

Streptococcus pneumoniae causes an acute bacterial infection. The bacterium, also called pneumococcus, was first isolated by Pasteur in 1881 from the saliva of a patient with rabies. The association between the pneumococcus and lobar pneumonia was first described by Friedlander and Talamon in 1883, but pneumococcal pneumonia was confused with other types of pneumonia until the development of the Gram stain in 1884. From 1915 to 1945, the chemical structure and antigenicity of the pneumococcal capsular polysaccharide, its association with virulence, and the role of bacterial polysaccharides in human disease were explained. More than 80 serotypes of pneumococci had been described by 1940.

Efforts to develop effective pneumococcal vaccines began as early as 1911. However, with the advent of penicillin in the 1940s, interest in pneumococcal vaccination declined, until it was observed that many patients still died despite antibiotic treatment. By the late 1960s, efforts were again being made to develop a polyvalent pneumococcal vaccine. The first pneumococcal vaccine was licensed in the United States in 1977. The first conjugate pneumococcal vaccine was licensed in 2000.

Streptococcus pneumoniae

Streptococcus pneumoniae bacteria are lancet-shaped, gram-positive, facultative anaerobic organisms. They are typically observed in pairs (diplococci) but may also occur singularly or in short chains. Most pneumococci are encapsulated, their surfaces composed of complex polysaccharides. Capsular polysaccharides are one determinant of the pathogenicity of the organism. They are antigenic and form the basis for classifying pneumococci by serotypes. Ninety-two serotypes have been documented as of 2011, based on their reaction with type-specific antisera. Type-specific antibody to capsular polysaccharide is protective. These antibodies and complement interact to opsonize pneumococci, which facilitates phagocytosis and clearance of the organism. Antibodies to some pneumococcal capsular polysaccharides may cross-react with related types as well as with other bacteria, providing protection against additional serotypes.

Most *S. pneumoniae* serotypes have been shown to cause serious disease, but only a few serotypes produce the majority of pneumococcal infections. The 10 most common serotypes are estimated to account for about 62% of invasive disease worldwide. The ranking and serotype prevalence differ by patient age group and geographic area. In the United States, prior to widespread use of 7-valent pneumococcal conjugate vaccine (PCV7), the seven most common serotypes isolated from blood or cerebrospinal fluid (CSF)

Pneumococcal Disease

- *S. pneumoniae* first isolated by Pasteur in 1881
- Confused with other causes of pneumonia until discovery of Gram stain in 1884
- More than 80 serotypes described by 1940
- First U.S. vaccine in 1977

Streptococcus pneumoniae

- Gram-positive organisms
- Polysaccharide capsule important pathogenicity factor
- 92 serotypes documented as of 2011
- Type-specific antibody is protective

of children younger than 5 years of age accounted for 80% of infections. These seven serotypes accounted for only about 50% of isolates from older children and adults.

Pneumococci are common inhabitants of the respiratory tract and may be isolated from the nasopharynx of 5% to 90% of healthy persons. Rates of asymptomatic carriage vary with age, environment, and the presence of upper respiratory infections. Among school-aged children, 20%–60% may be colonized. Only 5%–10% of adults without children are colonized although, on military installations, as many as 50%–60% of service personnel may be colonized. The duration of carriage varies and is generally longer in children than adults. In addition, the relationship of carriage to the development of natural immunity is poorly understood.

Clinical Features

The major clinical syndromes of pneumococcal disease are pneumonia, bacteremia, and meningitis.

Pneumococcal pneumonia is the most common clinical presentation of pneumococcal disease among adults. The incubation period of pneumococcal pneumonia is short, about 1 to 3 days. Symptoms generally include an abrupt onset of fever and chills or rigors. Classically there is a single rigor, and repeated shaking chills are uncommon. Other common symptoms include pleuritic chest pain, cough productive of mucopurulent, rusty sputum, dyspnea (shortness of breath), tachypnea (rapid breathing), hypoxia (poor oxygenation), tachycardia (rapid heart rate), malaise, and weakness. Nausea, vomiting, and headaches occur less frequently.

