HPV-type attribution in CIN2, CIN3, and AIS lesions in women aged 21–39 demonstrated that although nearly 50% were attributable to HPV16 and HPV18, an additional 25% of these lesions were attributable to HPV types 31, 33, 45, 52, or 58. Likewise, approximately 62% of HPV-associated cancers (range, 48% penile to 79% anal) are attributable to HPV16 and HPV18, but 11% (range, 8% anal to 18% vaginal) are attributable to the 5 additional types in 9vHPV. Clinical trials in women 16–26 years of age demonstrate noninferior HPV 6/11/16/18 immunogenicity of 9vHPV compared with HPV4, as well as nearly 97% protection against HPV 31/33/45/52/58-related disease. Immunobridging studies of 9vHPV in adolescents demonstrated noninferiority in adolescents versus adults. These studies also indicate that the safety profiles of 9vHPV and HPV4 are comparable. Additional data will be considered at future ACIP meetings, with GRADE presentation slated for the October 2014 ACIP meeting and final recommendations anticipated at the February 2015 meeting. In addition to these discussions, ACIP also voted to update the HPV policy statement to harmonize the wording on HPV2 and HPV4 in both males and females.

Meningococcal Vaccine in Response to Outbreaks

School-based Neisseria meningitidis serogroup B (MenB) outbreaks occurring in 2013 included Princeton University (March 2013–November 2013) and University of California Santa Barbara (November 2013). At Princeton University, 8 cases of MenB occurred among students or persons with links to Princeton University, for an attack rate of 134/100,000 among undergraduates. All 7 strains identified were identical. A MenB + OMV NZ (rMenB) vaccine (Bexsero, Novartis) has been accessed under an FDA investigational new drug (IND) application. To date, the rate of serious adverse events (SAEs) reported is 2.0/1000 vaccinees after the first dose, and 0.2/1000 vaccinees after the second dose. No SAEs have been determined to be causally related to rMenB. At the University of California Santa Barbara, 4 cases of MenB occurred in undergraduates for an attack rate of 21.1/100,000. No specific epidemiological links have been established among the 4 cases. A CDC-sponsored expanded access IND has been approved for use in this outbreak, with approximately 20,000 persons eligible for vaccination.

An ad hoc Meningococcal Outbreak Work Group has been established, the objectives of which are to review available data on the recent epidemiology of meningococcal disease and outbreaks, to consider options for updating the current meningococcal disease outbreak guidelines, and to develop guidance for use of meningococcal vaccines (both licensed and unlicensed) in an outbreak setting. Interim guidance will be presented at the June ACIP meeting.

Safety of Tetanus, Diphtheria, and Acellular Pertussis Vaccine in Pregnant Women

In 2013, ACIP recommended that providers of prenatal care implement a tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) immunization program for all pregnant women. Healthcare personnel should administer a dose of Tdap during each pregnancy, irrespective of the patient’s prior history of receiving Tdap. With this updated recommendation, ACIP has reviewed the ongoing VAERS safety monitoring, as well as available data in VSD. Vaccine Adverse Event Reporting System analysis demonstrated that no new unexpected vaccine safety concerns have been noted among pregnant women who received Tdap. Safety data from the VSD showed that receipt of Tdap during pregnancy was not associated with increased risks for adverse birth outcomes. However, chorioamnionitis occurred slightly more commonly in women who received Tdap compared with those who did not: 6.1% vs 5.5% (adjusted relative risk = 1.19 [1.13–1.27]). After adjustments, maternal age and comorbidities were not found to have contributed to the observed risk. The magnitude of the potential risk of chorioamnionitis is small, but it warrants further investigation. The Clinical Immunization Safety Assessment (CISA) study will implement investigation of Tdap safety in pregnant women this year, and enhanced VAERS surveillance will also continue.

Yellow Fever Vaccine

Yellow fever (YF) vaccine is recommended for persons aged ≥9 months who are traveling to or living in areas at
risk for YF virus transmission. Because of the risk of SAEs, healthcare providers should vaccinate only persons who are at risk for exposure to YF virus or require proof of vaccination for country entry. Yellow fever vaccine is the only vaccine covered under the International Health Regulations, which requires YF revaccination at 10-year intervals to boost antibody titers. The last ACIP recommendations on use of YF vaccine were published in July 2010. In 2013, the WHO Strategic Advisory Group of Experts on Immunization published an updated statement regarding the need for a booster dose every 10 years to maintain protection against YF. After a systematic review, they concluded that “a single dose of YF vaccine is sufficient to confer sustained life-long protective immunity against YF disease; a booster dose is not necessary” (http://www.who.int/wer/2013/wer8820.pdf?ua=1). This recommendation creates a discrepancy with the existing ACIP recommendations, and therefore the expanded Japanese Encephalitis and YF Vaccines Work Group has been charged with investigating these data and making recommendations for a future ACIP vote.

Additional information about the ACIP and its recommendations can be found online at http://www.cdc.gov/vaccines/acip. Up-to-the-minute information about vaccine supply can always be found at http://www.cdc.gov/vaccines/vac-gen/shortages/, and a listing of available influenza vaccines can be found at http://aapredbook.aappublications.org/site/news/vacstatus.xhtml#flu.

The next ACIP meeting is scheduled for June 25–26, 2014. The ACIP website includes information about registration and the meeting webcast. Slides shown during the February 2014 meeting will be posted on the ACIP web site as well as minutes of the meeting.

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