REVIEW

CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will assess patient risk for pneumococcal disease and select appropriate pneumococcal immunization

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Navigating pneumococcal vaccination in adults

ABSTRACT

With two nonequivalent vaccines available and different recommendations for different patient populations, vaccination against *Streptococcus pneumoniae* can be confusing. Here we try to clarify the situation.

KEY POINTS

At highest risk of invasive pneumococcal disease are people who are immunocompromised, very young, or very old.

Pneumococcal polysaccharide vaccine-23 (PPSV23) covers more serotypes of *S pneumoniae* than pneumococcal conjugate vaccine-13 (PCV13), but the latter induces a stronger antibody response.

The combination of both vaccines in sequence produces a better antibody response than either vaccine alone.

The Advisory Committee on Immunization Practices now recommends that immunocompromised and asplenic adults who need pneumococcal vaccination receive both vaccines, preferably PCV13 first, followed by PPSV23 8 weeks later. Those who have already received PPSV23 can receive PCV13 after at least 1 year has passed.

People with asplenia or immunocompromising conditions should receive a second dose of PPSV23 at least 5 years after the first dose.

Vaccination schedules and information are available from the US Centers for Disease Control and Prevention at www.cdc.gov.

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Streptococcus pneumoniae (the "pneumococcus") causes a variety of clinical syndromes that range from otitis media to bacteremia, meningitis, and pneumonia. Hardest hit are immunocompromised people and those at the extremes of age. Therefore, preventing disease through pneumococcal vaccination is very important in these groups.

This review summarizes the current guidelines from the Advisory Committee on Immunization Practices (ACIP) of the US Centers for Disease Control and Prevention (CDC) for pneumococcal immunization in adults.

STRIKES THE VERY YOUNG, VERY OLD, AND IMMUNOCOMPROMISED

Invasive pneumococcal disease is defined as infection in which *S pneumoniae* can be found in a normally sterile site such as the cerebrospinal fluid or blood, and it includes bacteremic pneumonia.[1] By far the most common type of pneumococcal disease is pneumonia, followed by bacteremia and meningitis (**Figure 1**)[2,3]; about 25% of patients with pneumococcal pneumonia also have bacteremia.[2]

Invasive pneumococcal disease most often occurs in children age 2 and younger, adults age 65 and older, and people who are immunocompromised. In 2010, the incidence was 3.8 per 100,000 in people ages 18 to 34 but was 10 times higher in the elderly and those with compromised immunity.[1]

Even now that vaccines are available, invasive pneumococcal disease continues to cause 4,000 deaths per year in the United States.[1]

TWO INACTIVATED VACCINES

S pneumoniae is a gram-positive coccus with

Commonly asked questions

Q: *A patient with human immunodeficiency virus infection received a dose of PCV13 at age 53. Does this patient need any additional doses of PCV13 after age 65?*

A: No. If the patient already received one dose of PCV13 before age 65, no additional doses are needed.[3]

Q: *A 28-year-old patient on hemodialysis presents to the clinic. Which pneumococcal vaccine or vaccines is this patient eligible for?*

A: End-stage renal disease places this patient in the immunocompromised risk category. She should therefore receive one dose of PCV13 followed by two doses of PPSV23 (**Table 1**).

Q: *Three months ago, a 20-year-old man with sickle cell disease received PPSV23. Is he eligible to receive PCV13 at today's office visit?*

A: No. If PPSV23 is given first, PCV13 can be given no sooner than 12 months later in immunocompromised patients.

Q: *A 70-year-old man presents to his primary care provider for a routine visit. The physician notes that he received PPSV23 at age 67. What is the minimum time between PPSV23 and PCV13 doses?*

A: For patients age 65 and older, ACIP recommends administering PCV13 12 months after PPSV23. Medicare will also reimburse for the second pneumococcal vaccination if it is given at least 11 full months after the month in which the first pneumococcal vaccination was given. This patient can receive PCV13 at today's visit.