Approximately 400,000 hospitalizations from pneumococcal pneumonia are estimated to occur annually in the United States. Pneumococci account for up to 36% of adult community-acquired pneumonia. Pneumococcal pneumonia has been demonstrated to complicate influenza infection. About 25–30% of patients with pneumococcal pneumonia also experience pneumococcal bacteremia. The case-fatality rate is 5%–7% and may be much higher among elderly persons. Other complications of pneumococcal pneumonia include empyema (i.e., infection of the pleural space), pericarditis (inflammation of the sac surrounding the heart), and endobronchial obstruction, with atelectasis and lung abscess formation.

More than 12,000 cases of pneumococcal bacteremia without pneumonia occur each year. The overall case-fatality rate for bacteremia is about 20% but may be as high as 60% among elderly patients. Patients with asplenia who develop bacteremia may experience a fulminant clinical course.

Pneumococcal Pneumonia Clinical Features

- Abrupt onset of fever
- Chills or rigors
- Pleuritic chest pain
- Productive cough
- Dyspnea, tachypnea, hypoxia
- Tachycardia, malaise, weakness

Pneumococcal Pneumonia

- Estimated 400,000 hospitalizations per year in the United States
- Up to 36% of adult community-acquired pneumonias
- Common bacterial complication of influenza
- Case-fatality rate 5%–7%, higher in elderly

Pneumococcal Bacteremia

- More than 12,000 cases per year in the United States
- Case-fatality rate ~20%; up to 60% among the elderly

Pneumococci cause over 50% of all cases of bacterial meningitis in the United States. An estimated 3,000 to 6,000 cases of pneumococcal meningitis occur each year. Some patients with pneumococcal meningitis also have pneumonia. The clinical symptoms, cerebrospinal fluid (CSF) profile and neurologic complications are similar to other forms of purulent bacterial meningitis. Symptoms may include headache, lethargy, vomiting, irritability, fever, nuchal rigidity, cranial nerve signs, seizures and coma. The case-fatality rate of pneumococcal meningitis is about 8% among children and 22% among adults. Neurologic sequelae are common among survivors.

Adults with certain medical conditions are at highest risk for invasive pneumococcal disease. For adults aged 18-64 years with hematologic cancer, the rate of invasive pneumococcal disease in 2010 was 186 per 100,000, and for persons with human immunodeficiency virus (HIV) the rate was 173 per 100,000. Other conditions that place adults at highest risk for invasive pneumococcal disease include other immunocompromising conditions, either from disease or drugs, functional or anatomic asplenia, and renal disease. Other conditions that increase the risk of invasive pneumococcal disease include chronic heart disease, pulmonary disease (including asthma in adults), liver disease, smoking cigarettes (in adults) CSF leak, and having a cochlear implant.

Pneumococcal Disease in Children

Bacteremia without a known site of infection is the most common invasive clinical presentation of pneumococcal infection among children 2 years of age and younger, accounting for approximately 70% of invasive disease in this age group. Bacteremic pneumonia accounts for 12%–16% of invasive pneumococcal disease among children 2 years of age and younger. With the decline of invasive Hib disease, *S. pneumoniae* has become the leading cause of bacterial meningitis among children younger than 5 years of age in the United States. Before routine use of pneumococcal conjugate vaccine, children younger than 1 year had the highest rates of pneumococcal meningitis, approximately 10 cases per 100,000 population.

Pneumococci are a common cause of acute otitis media and are detected in 28%–55% of middle ear aspirates. By age 12 months, more than 60% of children have had at least one episode of acute otitis media. Middle ear infections are the most frequent reasons for pediatric office visits in the United States, resulting in more than 20 million visits annually. Complications of pneumococcal otitis media may include mastoiditis and meningitis.

