Pneumococcal disease remains one of the most common causes of morbidity and mortality in the United States. Despite long-standing recommendations to vaccinate high-risk adults against pneumococcal disease, vaccination rates remain alarmingly low. This article explores pneumococcal vaccination strategies and recommendations through the following case report and analysis.
Case report

A 47-year-old female presented to the emergency department of her local hospital with severe shortness of breath. Her symptoms had started 2 days before with a shaking chill, fever, and productive cough. The patient was well known to hospital personnel because of her long history of treatment both as an inpatient and outpatient for alcoholism. The patient was hypoxic, hypotensive, and hypothermic at her initial evaluation, and her initial chest X-ray in the emergency department showed bilateral infiltrates. Initial laboratory was drawn, including blood cultures, and she was given broad-spectrum antibiotics intravenously. Because of her deteriorating condition, she was flown by air ambulance to a teaching hospital where she was immediately intubated and transferred to the intensive care unit (ICU) for treatment of septic shock.

Blood cultures drawn at her local hospital were positive for *Streptococcus pneumoniae* (penicillin sensitive). Her hospital stay was complicated by the development of a large empyema, development of adult respiratory distress syndrome requiring nearly 2 months of mechanical ventilation, bilateral pneumothoraces, and need for a tracheostomy and percutaneous gastrostomy tube for feeding. She was transferred for additional rehabilitation after a nearly 3-month stay in the hospital. During her hospital stay, all of her available past inpatient and outpatient medical records were reviewed. There was no evidence that the patient had ever been offered a pneumococcal vaccine.

Burden of pneumococcal disease in adults

*S. pneumoniae* (pneumococcus) is one of the most important causes of morbidity and mortality worldwide.\(^\text{1}\) Pneumococcus is responsible for diseases such as otitis media and sinusitis and represents a common cause of community- and hospital-acquired pneumonia. When pneumococcus invades areas of the body that are usually sterile (invasive pneumococcal disease), it can cause bacteremia, meningitis, endocarditis, peritonitis, empyema, and septic arthritis. According to the Centers for Disease Control and Prevention,\(^\text{2,3}\) pneumococcus is responsible for:

- Up to 400,000 cases of pneumococcal pneumonia annually in the United States. Approximately 36% of adult community-acquired and 50% of hospital-acquired pneumonia cases are the result of pneumococcus. The case-fatality rate is 5%-7%, but may be as high as 50% in the elderly.
- Approximately 12,000 cases of pneumococcal bacteremia each year. The overall case-fatality rate for bacteremia is approximately 15%, but may be as high as 60% among elderly patients.
- Approximately 3000 cases of pneumococcal meningitis annually. The case-fatality rate of pneumococcal meningitis is approximately 30%, but may be higher among elderly persons, approaching 80%. Neurological sequelae are common among survivors. Pneumococci cause 13%-19% of all cases of bacterial meningitis in the United States. In the most recent reporting year, there were 15,635 reported cases of invasive pneumococcal disease in the United States.\(^\text{4}\)

Despite questions about the efficacy of PPSV23 to prevent pneumococcal pneumonia, it is generally acknowledged that previous vaccination reduces the incidence of invasive pneumococcal disease.

Causative organism: pneumococcus

*S. pneumoniae* is a facultative anaerobic bacterium that appears as encapsulated Gram-positive, lancet-shaped diplococci on microscopic examination.\(^\text{5,6}\) There are over 90 known serotypes of pneumococcus. Each serotype of the bacteria has a chemically distinct polysaccharide capsule that contributes to the virulence of the strain and can also predict likely resistance to antibiotics.\(^\text{7}\) Not all serotypes of pneumococcus cause human disease. The majority of the burden of pneumococcal disease is associated with a limited number of serotypes.\(^\text{1}\) The 10 most common serotypes are estimated to account for approximately 62% of invasive disease worldwide.\(^\text{3}\)