Q: *A patient with lymphoma received a dose of PCV13 at age 18½. This is the only dose of PCV13 that this patient has received. Does this dose count as the single dose indicated in immunocompromised adults?*

A: Yes. This dose counts as a dose of PCV13 for immunocompromised patients at risk of invasive pneumococcal disease. The dose would also count if given at a younger age.[19]

Q: *A 66-year-old woman presents to the outpatient clinic in November. She would like to receive an influenza virus vaccine. The medical assistant notes that she is also eligible to receive pneumococcal vaccination with PCV13, as she has never received a pneumococcal vaccine. Can pneumococcal vaccines be administered concurrently with other vaccinations?*

A: Yes. Both PCV13 and PPSV23 are inactivated vaccines and can be given concurrently with other vaccines (ie, influenza vaccine, herpes zoster vaccine) with a few exceptions[20]:

- PCV13 and PPSV23 should not be given at the same time.
- Patients should receive PCV13 and conjugated meningococcal vaccine before splenectomy. If using meningococcal conjugate vaccine 4-D (MCV4-D, Menactra), PCV13 should be given first, and the MCV4-D 4 weeks later. If using meningococcal conjugate vaccine 4-CRM (MCV4-CRM, Menveo), PCV13 and MCV4-CRM can be given at the same time.

Q: *What is the maximum number of PPSV23 doses a patient with a C4 complement deficiency can receive in a lifetime?*

A: Immunocompromised patients at risk of invasive pneumococcal disease can receive up to three doses of PPSV23. They would first receive PCV13, the first dose of PPSV23 8 weeks later, and the second dose of PPSV23 5 years after the first dose. The final dose of PPSV23 would be given after age 65 and at least 5 years after the second dose of PPSV23.[21]

Q: *A 50-year-old man has an exacerbation of chronic obstructive pulmonary disease and is prescribed prednisone 20 mg daily for 7 days, then 10 mg daily for 7 days, then 5 mg daily for 7 days, then 5 mg every other day for 14 days. He has never received a pneumococcal vaccine. Which pneumococcal vaccine should he receive?*

A: Chronic obstructive pulmonary disease falls into the at-risk category for patients ages 19 to 64 with comorbidities. This patient is a candidate for PPSV23. The ACIP guidelines are silent on the additional need for PCV13 for multiple short courses of corticosteroids.

Vaccination schedules can be found at www.cdc.gov/vaccines/schedules/. Questions can be posted at www.cdc.gov/cdc-info/.

an outer capsule composed of polysaccharides that protect the bacterium from being ingested and killed by host phagocytic cells. Some 91 serotypes of this organism have been identified on the basis of genetic differences in capsular polysaccharide composition.

Currently, two inactivated vaccines are available that elicit antibody responses to the most common pneumococcal serotypes that infect humans.

- **PPSV23** (pneumococcal polysaccharide vaccine-23, or Pneumovax 23) contains purified capsular polysaccharides from 23 pneumococcal serotypes.
- **PCV13** (pneumococcal conjugate vaccine-13, or Prevnar 13) contains purified capsular polysaccharides from 13 serotypes that are covalently bound to (conjugated with) a carrier protein.

PPSV23 AND PCV13 ARE NOT THE SAME

Apart from the number of serotypes covered, the two vaccines differ in important ways. Both of them elicit a B-cell-mediated immune response, but only PCV13 produces a T-cell-dependent response, which is essential for maturation of the B-cell response and development of immune memory.

PPSV23 generally provides 3 to 5 years of immunity, and repeat doses do not offer additive or "boosted" protection. It is ineffective in children under 2 years of age.

Pneumococcal conjugate vaccine has been available since 2000 for children starting at 2 months of age. Since then it has directly reduced the incidence of invasive pneumococcal disease in children and indirectly in adults. The impact on pneumococcal disease rates in adults has probably been related to reduction in rates of pneumococcal nasopharyngeal carriage in children, another unique benefit of conjugated vaccines.[3]

In December 2011, the US Food and Drug Administration (FDA) approved PCV13 for adults on the basis of immunologic studies and anticipation that clinical efficacy would be similar to that observed in children.

HOW EFFECTIVE ARE THEY?

The efficacy and safety of PPSV23 and PCV13 have been studied in a variety of patient populations. Though antibody responses to PCV13 were similar to or better than those with PPSV23, no studies of specific correlations between immunologic responses and disease outcomes are available.[4,5]

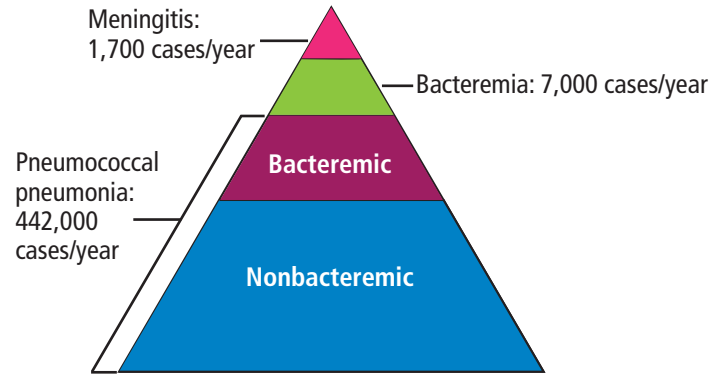

FIGURE 1. Incidence of pneumococcal disease in adults age 50 and older in the United States.