Pneumococcal Meningitis

- Estimated 3,000–6,000 cases per year in the United States
- Case-fatality rate 8% among children
- Case-fatality rate 22% among adults
- Neurologic sequelae common among survivors

Conditions That Increase Risk for Invasive Pneumococcal Disease

- Decreased immune function — including hematologic cancer and HIV infection
- Asplenia (functional or anatomic)
- Chronic heart, pulmonary (including asthma in adults), liver or renal disease
- Cigarette smoking (in adults)
- Cerebrospinal fluid (CSF) leak
- Cochlear implant

Pneumococcal Disease in Children

- Bacteremia without known site of infection most common clinical presentation
- *S. pneumoniae* leading cause of bacterial meningitis among children younger than 5 years of age
- Common cause of acute otitis media

Before routine use of pneumococcal conjugate vaccine, the burden of pneumococcal disease among children younger than 5 years of age was significant. An estimated 17,000 cases of invasive disease occurred each year, of which 13,000 were bacteremia without a known site of infection and about 700 were meningitis. An estimated 200 children died every year as a result of invasive pneumococcal disease. Although not considered invasive disease, an estimated 5 million cases of acute otitis media occurred each year among children younger than 5 years of age.

Burden of Pneumococcal Disease in Children*

Syndrome	Cases
Bacteremia	13,000
Meningitis	700
Death	200
Otitis media	5,000,000

*Prior to routine use of pneumococcal conjugate vaccine

Children at Increased Risk of Invasive Pneumococcal Disease

- Functional or anatomic asplenia, particularly sickle cell disease
- Immune compromise, including HIV infection
- Alaska Native, African American, American Indian (Navajo and White Mountain Apache)
- Child care attendance
- Cochlear implant

Children with functional or anatomic asplenia, particularly those with sickle cell disease, and children with immune compromise including human immunodeficiency virus (HIV) infection are at very high risk for invasive disease, with rates in some studies more than 50 times higher than those among children of the same age without these conditions (i.e., incidence rates of 5,000–9,000 per 100,000 population). Rates are also increased among children of certain racial and ethnic groups, including Alaska Natives, African Americans, and certain American Indian groups (Navajo and White Mountain Apache). The reason for this increased risk by race and ethnicity is not known with certainty but was also noted for invasive *Haemophilus influenzae* infection (also an encapsulated bacterium). Attendance at a child care center has also been shown to increase the risk of invasive pneumococcal disease and acute otitis media 2–3-fold among children younger than 59 months of age. Children with cochlear implants are at increased risk for pneumococcal meningitis.

Laboratory Diagnosis

A definitive diagnosis of infection with *S. pneumoniae* generally relies on isolation of the organism from blood or other normally sterile body sites. Tests are also available to detect capsular polysaccharide antigen in body fluids.

The appearance of lancet-shaped diplococci on Gram stain is suggestive of pneumococcal infection, but interpretation of stained sputum specimens may be difficult because of the presence of normal nasopharyngeal bacteria. The suggested criteria for obtaining a diagnosis of pneumococcal pneumonia using gram-stained sputum includes more than 25 white blood cells and fewer than 10 epithelial cells per high-power field, and a predominance of gram-positive diplococci.

A urinary antigen test based on an immunochromatographic membrane technique to detect the C-polysaccharide antigen of *Streptococcus pneumoniae* as a cause of community-acquired pneumonia among adults is commercially available and has

been cleared by FDA. The test is rapid and simple to use, has a reasonable specificity in adults, and has the ability to detect pneumococcal pneumonia after antibiotic therapy has been started.

Medical Management

Resistance to penicillin and other antibiotics was previously very common. However, following introduction of PCV7, antibiotic resistance declined and then began to increase again. Then, in 2008, the definition of penicillin resistance was changed such that a much larger proportion of pneumococci are now considered susceptible to penicillin. The revised susceptibility breakpoints for *S. pneumoniae*, published by the Clinical and Laboratory Standards Institute (CLSI) in January 2008, were the result of a reevaluation that showed clinical response to penicillin was being preserved in clinical studies of pneumococcal infection, despite reduced susceptibility response in vitro. Guidelines for treatment of meningitis and pneumonia are available from professional societies.

