Use of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine for Adults with Immunocompromising Conditions: Recommendations of the Advisory Committee on Immunization Practices (ACIP)

On June 20, 2012, the Advisory Committee on Immunization Practices (ACIP) recommended routine use of 13-valent pneumococcal conjugate vaccine (PCV13; Prevnar 13, Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer, Inc.) for adults aged ≥19 years with immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid (CSF) leaks, or cochlear implants (Table). PCV13 should be administered to eligible adults in addition to the 23-valent pneumococcal polysaccharide vaccine (PPSV23; Pneumovax 23, Merck & Co. Inc.), the vaccine currently recommended for these groups of adults (*1*). The evidence for the benefits and risk of PCV13 vaccination of adults with immunocompromising conditions was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework and designated as a Category A recommendation (*2,3*). This report outlines the new ACIP recommendations for PCV13 use; explains the recommendations for the use of PCV13 and PPSV23 among adults with immunocompromising conditions, functional or anatomic asplenia, CSF leaks, or cochlear implants; and summarizes the evidence considered by ACIP to make its recommendations.

Epidemiology of Pneumococcal Infection in Immunocompromised Adults

Streptococcus pneumoniae (pneumococcus) remains a leading cause of serious illness, including bacteremia, meningitis, and pneumonia among adults in the United States. An estimated 4,000 deaths occur in the United States each year because of *S. pneumoniae,* primarily among adults (*4*). The incidence of invasive disease ranges from 3.8 per 100,000 among persons aged 18–34 years to 36.4 per 100,000 among those aged ≥65 years (*4*). Adults with certain medical conditions also are at increased risk for invasive pneumococcal disease (IPD). For adults aged 18–64 years with hematologic cancer, the rate of IPD in 2010 was 186 per 100,000, and for persons with human immunodeficiency virus (HIV) the rate was 173 per 100,000 (CDC, unpublished data, 2012). The disease rates for adults in these groups can be more than 20 times those for adults without high-risk medical conditions.

PCV13 has been used for children since 2010, when it replaced an earlier version targeting seven serotypes (PCV7; Prevnar, Pfizer) that had been in use since 2000. The routine use of PCV7 in infants and young children resulted in significant reductions in IPD caused by vaccine serotypes in children, and because of indirect effects, also in adults. Rates of IPD caused by vaccine serotypes in adults aged 18–64 years without HIV decreased from six cases to one case per 100,000 during 2000–2007. However, even after indirect effects of the pediatric immunization had been realized fully, the incidence of IPD caused by the serotypes included in PCV7 remained high in HIV-infected persons aged 18–64 years at 64 cases per 100,000 persons with acquired immunodeficiency syndrome (AIDS) (*5*). Moreover, 50% of IPD cases among immunocompromised adults in 2010 were caused by serotypes contained in PCV13; an additional 21% were caused by serotypes only contained in PPSV23 (CDC, unpublished data, 2011).

> Recommendations for routine use of vaccines in children and adolescents are developed by the Advisory Committee on Immunization Practices (ACIP). ACIP is chartered as a federal advisory committee to provide expert external advice and guidance to the Director of CDC on use of vaccines in the civilian population of the United States. Recommendations are harmonized to the greatest extent possible with recommendations made by the American Academy of Pediatrics (AAP), the American Academy of Family Physicians (AAFP), and the American College of Obstetrics and Gynecology (ACOG). Recommendations for routine use of vaccines in adults are harmonized with recommendations of AAFP, ACOG, and the American College of Physicians. ACIP recommendations adopted by the Director of CDC become recommendations of the agency on the date published in *MMWR*.

PCV13 Vaccine in Adults

PCV13 was licensed by the Food and Drug Administration (FDA) for prevention of IPD and otitis media in infants and young children in February 2010, supplanting PCV7 (*6*). PCV13 is identical in formulation for the seven common serotypes in PCV7, but it includes six additional antigens. One dose of PCV13 is recommended by ACIP for children aged 6–18 years with high-risk conditions such as functional or anatomic asplenia, immunocompromising conditions, cochlear implants, or CSF leaks. In December 2011, FDA licensed PCV13 for prevention of pneumonia and IPD in adults aged ≥50 years (*7*). The license for adult use was granted under FDA's

accelerated approval pathway, which allows the agency to approve products for serious or life-threatening diseases on the basis of early evidence of a product's effectiveness that is reasonably likely to predict clinical benefit. Approval of PCV13 for adults was based on immunogenicity studies that compared antibody responses to PCV13 with antibody responses to PPSV23 (*7*).