The natural reservoir for pneumococcus is the human nasopharynx, with children serving as major carriers of the organism.\(^\text{8}\) Colonization of the nasopharynx is usually a precursor of clinical disease and a common source of transmission of the organism. Pneumococci may be isolated from the nasopharynx of 5%-70% of adults, depending on the population and setting. Only 5%-10% of adults without children are carriers. Approximately 25%-50% of students and as many as 50%-60% of service personnel on military installations may be carriers.\(^\text{8,9}\) The duration of carriage varies and is generally longer in children than adults. Transmission of pneumococcus occurs as the result of direct person-to-person contact through respiratory droplets and by autoinoculation in persons carrying the bacteria in their upper respiratory tract.\(^\text{4}\) Actual disease is caused by spread of the organism from the nasopharynx to the sinuses or middle ear, aspiration into the lung, or by direct invasion of the bloodstream.\(^\text{10}\)

Risk factors for invasive pneumococcal disease

Pneumococcal pneumonia is the most common clinical syndrome that occurs from infection with *S. pneumoniae* in adults. Patients who
The incidence of invasive pneumococcal disease is particularly increased for persons at the extremes of age (<2 years or ≥65 years) and in persons with chronic illness.

develop pneumococcal pneumonia often have underlying pulmonary disease, though the infection can occur in patients with normal lung function.

There are numerous conditions that increase the risk of pneumococcal disease in adults. The incidence of invasive pneumococcal disease is particularly increased for persons at the extremes of age (<2 years or ≥65 years) and in persons with chronic illness. All immunosuppressed patients are at risk of invasive pneumococcal disease, and immunocompetent patients with certain conditions have greater risk. Some of the commonly identified risk factors for invasive pneumococcal disease include:

- **Demographic factors (age, ethnicity, and socioeconomic factors):** As noted, the highest reported incidence for invasive pneumococcal disease in the United States is in patients who are age younger than 1 year (14.4 cases per 100,000 population) and those who are aged 65 years or older (21.5 cases per 100,000 population). The risk of invasive disease is increased in preterm and low-birth-weight infants and in children who attend day care. Rates of invasive disease are also increased in certain racial and ethnic groups. Alaska Native, African American, and certain American Indian groups have higher rates of invasive pneumococcal disease. Though the reasons for the increased risk by race and ethnicity are not known, socioeconomic factors likely play a role in disease risk.  

- **Substance use (alcohol and smoking):** Numerous studies have demonstrated the increased risk of invasive pneumococcal disease in patients who smoke and in patients who abuse alcohol. A recent systematic review of studies evaluating the relationship of smoking to the risk of invasive pneumococcal disease reported an increased risk ranging from an odds ratio of 2.2 (1.7-3.0) for bacteremic pneumococcal pneumonia to 4.1 (2.4-7.3) for all invasive pneumococcal disease. Of 6 studies that considered alcohol as a risk factor for invasive pneumococcal disease, 4 reported a significantly increased risk, ranging from a 2.9- to 11.4-fold increased risk. Generally, studies have suggested a dose-response relationship between smoking and alcohol use and the risk of invasive pneumococcal disease. The risk of invasive disease is greater with increases in the number of cigarettes smoked daily, and invasive pneumococcal disease is increased with heavy use of alcohol.  

- **Comorbid medical conditions in immunocompetent patients:** A number of medical conditions are known to be associated with an increased risk of pneumococcal disease. Common conditions such as heart disease, chronic
obstructive lung disease including asthma, and diabetes mellitus are associated with an increased risk of pneumococcal pneumonia and invasive pneumococcal disease.\textsuperscript{1,17-23} Patients with a history of chronic liver disease or cirrhosis are also at increased risk. Recent influenza infection increases the risk of invasive pneumococcal disease, and patients who are institutionalized are at increased risk.\textsuperscript{11,24,25}

Patients who undergo cochlear implant surgery or who have cerebrospinal fluid leaks are known to be at particularly high risk of recurrent pneumococcal meningitis.\textsuperscript{26,27} Direct inoculation of \textit{S. pneumoniae} from the nasopharynx in these cases results in the high risk of infection.

**Immunosuppressed patients:** Patients with both congenital and acquired immunodeficiency are at increased risk of recurrent pneumococcal disease.\textsuperscript{11,14,28} Patients with a variety of hematologic and solid organ malignancies, organ transplants, human immunodeficiency virus infection, as well as patients with chronic renal failure are at increased risk of invasive disease (Table 1).