Epidemiology

Occurrence

Pneumococcal disease occurs throughout the world.

Reservoir

S. pneumoniae is a human pathogen. The reservoir for pneumococci is the nasopharynx of asymptomatic humans. There is no animal or insect vector.

Transmission

Transmission of *S. pneumoniae* occurs as the result of direct person-to-person contact via respiratory droplets and by autoinoculation in persons carrying the bacteria in their upper respiratory tract. Different pneumococcal serotypes have different propensities for causing asymptomatic colonization, otitis media, meningitis, and pneumonia. The spread of the organism within a family or household is influenced by such factors as household crowding and viral respiratory infections.

Temporal Pattern

Pneumococcal infections are more common during the winter and in early spring when respiratory diseases are more prevalent.

Communicability

The period of communicability for pneumococcal disease is unknown, but presumably transmission can occur as long as the organism appears in respiratory secretions.

**Pneumococcal Disease
Epidemiology**

Reservoir	Human Carriers
Transmission	Respiratory and Autoinoculation
Temporal pattern	Winter and early spring
Communicability	Unknown (Probably as long as organism appears in respiratory secretions)

Secular Trends in the United States

Estimates of the incidence of pneumococcal disease have been made from a variety of population-based studies. More than 35,000 cases and more than 4,200 deaths from invasive pneumococcal disease (bacteremia and meningitis) are estimated to have occurred in the United States in 2011. More than half of these cases occurred in adults who had an indication for pneumococcal polysaccharide vaccine.

Data from the Active Bacterial Core surveillance (ABCs) system suggest that the use of pneumococcal conjugate vaccine has had a major impact on the incidence of invasive disease among young children. The reductions in incidence resulted from a 99% decrease in disease caused by the seven serotypes in PCV7 and serotype 6A, a serotype against which PCV7 provides some cross-protection. The decreases have been offset partially by increases in invasive disease caused by serotypes not included in PCV7, in particular 19A.

Pneumococcal Vaccines

Characteristics

Pneumococcal Polysaccharide Vaccine

Pneumococcal polysaccharide vaccine is composed of purified preparations of pneumococcal capsular polysaccharide. The first polysaccharide pneumococcal vaccine was licensed in the United States in 1977. It contained purified capsular polysaccharide antigen from 14 different types of pneumococcal bacteria. In 1983, a 23-valent polysaccharide vaccine (PPSV23) was licensed and replaced the 14-valent vaccine, which is no longer produced. PPSV23 contains polysaccharide antigen from 23 types of pneumococcal bacteria that cause 60-76% of invasive disease.

The polysaccharide vaccine currently available in the United States (Pneumovax 23, Merck) contains 25 mcg of each antigen per dose and contains 0.25% phenol as a preservative. The vaccine is available in a single-dose vial or syringe, and in a 5-dose vial. Pneumococcal vaccine is given by injection and may be administered either intramuscularly or subcutaneously.

Pneumococcal Conjugate Vaccine

The first pneumococcal conjugate vaccine (PCV7) was licensed in the United States in 2000. It includes purified capsular polysaccharide of seven serotypes of *S. pneumoniae* (4, 9V, 14, 19F, 23F, 18C, and 6B) conjugated to a nontoxic variant of diphtheria toxin known as CRM197. In 2010 a 13-valent pneumococcal conjugate vaccine (PCV13) was licensed in the United States. It contains the 7 serotypes of *S. pneumoniae* as PCV7 plus serotypes 1, 3, 5, 6A, 7F and 19A

Pneumococcal Vaccines

Year	Vaccine
1977	14-valent polysaccharide vaccine licensed
1983	23-valent polysaccharide vaccine licensed (PPSV23)
2000	7-valent polysaccharide conjugate vaccine licensed (PCV7)
2010	13-valent PCV licensed

Pneumococcal Polysaccharide Vaccine

- Purified capsular polysaccharide antigen from 23 types of pneumococcus
- Account for 60% –76% of bacteremic pneumococcal disease