Information from references 2 and 3.

In large studies in healthy adults, both vaccines reduced the incidence of invasive pneumococcal disease. A study in more than 47,000 adults age 65 and older showed a significant reduction in pneumococcal bacteremia (hazard ratio 0.56, 95% confidence interval 0.33–0.93) in those who received PPSV23 compared with those who received placebo.[6] However, PPSV23 was not effective in preventing nonbacteremic and noninvasive pneumococcal community-acquired pneumonia when all bacterial serotypes were considered.[6]

In a placebo-controlled trial in more than 84,000 people age 65 and older, PCV13 prevented both nonbacteremic and bacteremic community-acquired pneumococcal pneumonia due to serotypes included in the vaccine (relative risk reduction 45%, $P < .007$) and overall invasive pneumococcal disease due to serotypes included in the vaccine (relative risk reduction 70%, $P < .001$).[7]

Both vaccines have also demonstrated efficacy in immunocompromised adults. Several studies showed an equivalent or superior antibody response to a seven-valent pneumococcal conjugate vaccine (PCV7, which has been replaced by PCV13) compared with PPSV23 in adults with human immunodeficiency virus (HIV) infection.[8,9] While specific clinical studies of the efficacy of PCV13 among immunocompromised people are not available, a study

Even now that vaccines are available, invasive pneumococcal disease kills about 4,000 per year in the United States

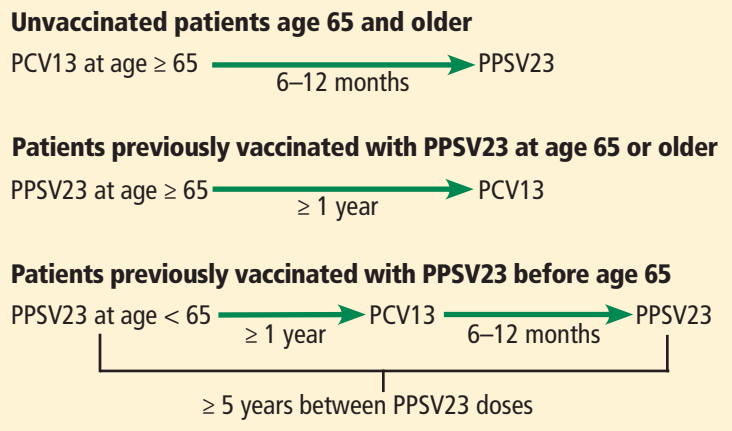

FIGURE 2. Intervals of administration of pneumococcal conjugate vaccine-13 (PCV13) and pneumococcal polysaccharide vaccine-23 (PPSV23) in adults age 65 and older.

Information from references 3 and 14.

of vaccination with PCV7 in 496 people in Malawi, of whom 88% were infected with HIV, found that the vaccine was effective in preventing invasive pneumococcal disease (hazard ratio 26%, 95% confidence interval 0.10–0.70).[10]

AT-RISK PATIENT POPULATIONS

The ACIP now recommends that everyone 65 and older receive one dose of PCV13 and one dose of PPSV23

Since both PPSV23 and PCV13 are approved for use in adults, it is important to understand appropriate indications for their use. The ACIP recommends pneumococcal vaccination in adults at an increased risk of invasive pneumococcal disease: ie, people age 65 and older, at-risk people ages 19 to 64, and people who are immunocompromised or asplenic.

A more robust antibody response has been shown with PCV13 compared to PPSV23 in healthy people.[5] Of note, when PPSV23 is given before PCV13, there is a diminished immune response to PCV13.[11,12] Therefore, unvaccinated people who will receive both PCV13 and PPSV23 should be given the conjugate vaccine PCV13 first. (See **Commonly asked questions** on page 428.)

