Streptococcus pneumoniae, otherwise known as pneumococcus, is the causative organism in a number of different infections, including otitis media, sinusitis, pneumonia, meningitis, peritonitis, and bacteremia. It is a gram-positive, aerobic bacterium that has an external capsule composed of polysaccharides. The external capsule allows the bacteria to adhere to human cells and facilitates invasion and infection.¹

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Understanding adult pneumococcal vaccine efficacy
I nvasive disease, defined as bacteria invading normally sterile areas, most commonly presents as pneumonia with bacteremia, bacteremia, and meningitis. Pneumococcus is capable of producing a variety of polysaccharides on the external capsule, and this variety in polysaccharides is responsible for the formation of 91 different serotypes of Streptococcus pneumoniae. The polysaccharides also provide the mechanisms for pneumococcal vaccines. The vaccines introduce the polysaccharides to the immune system, which produces an antibody response and provides protection against disease.

Vaccination is an important tool to help combat infections caused by Streptococcus pneumoniae, which continues to cause significant disease in the United States. Statistics show that nearly all of the deaths attributed to pneumococcal disease in 2009 were in adults. Despite widespread availability of pneumococcal vaccines, however, the rate of pneumococcal vaccination among adults remains low. One study focusing on vaccine efficacy in the population infected with human immunodeficiency virus (HIV) reports that about 50% of the enrolled subjects had not been vaccinated prior to their participation in the study.

The purpose of this article is to review the differences between pneumococcal vaccines available for the adult population, and to review the current Advisory Committee on Immunization Practices (ACIP) guidelines for adult pneumococcal immunization.

**Vaccine benefits**

Several benefits, both direct and indirect, can be derived from pneumococcal vaccination. One of the primary goals of any vaccine program is to reduce the incidence of disease. The number of cases of invasive pneumococcal disease (IPD) has declined with the introduction of pneumococcal vaccines. IPD incidence in 2010 was 3.8 cases per 100,000 adults aged 18-34 years, and 6.4 per 100,000 adults aged 65 or older. The rate increased to 173 cases per 100,000 for those persons infected with HIV, and 186 cases per 100,000 for those persons aged 18-64 years who were diagnosed with hematologic cancer. In 2010, there were an estimated 39,750 cases of IPD and 4000 deaths. This number has decreased significantly from the estimated 64,400 cases and 7300 deaths in 1999.

The decline in cases occurred after the 7-valent pneumococcal conjugate vaccine for children was introduced in 2000. The IPD rate in healthy adults, caused by serotypes contained in the 7-valent conjugate vaccine, dropped 6 cases per 100,000 in 2000 to 1 case per 100,000 in 2007.

However, in immunocompromised individuals, the case rates remain elevated, because 50% of IPD is caused by serotypes contained in the 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine. Another benefit of vaccination is reduction in the severity of pneumococcal disease. Pneumococcal vaccination is associated with a 40%-70% reduced risk of in-hospital mortality, and has reduced hospital length of stay from an average of 6.5 days in patients without prior vaccination, to 4.5 days in patients who were vaccinated prior to admission.

The vaccine program has provided other indirect benefits, beyond its primary goal of reducing the number of infections and mortality from IPD. Pneumococcal vaccination has reduced the number of pneumococcal infections in unvaccinated persons through a herd immunity effect. In addition, by preventing pneumococcal infections, the 7-valent pneumococcal conjugate vaccine (PCV7) also has prevented infections with resistant strains of pneumococcus. Rates of pneumococcal resistance to penicillin and cephalosporin have decreased since PCV7 was introduced for vaccination in children. In 1999, penicillin resistance was estimated at 26.8% and cephalosporin resistance was 16.9% based on sampling from reference laboratories. By 2010, those numbers had fallen to 10.6% and 8.6%, respectively (see Figure 1, page 6).

History of pneumococcal vaccines

Recommendations and vaccine strategies have evolved over the years as new vaccines have become available. This holds true for pneumococcal vaccines. The 23-valent pneumococcal polysaccharide vaccine (PPSV23), marketed as Pneumovax 23 by Merck, was approved for use in adults in 1983. In 2000, the PCV7 was introduced for use in infants and young children. The PCV7 was replaced by the 13-valent pneumococcal conjugate vaccine (PCV13) in 2010. The PCV13 contains the same 7 serotypes as the PCV7, plus an additional 6 serotypes.