Pneumococcal Conjugate Vaccine

- Purified capsular polysaccharide from 13 types of pneumococcus conjugated to nontoxic diphtheria toxin (CRM197)
- In 2008 vaccine serotypes contained in PCV13 accounted for 61% of invasive pneumococcal disease cases among children younger than 5 years

which are also conjugated to CRM197. A 0.5-mL PCV13 dose contains approximately 2.2 µg of polysaccharide from each of 12 serotypes and approximately 4.4 µg of polysaccharide from serotype 6B; the total concentration of CRM197 is approximately 34 µg. The vaccine contains 0.02% polysorbate 80 (P80), 0.125 mg of aluminum as aluminum phosphate (AlPO₄) adjuvant, 5mL of succinate buffer, and no thimerosal preservative. Except for the addition of six serotypes, P80, and succinate buffer, the formulation of PCV13 is the same as that of PCV7.

ABCs data indicate that in 2008, before PCV13 replaced PCV7 for routine use among children, approximately 61% of invasive pneumococcal disease cases among children younger than 5 years were attributable to the serotypes included in PCV13, with serotype 19A accounting for 43% of cases; PCV7 serotypes caused less than 2% of cases.

Indirect effects from PCV13 use among children, if similar to those observed after PCV7 introduction, might further reduce the remaining burden of adult pneumococcal disease caused by PCV13-types. A preliminary analysis using a probabilistic model following a single cohort of persons 65 years old or older demonstrated that adding a dose of PCV13 to the current PPSV23 recommendations, would lead to additional health benefits. This strategy would prevent an estimated 230 cases of IPD and approximately 12,000 cases of community-acquired pneumonia over the lifetime of a single cohort of persons 65 years old, assuming current indirect effects from the child immunization program and PPSV23 vaccination coverage among adults 65 years old or older (approximately 60%). In a setting of fully realized indirect effects assuming the same vaccination coverage, the expected benefits of PCV13 use among this cohort will likely decline to an estimated 160 cases of IPD and 4,500 cases of community-acquired pneumonia averted among persons 65 years old or older.

In December 2011 the Food and Drug Administration approved PCV13 as a single dose for the prevention of pneumonia and invasive disease caused by vaccine serotypes of *S. pneumoniae* in persons 50 years of age and older. Licensure was based on serological studies comparing immune response of PCV13 recipients to a response following a dose of PPSV23. In two randomized, multicenter immunogenicity studies conducted in the United States and Europe, immunocompetent adults aged 50 years and older received a single dose of PCV13 or PPSV23. In adults age 60 through 64 years and age 70 years and older, PCV13 elicited opsonophagocytic activity (OPA) geometric mean antibody titers (GMTs) that were comparable with, or higher than, responses elicited by PPSV23. Persons who received PPSV23 as the initial study dose had lower opsonophago-

cytic antibody responses after subsequent administration of a PCV13 dose 1 year later than those who had received PCV13 as the initial dose. Approximately, 20%–25% of IPD cases and 10% of community-acquired pneumonia cases in adults aged ≥ 65 years are caused by PCV13 serotypes and are potentially preventable with the use of PCV13 in this population.

Immunogenicity and Vaccine Efficacy

Pneumococcal Polysaccharide Vaccine

More than 80% of healthy adults who receive PPSV23 develop antibodies against the serotypes contained in the vaccine, usually within 2 to 3 weeks after vaccination. Older adults, and persons with some chronic illnesses or immunodeficiency may not respond as well, if at all. In children younger than 2 years of age, antibody response to PPSV23 is generally poor. Elevated antibody levels persist for at least 5 years in healthy adults but decline more quickly in persons with certain underlying illnesses.

PPSV23 vaccine efficacy studies have resulted in various estimates of clinical effectiveness. Overall, the vaccine is 60%–70% effective in preventing invasive disease caused by serotypes included in the vaccine. Despite the vaccine's reduced effectiveness among immunocompromised persons, PPSV23 is still recommended for such persons because they are at high risk of developing severe disease. There is no consensus regarding the ability of PPSV23 to prevent non-bacteremic pneumococcal pneumonia. For this reason, providers should avoid referring to PPSV23 as “pneumonia vaccine”.