ADULTS AGE 65 AND OLDER: ONE DOSE EACH OF PCV13 AND PPSV23

Before September 2014, the ACIP recommended one dose of PPSV23 for adults age 65 and older to prevent invasive pneumococcal disease.[13] With evidence that PCV13 also produces an antibody response and is clinically effective against pneumococcal pneumonia in older people, the ACIP now recommends that all adults age 65 and older receive one dose of PCV13 and one dose of PPSV23.[3,14]

Based on antibody studies, the ACIP recommends giving PCV13 first and PPSV23 12 months after.[11,12] Patients who received PPSV23 at age 65 or older should receive PCV13 at least 1 year after PPSV23 (**Figure 2**).[3,14] Patients who had previously received one dose of PPSV23 before age 65 who are now age 65 or older should receive one dose of PCV13 at least 1 year after PPSV23 and an additional dose of PPSV23 at least 5 years after the first dose of PPSV23 and at least 1 year after the dose of PCV13.[3] Patients who received a dose of PCV13 before age 65 do not need an additional dose after age 65.

The Centers for Medicare and Medicaid Services have updated the reimbursement for pneumococcal vaccines to include both PCV13 and PPSV23. Patients can receive one dose of pneumococcal vaccine followed by a different, second pneumococcal vaccine at least 11 full months after the month in which the first pneumococcal vaccine was administered.[15]

AT-RISK PATIENTS AGES 19 TO 64

Before 2012, the ACIP recommended that patients at risk, including immunocompromised patients and those without a spleen, with cerebrospinal fluid leaks, or with cochlear implants, receive only PPSV23 before age 65.[13] In 2010, 50% of cases of invasive pneumococcal disease in immunocompromised adults were due to serotypes contained in PCV13.[16] Additionally, according to CDC data from 2013, in adults ages 19 to 64 at risk of pneumococcal disease, only 21.2% had received pneumococcal vaccine.[17] With information on epidemiology, safety, and efficacy, as well as expanded FDA approval of PCV13 for adults in 2011, the ACIP updated its guidelines for pneumococcal immunization of adults with immunocompromising conditions in October 2012.[16] The updated guidelines now include giving PCV13 to adults at increased risk of invasive pneumococcal disease.[16]

Adults under age 65 at risk of invasive pneumococcal disease can be further divided into those who are immunocompetent with comor-

TABLE 1

Indications for PCV13 and PPSV23 for at-risk adults[a]

Risk group	PCV13	PPSV23	PPSV23 revaccination 5 years after first dose
At-risk patients ages 19 to 64 with comorbid conditions			
Immunocompetent persons with chronic heart disease,[b] chronic lung disease,[c] diabetes mellitus, alcoholism, chronic liver disease, cirrhosis, or cigarette smoking	No	Yes	No
Persons with cerebrospinal fluid leak or cochlear implants	Yes	Yes	No
Immunocompromised and asplenic patients			
Persons with functional or anatomic asplenia (sickle cell disease, other hemoglobinopathy, or congenital or acquired asplenia)	Yes	Yes	Yes
Immunocompromised persons, ie, with congenital or acquired immunodeficiency,[d] human immunodeficiency virus infection, chronic renal failure, nephrotic syndrome, leukemia, lymphoma, Hodgkin disease, generalized malignancy, iatrogenic immunosuppression,[e] solid organ transplant, or multiple myeloma	Yes	Yes	Yes

PCV13 = pneumococcal conjugate vaccine-13; PPSV23 = pneumococcal polysaccharide vaccine-23

[a] All adults age 65 and older should receive a dose of PPSV23, regardless of previous history of vaccination with pneumococcal vaccine.

[b] Including congestive heart failure and cardiomyopathies, excluding hypertension.

[c] Including chronic obstructive pulmonary disease, emphysema, and asthma.

[d] Includes B- (humoral) or T-lymphocyte deficiency, complement deficiencies (particularly C1, C2, C3, and C4 deficiencies), and phagocytic disorders (excluding chronic granulomatous disease).

[e] Diseases requiring treatment with immunosuppressive therapy, including long-term systemic corticosteroids and radiation therapy.

Adapted from US Centers for Disease Control and Prevention (CDC). 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). MMWR Morb Mortal Wkly Rep 2012; 61:816–819.

bid conditions, and those with cochlear implants or cerebrospinal fluid leak. (**Table 1**).[16]

Patients with **cochlear implants or cerebrospinal fluid leaks** should receive one dose of PCV13 followed by one dose of PPSV23 8 weeks later. If PPSV23 is given first in this group, PCV13 can be given 1 year later.