On December 11, 2011, the US Food and Drug Administration (FDA) approved the use of PCV13, marketed as Prevnar 13 by Wyeth Pharmaceuticals, Inc., for use in adults 50 years and older based on studies comparing the immune response of PCV13 to that of PPSV23. Studies on adults show that among the 12 serotypes common to both vaccines, PCV13 induced an antibody level comparable to or higher than the levels induced by PPSV23. Additional trials are being conducted. The approval was granted under the FDA’s accelerated approval pathway. On June 20, 2012, ACIP recommended the use of PCV13 for adults 19 years and older with immunocompromising conditions, asplenia, cerebral spinal fluid (CSF) leaks, or cochlear implants.

Comparison of PPSV23 and PCV13

The 2 vaccines now licensed for use among adults differ in a few areas, including the number of serotypes they protect against, the way they stimulate the immune system, and the magnitude of the immune response. The PPSV23 vaccine contains polysaccharides from 23 different serotypes of Streptococcus pneumoniae (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F).

<table>
<thead>
<tr>
<th>Type of Vaccine</th>
<th>Description</th>
<th>Indicated for:</th>
</tr>
</thead>
<tbody>
<tr>
<td>23-Valent polysaccharide (PPSV23)</td>
<td>Contains polysaccharides from 23 serotypes of <em>Streptococcus pneumoniae</em></td>
<td>All adults &gt;65 years of age and for at-risk adults 19-64 of age</td>
</tr>
<tr>
<td>13-Valent pneumococcal conjugate (PCV13)</td>
<td>Contains 13 <em>Streptococcus pneumoniae</em> serotypes</td>
<td>One dose for at-risk adults (&gt;19 years of age)</td>
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</tbody>
</table>
Of the 23 serotypes, 12 are the same as those contained in the PCV13. Epidemiologic data from 2008 show that the serotypes contained in the PPSV23 were responsible for 78% of IPD in the group aged 18-49 years, 76% in the group aged 50-64 years, and 66% of people in the group aged 65 or older. The PCV13 vaccine contains 13 pneumococcal serotypes: 1, 3, 4, 5, 6a, 6b, 7f, 9v, 14, 18C, 19F, 19A, and 23F. Those serotypes were responsible for 53% of IPD in persons age 18-49 years, 49% in the group aged 50-64 years, and 44% of those 65 years and older in 2008. The serotype 19A is responsible for most infections with drug-resistant pneumococcus and is included in both vaccines.

The 2 vaccines also differ in how they stimulate the immune system. The PPSV23 vaccine works by inducing type-specific antibodies that enhance the immune system’s ability to kill pneumococcus through opsonization and phagocytosis. The polysaccharides contained in the PCV13 are conjugated to a carrier protein that stimulates a T-cell-dependent immune response in addition to the B-cell antibody-mediated response. Studies show that the PCV13 does elicit an increased antibody response among those with compromised immune systems, including HIV patients and transplant recipients. The degree to which the immune system is stimulated, measured by the geometric mean antibody titers and the opsonophagocytic activity (OPA) produced following vaccination, is used to estimate a vaccine’s effectiveness.

**Vaccine efficacy**

Vaccine efficacy and immune response varies among risk groups. The overall efficacy of the PPSV23 is 74%, and ranges from 50%-80% among immunocompetent adults with underlying medical conditions. OPA provides a measure of the ability of serum antibodies to eliminate pneumococci. Immunogenicity studies comparing PPSV23 and PCV13 revealed the OPA, and geometric mean antibody titers for PCV13 were comparable or higher than those of PPSV23. It was these data that prompted the approval of the PCV13 for use in adults. These studies were conducted in healthy individuals.

Vaccine efficacy in the HIV population has met with conflicting evidence. One randomized, double-blinded, placebo-controlled trial conducted on patients infected with HIV in Uganda reports a lack of efficacy in preventing IPD in this population. However, the results of this study are not considered applicable to the HIV-infected population in developed countries, where there is greater access to antiretroviral therapy.