Studies comparing patterns of pneumococcal carriage before and after PPSV23 vaccination have not shown clinically significant decreases in carrier rates among vaccinees. In addition, no population-level change in the distribution of vaccine-type and non-vaccine-type organisms causing invasive disease has been observed despite modest increases in PPSV23 coverage among adults.

Pneumococcal Conjugate Vaccine

In a large clinical trial, PCV7 was shown to reduce invasive disease caused by vaccine serotypes by 97%. Children who received PCV7 had 20% fewer episodes of chest X-ray confirmed pneumonia, 7% fewer episodes of acute otitis media and underwent 20% fewer tympanostomy tube placements than did unvaccinated children. There is evidence that PCV7 reduces nasopharyngeal carriage, among children, of pneumococcal serotypes included in the vaccine.

PCV13 was licensed in the United States based upon studies that compared the serologic response of children who

Pneumococcal Polysaccharide Vaccine

- Purified pneumococcal polysaccharide (23 types)
- Not effective in children younger than 2 years
- 60%–70% against invasive disease
- Less effective in preventing pneumococcal pneumonia

Pneumococcal Conjugate Vaccine

- More than 90% effective against invasive disease caused by vaccine serotypes in children
- 45% effective against vaccine-type non-bacteremic pneumococcal pneumonia in adults older than 65 years
- 75% effective against vaccine-type invasive disease in adults older than 65 years

received PCV13 to those who received PCV7. These studies showed that PCV13 induced levels of antibodies that were comparable to those induced by PCV7 and shown to be protective against invasive disease.

In another study of PCV13, children 7-11 months, 12-23 months, and 24-71 months of age who had not received pneumococcal conjugate vaccine doses previously were administered 1, 2, or 3 doses of PCV13 according to age-appropriate immunization schedules. These schedules resulted in antibody responses to each of the 13 serotypes that were comparable to those achieved after the 3-dose infant PCV13 series in the U.S. immunogenicity trial, except for serotype 1, for which IgG geometric mean concentration (GMC) was lower among children aged 24-71 months.

A randomized placebo-controlled trial (CAPiTA trial) was conducted in the Netherlands among approximately 85,000 adults 65 years old or older during 2008-2013 to evaluate the clinical benefit of PCV13 in the prevention of pneumococcal pneumonia. The results of the CAPiTA trial demonstrated 45.6% efficacy of PCV13 against vaccine-type pneumococcal pneumonia, 45.0% efficacy against vaccine-type nonbacteremic pneumococcal pneumonia and 75.0% efficacy of PCV13 against vaccine-type invasive pneumococcal disease (IPD).

Vaccination Schedule and Use

Pneumococcal Conjugate Vaccine

All children 2 through 59 months of age should be routinely vaccinated with PCV13. The primary series beginning in infancy consists of three doses routinely given at 2, 4, and 6 months of age. The first dose can be administered as early as 6 weeks of age. A fourth (booster) dose is recommended at 12-15 months of age. PCV13 should be administered at the same time as other routine childhood immunizations, using a separate syringe and injection site. For children vaccinated at younger than 12 months of age, the minimum interval between doses is 4 weeks. Doses given at 12 months of age and older should be separated by at least 8 weeks. A PCV schedule begun with PCV7 should be completed with PCV13.

A detailed PCV13 vaccination schedule by age and number of previous doses is available in the December 2010 PCV13 ACIP statement.