In two randomized, multicenter immunogenicity studies conducted in the United States and Europe, immunocompetent adults aged ≥50 years received a single dose of PCV13 or PPSV23 (*8*). In adults aged 60–64 years and aged >70 years, PCV13 elicited opsonophagocytic activity (OPA) geometric mean antibody titers (GMTs) that were comparable with, or higher than, responses elicited by PPSV23. OPA GMTs elicited by PCV13 in adults aged 50–59 years for all 13 serotypes were comparable with the corresponding GMTs elicited by administration of PCV13 in adults aged 60–64 years. Persons who received PPSV23 as the initial study dose had lower opsonophagocytic antibody responses after subsequent administration of a PCV13 dose 1 year later than those who had received PCV13 as the initial dose (*8*). Data on the immunogenicity of PCV13 in immunocompromised adults are not available.

Safety of PCV13 was evaluated in approximately 6,000 PPSV23-naïve and PPSV23-experienced adults aged ≥50 years (*8*). Overall incidence of serious adverse events reported within 1 month of an initial study dose was <2% for both vaccines, with no significant differences between treatment groups. Common adverse reactions reported with PCV13 were pain, redness, and swelling at the injection site; limitation of movement of the injected arm; fatigue; and headache (*8*). Safety studies presented for licensure did not enroll immunocompromised subjects.

Although clinical trial data are not yet available for PCV13, a randomized, controlled trial of PCV7 efficacy among 496 HIV-infected adults in Malawi demonstrated vaccine efficacy of 75% (95% confidence interval = 29%–92%) in preventing IPD (*9*). The study population differed from the general U.S. HIV-infected population, however, in that all participants had survived a previous episode of IPD, only 13% were on antiretrovirals, and the all-cause mortality rate was >25%. The number of serious adverse events within 14 days after vaccination was significantly lower (three versus 17; p=0.002) in the vaccine group (248 persons) than in the placebo group (248 persons), whereas minor adverse events were significantly more common in the vaccine group (41 versus 13; p=0.003) (*9*).

Four studies of PCV7 immunogenicity involving 699 HIV-infected subjects, all with CD4 counts of >200 cells/μL, were conducted in the United States and Europe. Antibody response to a single dose of PCV7 was comparable with PPSV23 for the serotypes evaluated, at all times studied (*10–13*). When PPSV23 and PCV7 were administered in series, greater immune response was demonstrated when PCV7 was given first (*8,11*). None of the studies were designed to evaluate the optimal interval between doses; however, in another study, no evidence of blunting of an immune response to PCV7 was observed when a dose of PPSV23 was given 5 years (range: 3.5–6.6 years) before a dose of PCV7 (*14*).

PPSV23 Vaccine

PPSV23 contains 12 of the serotypes included in PCV13, plus 11 additional serotypes. PPSV23 is recommended for prevention of IPD among all adults aged ≥65 years, and for adults at high risk aged 19–64 years (*1,3*). Although conflicting evidence regarding PPSV23 efficacy in HIV-infected adults has been published (*15,16*), the GRADE evaluation reviewed by ACIP concluded that potential benefits from PPSV23 use in this population outweigh any potential harms. Given the high burden of IPD caused by serotypes in PPSV23 but not in PCV13, broader protection might be provided through use of both pneumococcal vaccines.

The current ACIP PPSV23 recommendations call for vaccination of adults at high risk aged 19–64 years at the time of diagnosis of the high-risk condition. A one-time revaccination dose of PPSV23 is recommended 5 years after the first dose for persons with functional or anatomic asplenia and for immunocompromised persons (Table). All adults are eligible for a dose of PPSV23 at age 65 years, regardless of previous PPSV23 vaccination; however, a minimum interval of 5 years between PPSV23 doses should be maintained (*1*).