A case-controlled study conducted in 4 hospitals in Spain demonstrated that administering the PPSV23 to HIV-infected adults did convey a protective effect. In this study the protective effect was stronger for those whose CD4 lymphocyte count was below 200, compared with those who had a CD4 count above 200. In a randomized trial comparing revaccination of HIV-infected patients with PPSV23 versus HIV-infected patients with PCV7, a greater number of HIV-infected patients achieved a 2-fold rise in antibody levels in the PCV7 group, when compared with the number in the PPSV23 group. The difference in antibody titers waned after 180 days. Another trial studied the efficacy of PSV7 vaccine in HIV-infected adults.
who survived an episode of IPD. The study participants were given 2 doses of PCV7, at 4 weeks apart. The vaccine was effective and prevented 74% of recurrent IPD. These studies help lay the foundation for recommending PCV13 use in the HIV-infected population, as well as in other immunocompromised adults.

### Adverse effects

Both vaccines produce similar adverse effects. The most common adverse reactions reported occur at the injection site. Those reactions include pain, swelling and redness, and limitation of movement in the injected arm. Other adverse effects include chills, fever, fatigue, headache, appetite loss, and generalized muscle and joint pain. In general, the vaccines are well tolerated. The overall incidence of side effects reported in the first 30 days after vaccination is less than 2% for both vaccines.

### Indications for pneumococcal vaccination

Recommendations on who should receive the pneumococcal vaccine, and which vaccine they should receive, are based on IPD risk factors. IPD rates differ among demographic variables, the strength of an individual’s immune system, and with the presence of those with certain underlying medical conditions.

Demographic risk factors have remained fairly constant over the years. The case rates for IPD are highest among the very young (children 1 year old or less) and the elderly (adults 65 and older). All children, and all adults 65 years and older are encouraged to receive pneumococcal vaccination. Other populations that historically have been at risk are the Alaskan Native and American Indian populations, both children and adults. The majority of adult IPD cases in this demographic occur in individuals with other risk factors, such as underlying medical conditions. Thus, when the adult pneumococcal vaccination guidelines were revised in 2010, the Alaskan Native and the American Indian populations were no longer given as a separate indication category, as they were included with those individuals with underlying medical conditions.

Another indication for adult pneumococcal vaccination is persons with underlying medical conditions. From 1999 to 2007, the rate of adult IPD cases in individuals aged 18-64 years with underlying medical conditions increased from 52% to 59%. The rate increase suggests that this group does not derive as much benefit from herd immunity as the general population does. The list of medical conditions that put an individual at risk for IPD continues to be evaluated and adjusted. The most recent additions to this list include individuals who smoke and those who are diagnosed with asthma. Cigarette smokers have 4 times the risk for IPD compared with persons who have never smoked. Smoking also further increases the risk of IPD in other high-risk groups, such as those adults who are immunocompromised. One study indicated that in addition to receiving a pneumococcal vaccine, smokers can further reduce their risk of IPD by smoking cessation. For adults with asthma, particularly severe disease, the risk of IPD is nearly double that of the general adult population. The full list of medical conditions that place an adult at higher risk for IPD, and thus should be vaccinated, is as follows:

- congenital or acquired immunodeficiency
- abnormal innate immune response
- HIV infection
- functional or anatomic asplenia
- chronic renal disease
- nephrotic syndrome
- hematologic malignancies
- generalized malignancies
- recipients of a solid organ transplant
- treatment with immunosuppressive medications

In particular, the IPD risk for those individuals infected with HIV has been well documented. *Streptococcus pneumoniae* is the most common cause of bacterial pneumonia in adults infected with HIV. IPD is more common in HIV-infected patients whose CD4 count is below 200, than in those whose CD4 count is above 200. In addition to pneumococcal vaccination, treatment with antiretroviral therapy has reduced the incidence of pneumococcal disease in the HIV-infected population by 50%.