Unvaccinated children 7 months of age and older do not require a full series of four doses. The number of doses a child needs to complete the series depends on the child's current age and the age at which the first dose of PCV13

Pneumococcal Conjugate Vaccine Recommendations

- Routine vaccination of children 2 through 59 months of age
- Doses at 2, 4, 6, months of age, booster dose at 12-15 months of age
- First dose as early as 6 weeks
- Unvaccinated children 7 months of age or older require fewer doses
- Adults 65 years old and older

Pneumococcal Conjugate Vaccine Schedule for Unvaccinated Older Children-Primary Series

Age at first dose	# of Doses	Booster
7-11 months	2 doses	Yes
12-23 months	2 doses*	No
24-59 months, healthy	1 dose	No
24-71 months, medical conditions**	2 doses*	No

*separated by at least 8 weeks *MMWR* 2010;59(RR-11):1-19

** chronic heart, lung disease, diabetes, CSF leak, cochlear implant, sickle-cell disease, other hemoglobinopathies, functional or anatomic asplenia, HIV infection, immunocompromising conditions

Pneumococcal Conjugate Vaccine High-risk Schedule — Children 6 years through 18 years

- Single dose if no dose of PCV13 received previously
- Anatomic asplenia (including sickle-cell disease)
- Immunocompromising conditions (e.g. HIV infection)
- Cochlear implant
- Cerebrospinal fluid leak

Pneumococcal Conjugate Vaccine for Persons 65 Years Old and Older

- For those who have not received PCV13 previously, administer a dose of PCV13
- A dose of PPSV23 should be administered 6-12 months after the dose of PCV13
- Do not administer the two vaccines simultaneously
- Adults who previously received a dose of PPSV23 should receive PCV13 no earlier than 1 year after the dose of PPSV23

was received. Unvaccinated children aged 7 through 11 months should receive two doses of vaccine at least 4 weeks apart, followed by a booster dose at age 12 through 15 months. Unvaccinated children aged 12 through 23 months should receive two doses of vaccine, at least 8 weeks apart. Previously unvaccinated healthy children 24 through 59 months of age should receive a single dose of PCV13.

Unvaccinated children 24 through 71 months of age with certain chronic medical conditions should receive 2 doses of PCV13 separated by at least 8 weeks. These conditions include chronic heart and lung disease, diabetes, CSF leak, cochlear implant, sickle cell disease and other hemoglobinopathies, functional or anatomic asplenia, HIV infection, or immunocompromising conditions resulting from disease or treatment of a disease.

A single supplemental dose of PCV13 is recommended for all children 14 through 59 months of age who have received 4 doses of PCV7 or another age-appropriate, complete PCV7 schedule. For children who have an underlying medical condition, a single supplemental PCV13 dose is recommended through 71 months. This includes children who have received PPSV23 previously. PCV13 should be administered at least 8 weeks after the most recent dose of PCV7 or PPSV23. This will constitute the final dose of PCV for these children.

A single dose of PCV13 should be administered for children 6 through 18 years of age who have not received PCV13 previously and are at increased risk for invasive pneumococcal disease because of anatomic or functional asplenia (including sickle cell disease), immunocompromising conditions such as HIV-infection, cochlear implant, or cerebrospinal fluid leaks, regardless of whether they have previously received PCV7 or PPSV23. Routine use of PCV13 is not recommended for healthy children 5 years of age or older.

Children who have received PPSV23 previously also should receive the recommended PCV13 doses. Children 24 through 71 months of age with an underlying medical condition who received fewer than 3 doses of PCV7 before age 24 months should receive a series of 2 doses of PCV13 followed by 1 dose of PPSV23 administered at least 8 weeks later. Children 24 through 71 months of age with an underlying medical condition who received any incomplete schedule of 3 doses of PCV7 before age 24 months should receive 1 dose of PCV13 followed by 1 dose of PPSV23 administered at least 8 weeks later. When elective splenectomy, immunocompromising therapy, or cochlear implant placement is being planned, PCV13 and/or PPSV23 vaccination should be completed at least 2 weeks before surgery or initiation of therapy.

Adults 65 years old or older who have not previously received pneumococcal vaccine or whose previous vaccination history is unknown should receive a dose of PCV13. A dose of PPSV23 should be given 6-12 months after the dose of PCV13. If PPSV23 cannot be given during this time window, the dose of PPSV23 should be given during the next visit after 12 months. The two vaccines should not be administered simultaneously (the same clinic day) and the minimum acceptable interval between PCV13 and PPSV23 is 8 weeks.