Cost-Effectiveness

A cost-effectiveness analysis was performed using a lifetime cohort model of an implemented vaccine program wherein persons with selected immunocompromising conditions were immunized with PCV13 at the time of diagnosis and then followed current PPSV23 vaccination guidelines starting 1 year later. PCV13 vaccine efficacy against IPD and pneumonia (used as a proxy for effectiveness in the model) was 75% and 13%, respectively, for persons with HIV/AIDS and persons requiring dialysis, and 25% and 0%, respectively, for persons with hematologic cancer and for organ transplant recipients. Using the current costs of PCV13, PPSV23, and administration, the modeled program resulted in a cost saving of $7,600,000, added 1,360 quality-adjusted life years, and averted 57 cases of IPD (CDC, unpublished data, 2012). These savings accrued largely as a result of protection among patients on dialysis and those with HIV/AIDS. Heterogeneity across risk groups was driven by differences in pneumococcal serotypes causing disease and assumed vaccine efficacy in each subgroup. The model was sensitive to assumptions about vaccine efficacy, whereby increased estimation of PCV13 efficacy led to increases in cost-effectiveness.

ACIP Recommendations for PCV13 and PPSV23 Use

Adults with specified immunocompromising conditions who are eligible for pneumococcal vaccine should be vaccinated with PCV13 during their next pneumococcal vaccination opportunity.

Pneumococcal vaccine-naïve persons. ACIP recommends that adults aged ≥19 years with immunocompromising conditions, functional or anatomic asplenia, CSF leaks, or cochlear implants, and who have not previously received PCV13 or PPSV23, should receive a dose of PCV13 first, followed by a dose of PPSV23 at least 8 weeks later (Table). Subsequent doses of PPSV23 should follow current PPSV23 recommendations for adults at high risk. Specifically, a second PPSV23 dose is recommended 5 years after the first PPSV23 dose for persons aged 19–64 years with functional or anatomic asplenia and for persons with immunocompromising conditions. Additionally, those who received PPSV23 before age 65 years for any indication should receive another dose of the vaccine at age 65 years, or later if at least 5 years have elapsed since their previous PPSV23 dose.

Previous vaccination with PPSV23. Adults aged ≥19 years with immunocompromising conditions, functional or anatomic asplenia, CSF leaks, or cochlear implants, who previously have received ≥1 doses of PPSV23 should be given a PCV13 dose ≥1 year after the last PPSV23 dose was received. For those who require additional doses of PPSV23, the first such dose should be given no sooner than 8 weeks after PCV13 and at least 5 years after the most recent dose of PPSV23.

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TABLE. Medical conditions or other indications for administration of 13-valent pneumococcal conjugate vaccine (PCV13), and indications for 23-valent pneumococcal polysaccharide vaccine (PPSV23) administration and revaccination for adults aged ≥19 years,* by risk group — Advisory Committee on Immunization Practices, United States, 2012

		PCV13	PPSV23	
Risk group	Underlying medical condition	Recommended	Recommended	Revaccination 5 yrs after first dose
Immunocompetent persons	Chronic heart disease†		✓	
	Chronic lung disease§		✓	
	Diabetes mellitus		✓	
	Cerebrospinal fluid leak	✓	✓	
	Cochlear implant	✓	✓	
	Alcoholism		✓	
	Chronic liver disease, cirrhosis		✓	
	Cigarette smoking		✓	
Persons with functional or anatomic asplenia	Sickle cell disease/other hemaglobinopathy	✓	✓	✓
	Congenital or acquired asplenia	✓	✓	✓
Immunocompromised persons	Congenital or acquired immunodeficiency¶	✓	✓	✓
	Human immunodeficiency virus infection	✓	✓	✓
	Chronic renal failure	✓	✓	✓
	Nephrotic syndrome	✓	✓	✓
	Leukemia	✓	✓	✓
	Lymphoma	✓	✓	✓
	Hodgkin disease	✓	✓	✓
	Generalized malignancy	✓	✓	✓
	Iatrogenic immunosuppression**	✓	✓	✓
	Solid organ transplant	✓	✓	✓
	Multiple myeloma	✓	✓	✓

* All adults aged ≥65 years should receive a dose of PPSV23, regardless of previous history of vaccination with pneumococcal vaccine.
† Including congestive heart failure and cardiomyopathies, excluding hypertension.
§ Including chronic obstructive pulmonary disease, emphysema, and asthma.
¶ Includes B- (humoral) or T-lymphocyte deficiency, complement deficiencies (particularly C1, C2, C3, and C4 deficiencies), and phagocytic disorders (excluding chronic granulomatous disease).
** Diseases requiring treatment with immunosuppressive drugs, including long-term systemic corticosteroids and radiation therapy.

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