Patients with acquired or congenital asplenia are at very high risk of pneumococcal infection and life-threatening bacteremia, including purpura fulminans.\textsuperscript{29} Patients with sickle cell disease and other hemoglobinopathies who develop functional asplenia are at risk of serious infections and bacteremia resulting from encapsulated organisms such as \textit{S. pneumoniae}.

**Pneumococcal vaccines**

Currently, there are 2 pneumococcal vaccines that are licensed for use in the United States: 23-valent pneumococcal polysaccharide vaccine (PPSV23) and the 13-valent pneumococcal conjugate vaccine (PCV13).\textsuperscript{7} Both are currently recommended for use to prevent pneumococcal disease in adults.

**Pneumococcal polysaccharide vaccine (PPSV23)**

First licensed in 1983, PPSV23 (Pneumovax 23; Merck & Co., Inc., Whitehouse Station, NJ) is composed of purified polysaccharides from the surface capsules of 23 serotypes of \textit{S. 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). In 2008, these 23 serotypes of \textit{S. pneumoniae} were implicated in up to 78\% of cases of pneumococcal bacteremia that occur in patients ages 18-49 and up to 66\% of cases of invasive disease in patients aged 65 years or older.\textsuperscript{30} This vaccine induces humoral immunity by stimulating antibody (Ab) production against the serotype-specific polysaccharides; however, because the immune response is T-cell independent, there is poor stimulation of immunologic memory.\textsuperscript{11} The vaccine does not stimulate an immune response in children younger than 2 years.

**Pneumococcal conjugate vaccine (PCV13)**

Licensed in February 2010, PCV13 (Prevnar 13; Wyeth Pharmaceuticals, Inc. [Andover, MA], a subsidiary of Pfizer, Inc. [New York, NY]) is composed of the capsular polysaccharides for 13 serotypes of \textit{S. pneumoniae} (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F). The 13 polysaccharides are conjugated to a carrier protein (diphtheria CRM197 protein), which elicits a T-cell response resulting in immunologic priming and an immunologic memory response. The T-cell response results in mucosal immunity, which is important because this results in decreased nasopharyngeal carriage of pneumococcus. The immunologic memory response primes the immune system for future natural exposure to pneumococcus or for a subsequent booster effect with revaccination.\textsuperscript{7,11,31} In 2008, these
13 serotypes of *S. pneumoniae* were implicated in up to 53% of cases of invasive pneumococcal disease that occur in patients ages 18-49 and up to 44% of cases of invasive disease in patients aged 65 years or older.30 PCV13 is effective in children younger than 2 years and is recommended routinely in this age group.

**Pneumococcal vaccine efficacy**  
The efficacy of PPSV23 to prevent pneumococcal disease—particularly pneumococcal pneumonia—has been questioned. A large number of randomized, controlled trials and observational studies with PPSV23 have been done and have generally shown nonsignificant trends toward reduction of pneumococcal pneumonia cases.32 However, many of the clinical trials are quite old and many had methodologic problems, including unrepresentative populations of study patients, inadequate sample sizes, and study of outcomes associated with diagnostic uncertainty.33 Several observational studies that have evaluated outcomes for patients hospitalized with community-acquired pneumonia have shown reduced complications, such as respiratory failure, shorter hospital length of stay, fewer ICU admissions, and lower mortality in patients who have been previously vaccinated with PPSV23.34,35 Some studies have suggested lower rates of acute coronary syndrome in patients hospitalized with pneumonia who have previously received PPSV23.36

Despite questions about the efficacy of PPSV23 to prevent pneumococcal pneumonia, it is generally acknowledged that previous vaccination reduces the incidence of invasive pneumococcal disease.3,32 Studies have generally demonstrated an efficacy of 50%-75% for the prevention of invasive pneumococcal disease.

The introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) in 2000 and subsequent introduction of PCV13 in 2010 has had a profound impact on the incidence of pneumococcal infections, infection caused by penicillin-resistant strains of pneumococcus, deaths resulting from pneumococcal disease, and rates of all invasive pneumococcal disease in children and adults.30,37-40 After the introduction of PCV7 for children in 2000, there were marked declines in the incidence of invasive pneumococcal disease in children (direct vaccine benefit) and also in nonvaccinated adults (indirect vaccine benefit). Infections caused by strains of *S. pneumoniae* that were included in the conjugate vaccine declined significantly. Multiple studies have demonstrated reduced nasopharyngeal colonization with strains of *S. pneumoniae* contained in the available conjugate vaccines. Studies have generally demonstrated an efficacy of 63%-97% for the prevention of invasive pneumococcal disease with use of the conjugated pneumococcal vaccines.3,11

For both vaccines, efficacy is

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**Table 1. Current recommendations for vaccination of adults with the pneumococcal vaccines**

<table>
<thead>
<tr>
<th>Immunocompetent patients</th>
<th>19-64 YEARS</th>
<th>65 YEARS OR OLDER*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV13</td>
<td>Cerebrospinal fluid Leak</td>
<td>Chronic heart disease†</td>
</tr>
<tr>
<td></td>
<td>Cochlear implant</td>
<td>Chronic lung disease‡</td>
</tr>
<tr>
<td>PPSV23</td>
<td>Chronic heart disease†</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Cerebrospinal fluid leak</td>
<td>Cerebrospinal fluid leak</td>
</tr>
<tr>
<td></td>
<td>Cochlear implant</td>
<td>Alcoholism</td>
</tr>
<tr>
<td></td>
<td>Chronic liver disease, cirrhosis</td>
<td>Chronic liver disease, cirrhosis</td>
</tr>
<tr>
<td></td>
<td>Cigarette smoking</td>
<td>Cigarette smoking</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immunocompromised patients or persons with functional asplenia</th>
<th>PCV13 and PPSV23§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle cell disease/other hemoglobinopathy</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Congenital or acquired asplenia</td>
<td>Leukemia</td>
</tr>
<tr>
<td>Congenital or acquired immunodeficiency©</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Human immunodeficiency virus infection</td>
<td>Hodgkin disease</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>Generalized malignancy</td>
</tr>
<tr>
<td></td>
<td>Iatrogenic immunosuppression¶</td>
</tr>
<tr>
<td></td>
<td>Solid organ transplant</td>
</tr>
<tr>
<td></td>
<td>Multiple myeloma</td>
</tr>
</tbody>
</table>

*See figure 1.33†  
Including congestive heart failure and cardiomyopathies (excluding hypertension).  
‡ Including chronic obstructive pulmonary disease, emphysema, and asthma.  
§ Including 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 corticosteroids and radiation therapy.  
§ Including recent PPSV23 dose.
Recommendations for pneumococcal vaccination of adults

Current recommendations from the Advisory Committee on Immunization Practices (ACIP) for pneumococcal vaccination of adults are summarized in the Table 1 and Figure 1. The most recent update to ACIP recommendations is to administer both PCV13 and PPSV23 to all adults aged 65 years or older. This recommendation was based on the results of a large, randomized trial conducted in the Netherlands showing the efficacy of PCV13 in this age group to reduce vaccine-type nonbacteremic pneumococcal pneumonia (45% efficacy) and vaccine-type invasive pneumococcal disease (75% efficacy). When possible, PCV13 should be administered first, followed in 6-12 months by vaccination with PPSV23. This is because studies evaluating sequential administration of either PCV7 or PCV13 followed by PPSV23 demonstrated higher Ab responses than when PPSV23 was administered first. The optimal interval between the 2 pneumococcal vaccines in this age group is not known.