### Pneumococcal vaccine recommendations

ACIP updated its recommendations for adult pneumococcal vaccine in October 2012 to reflect the approval of PCV13 in this age group. These recommendations can be stratified based on the at-risk groups. All adults 65 years or older should receive a
Table 3. ACIP recommendations for pneumococcal vaccination

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>19-49 years</th>
<th>50-64 years</th>
<th>&gt;65 years</th>
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<tbody>
<tr>
<td>23-Valent pneumococcal polysaccharide (PPSV23)</td>
<td>1 or 2 doses for at-risk adults(^a)</td>
<td>1 dose(^b)</td>
<td></td>
</tr>
<tr>
<td>13-Valent pneumococcal conjugate (PCV13)</td>
<td>1 dose for at-risk adults(^c) in addition to vaccination with pneumococcal polysaccharide vaccinated</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Chronic lung disease, chronic cardiovascular diseases, diabetes mellitus, chronic liver disease, alcoholism, cochlear implants, cerebrospinal fluid leaks, immunocompromising conditions, and functional or anatomic asplenia. Nursing home or long-term facility residents, smokers, and persons with HIV. One-time revaccination is recommended 5 years after first dose.

\(^b\) Revaccination recommended for people who received 1 or 2 doses of PPSV23 before age 65 if at least 5 years have passed since previous dose.

\(^c\) Immunocompromising conditions (eg, chronic renal failure and nephrotic syndrome), functional or anatomic asplenia, cerebrospinal fluid leaks, or cochlear implants.

\(^d\) At-risk adults who have previously received ≥1 dose of PPSV23 should be vaccinated with PCV13 one or more years after the last PPSV23 dose was received.

dose of the PPSV23 vaccine, even if they have been previously vaccinated.\(^6\) Adults 19 years or older, with 1 of the indicated chronic medical conditions listed earlier, should receive a dose of PPSV23 at the time of diagnosis.\(^4\) The PCV13 vaccine and the PPSV23 vaccines both are recommended for adults, aged 19 and older, who have an immunocompromising condition, asplenia, CSF leak, or cochlear implant. If a patient is naive to pneumococcal vaccine, they should be given the PCV13 vaccine at the time of diagnosis, and then the PPSV23 vaccine at least 8 weeks later.\(^6\) Studies show a higher concentration of antibodies develops if the vaccines are given in sequence, pneumococcal conjugate then pneumococcal polysaccharide, over those vaccinated with the pneumococcal polysaccharide vaccine alone.\(^13\) Adults in this category who have previously received the PPSV23 should receive a one-time dose of the PCV13 vaccine at least 1 year after the last PPSV23 dose.\(^6\) Ideally, adults with HIV infection should be vaccinated when their CD4 count is above 200. Geometric mean antibody concentrations against pneumococcal polysaccharides are lower when the CD4 count is below 200 at the time adults with HIV are vaccinated.\(^13\)

Recommendations for revaccination depend on the risk group. If an adult is receiving his or her first PPSV32 vaccine dose at age 65, they will not need to be revaccinated.\(^4,6\) If a person has been vaccinated prior to the age of 65 for any reason, he or she should receive another dose of PPSV23 at age 65, or later if 5 years have not yet elapsed between vaccines.\(^4,6\) Adults who should receive a second dose of PPSV23 vaccine include those who have asplenia, CSF leaks, cochlear implants, and those who are immunocompromised.\(^6\)

The second vaccine should be given 5 years after the first dose. ACIP does not recommend multiple revaccination doses because data are insufficient to indicate additional clinical benefit or protection from repeated vaccine doses.\(^4\) Currently, a second, or booster, dose of the PCV13 vaccine is not indicated in adults.

Final notes
Pneumococcal vaccination provides physicians with an effective tool to help combat IPD. The introduction of PCV13 for adult use has expanded the options available for protecting patients against infection.

Questions about the efficacy of pneumococcal vaccines in the immunocompromised population remain, particularly in HIV-infected individuals. However, the potential benefit from vaccination outweighs the potential harm in this group. New trials are attempting to clarify further the best vaccination strategies to protect adults against pneumococcal disease.

References


About the Author
Bridget Branstetter, DO, has worked for Midwest Infectious Disease Specialists since August 2008; she also serves as the hospital epidemiologist and as chair of the Infection Control Committee at Centerpoint Medical Center in Independence, Mo. Dr. Branstetter is board certified in internal medicine and infectious disease. She can be reached at branstb@gmail.com.