Immunocompetent patients with **comorbid conditions**, including cigarette smoking, chronic heart, liver, or lung disease, asthma, cirrhosis, and diabetes mellitus, should receive one dose of PPSV23 before age 65 (**Table 1**).[16]

IMMUNOCOMPROMISED AND ASPLENIC PATIENTS

Immunocompromised patients at risk for invasive pneumococcal disease include patients with functional or anatomic asplenia or immunocompromising conditions such as HIV infection, chronic renal failure, generalized malignancy, solid organ transplant, iatrogenic immunosuppression (eg, due to corticosteroid therapy), and other immunocompromising conditions.[16] Patients on corticosteroid therapy are considered immunosuppressed if they take 20 mg or more of prednisone daily (or an equivalent corticosteroid dose) for at least 14 days.[16] These immunocompromised patients should receive one dose of PCV13, followed by a PPSV23 dose 8 weeks later and a second PPSV23 dose 5 years after the first.[16]

The time between vaccinations is also important. If PCV13 is given first, PPSV23 can be given after at least 8 weeks. If PPSV23 is given first, PCV13 should be given after 12

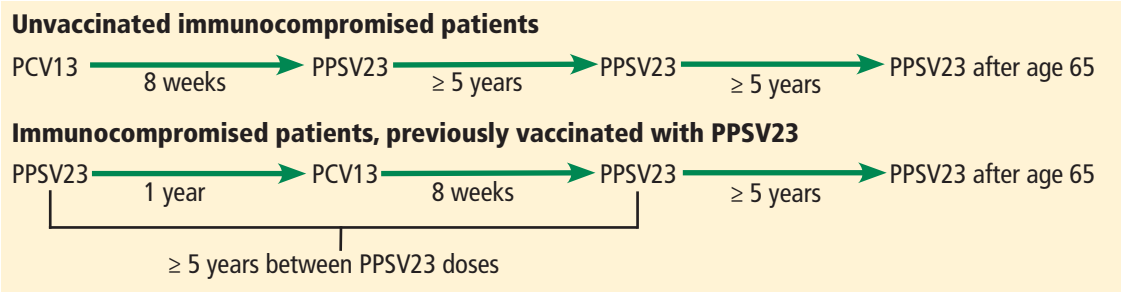

FIGURE 3. Intervals of administration of pneumococcal conjugate vaccine-13 (PCV13) and pneumococcal polysaccharide vaccine-23 (PPSV23) in immunocompromised patients.

Information from reference 16.

months. The time between PPSV23 doses is 5 years (**Figure 3**).[16]

ADDRESSING BARRIERS TO PNEUMOCOCCAL VACCINATION

In 2013, only 59.7% of adults age 65 and older and 21.1% of younger, at-risk adults with immunocompromising conditions had received pneumococcal vaccination.[17] Healthcare providers have the opportunity to improve pneumococcal vaccination rates. The National Foundation for Infectious Diseases (**www.nfid.org**) summarized challenges in vaccinating at-risk patients and recommended strategies to overcome barriers.[18]

Ask questions about vaccination at www.cdc.gov/cdc-info

Challenges include the cost of vaccine coverage, limited time (with competing priorities during office appointments or hospitalizations), patient refusal, and knowledge gaps.

Strategies to overcome barriers include incorporating vaccination into protocols and procedures; educating healthcare providers and patients about pneumococcal disease, vaccines, costs, and reimbursement; engaging nonclinical staff members; and monitoring local vaccination rates. However, the most important factor affecting whether adults are vaccinated is whether the healthcare provider recommends it.

AN OPPORTUNITY TO IMPROVE

In the last 30 years, great strides have been made in recognizing and preventing pneumococcal disease, but challenges remain. Adherence to the new ACIP guidelines for pneumococcal vaccination in immunocompromised, at risk and elderly patients is important in reducing invasive pneumococcal disease.

Healthcare providers have the opportunity to improve pneumococcal vaccination rates at outpatient appointments to decrease the burden of invasive pneumococcal disease in at-risk populations. A comprehensive understanding of the guideline recommendations for pneumococcal vaccination can aid the provider in identifying patients who are eligible for vaccination.

Adult pneumococcal immunization rates are low due to missed opportunities. Healthcare providers can improve these rates by viewing every patient encounter as a chance to provide vaccination.

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