The ACIP recommendations for pneumococcal vaccination of patients aged 19-64 years are summarized in the Table 1. All patients in this age group who are immunosuppressed or who have functional or anatomic asplenia should receive both vaccines. As in older adults, the preferred sequence for pneumococcal vaccine-naïve persons is to administer PCV13 first. However, the recommended interval between administrations of the 2 vaccines differs for this age group. The ACIP recommends an interval of at least 8 weeks after administration of PCV13 before PPSV23 is administered. All patients who are immunosuppressed or who have functional or anatomic asplenia should receive a second dose of PPSV23 at least 5 years after their previous PPSV23 dose. For immunocompetent adults aged 19-64 years who have chronic disease or risk factors for infection (see Table 2), the ACIP still recommends administration of PPSV23 alone. However, patients who have a cerebrospinal leak or cochlear implant, which, as noted above, puts the patients at very high risk of invasive pneumococcal disease—particularly meningitis—should receive PCV13 followed, at least 8 weeks later, by PPSV23. In 2010, the ACIP added asthma and cigarette smoking to the indications for PPSV23 in this age group. For all patients who receive PPSV23 before the age of 65 for any indication, the ACIP recommends another dose of PPSV23 at age 65 (or at least 5 years after the last dose if the patient was aged 61-64 at the time of their first PPSV23 dose).

Vaccine safety

Both pneumococcal vaccines are very safe, with severe adverse reactions rarely reported. Common to both vaccines are local reactions, such as pain, swelling, or redness, at the injection site (30%-50% of patients). Systemic symptoms, such as fever or malaise, are very uncommon for PPSV23. Fever and malaise do occur in up to 25%-35% of children who receive their primary series of PCV13 doses, but are not common symptoms in adults. Both vaccines are contraindicated in patients known to have a severe allergic reaction to any component of the vaccines, or to diphtheria toxoid-containing vaccines for PCV13. Both vaccines can be safely administered with the influenza vaccine.
The most recent update to ACIP recommendations is to administer both PCV13 and PPSV23 to all adults aged 65 years or older.

Despite ACIP-published recommendations for the administration of pneumococcal vaccines to adults dating back to 1989, vaccination rates remain exceedingly low. Based on the National Health Interview Survey in 2012, only 20% of high-risk adults aged 19-64 years had ever received a pneumococcal vaccine. The lowest rates of vaccination in this age group were noted in Asian and Hispanic people (13.2% and 13.8%, respectively). For adults aged 65 years or older, only 59.9% reported ever receiving a pneumococcal vaccine. Again, rates of vaccination were lowest for Asian and Hispanic people (41.3% and 43.4%, respectively).44

Strategies to improve rates of adult vaccination
Numerous strategies have been identified to improve rates of adult vaccination.45 The most effective of the strategies is to develop and implement standing orders programs. Standing orders programs authorize nurses and pharmacists to administer vaccinations according to an institution- or physician-approved protocol without a physician’s exam.46 These programs are typically used by city, county, and state health departments to facilitate vaccination of adults and children in their facilities. Standing orders programs have improved vaccination rates among adults in inpatient and outpatient facilities, long-term care facilities, managed care organizations, assisted living facilities, correctional facilities, pharmacies, adult workplaces, and home health care agencies.46 In addition, the meaningful use of electronic medical records can support vaccination programs through use of decision support tools.

Despite known strategies for improving adult vaccination, barriers persist. A recent survey of primary care physicians highlighted a lack of systems-based tools to facilitate vaccination and persistent financial barriers to office-based adult vaccination programs.47

Final notes
Pneumococcal disease remains one of the most common causes of morbidity and mortality in the United States. Despite long-standing recommendations to vaccinate high-risk adults against pneumococcal disease, vaccination rates remain alarmingly low. The recent introduction of PCV7 in 2000 and subsequent licensing of PCV13 in 2010 have had a profound impact on the epidemiology of pneumococcal disease in adults. The ACIP has recently updated recommendations for use of PCV13 and PPSV23 in adults. Increasing adult vaccination rates will require the implementation of systems-based interventions, such as standing orders programs, that have been shown to improve rates of vaccination.48

References

Table 2. PPSV23 recommended for adults aged 19-65 with common chronic conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>PPSV23 Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Yes</td>
</tr>
<tr>
<td>Lung disease (eg, asthma, COPD)</td>
<td>Yes</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>Yes</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Yes</td>
</tr>
<tr>
<td>Kidney disease (except ESRD, nephrotic syndrome)</td>
<td>Yes</td>
</tr>
<tr>
<td>All cigarette smokers</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Source: CDC.