Adults 65 years old or older who have previously received one or more doses of PPSV23 should receive a dose of PCV13 if they have not received it. A dose of PCV13 should be given one or more years after receipt of the most recent PPSV23 dose. For those for whom an additional dose of PPSV23 is indicated, this subsequent PPSV23 dose should be given 6-12 months after PCV13 and five or more years after the most recent dose of PPSV23. Only one dose of PPSV23 is recommended on or after the 65th birthday.

The recommendations for routine use of PCV13 among adults 65 years old or older will be reevaluated in 2018 and revised as needed.

In June 2012, ACIP recommended vaccination of adults with specific risk factors. All PCV13-naïve adults 19 years and older with functional or anatomic asplenia (e.g., from sickle cell disease or splenectomy), HIV infection, leukemia, lymphoma, Hodgkin disease, multiple myeloma, generalized malignancy, chronic renal failure, nephrotic syndrome, or other conditions associated with immunosuppression (e.g., organ or bone marrow transplantation) and those receiving immunosuppressive chemotherapy, including long-term corticosteroids, or those with CSF leak or cochlear implants, should receive a dose of PCV13 vaccine. PCV13 should be administered to eligible adults with one of these risk factors prior to PPSV23, the vaccine recommended for these groups of adults since 1997. Eligible adults with one of these risk factors who have not previously received PPSV23 should receive a dose of PCV13 first followed by a dose of PPSV23 at least 8 weeks later. Subsequent doses of PPSV23 should follow PPSV23 recommendations for these adults. Adults 19 years of age or older with the aforementioned conditions who have previously received one or more doses of PPSV23 should be given a dose of PCV13 one or more years 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 since the most recent dose of PPSV23.

Providers should not withhold vaccination in the absence of an immunization record or complete record. The patient's

Pneumococcal Conjugate Vaccine High-risk Schedule – Adults 19 and older

- Anatomic asplenia (including sickle-cell disease)
- Immunocompromising conditions (e.g. HIV infection)
- Cochlear implant
- Cerebrospinal fluid leak
- PPSV23 should also be recommended, if not received previously
- PCV13 administered first followed by a dose of PPSV23 8 weeks later

Pneumococcal Polysaccharide Vaccine Recommendations

- Adults 65 years and older
- Persons 2 years and older with
 - chronic illness
 - anatomic or functional asplenia
 - immunocompromised (disease, chemotherapy, steroids)
 - HIV infection
 - environments or settings with increased risk
 - cochlear implant
 - CSF leak

Pneumococcal Polysaccharide Vaccine Revaccination — High-risk Immunocompetent Persons

- Routine revaccination of immunocompetent persons is not recommended
- Revaccination recommended for immunocompetent persons 2 through 64 years of age who are at high risk of serious pneumococcal infection
 - chronic heart disease
 - pulmonary disease (including asthma, 19 years and older)
 - liver disease
 - alcoholism
 - CSF leaks
 - cochlear implants
 - those who smoke cigarettes (19 years and older)
- Single revaccination dose at least 5 years after the first dose and after the 65th birthday

verbal history may be used to determine vaccination status. Persons with uncertain or unknown vaccination status should be vaccinated.

The target groups for pneumococcal vaccines (polysaccharide or conjugate) and influenza vaccine overlap. Both pneumococcal vaccines can be given at the same time as influenza vaccine but at different sites if indicated. Pneumococcal polysaccharide vaccine should never be given during the same visit as pneumococcal conjugate vaccine. Most adults need only a single lifetime dose of each PCV13 and PPSV23 (see Revaccination).

Pneumococcal Polysaccharide Vaccine

Pneumococcal polysaccharide vaccine should be administered routinely to all adults 65 years of age and older, regardless of previous PCV receipt. A single dose of the vaccine is also indicated for immunocompetent persons 2 years of age and older with a normal immune system who have a chronic illness, including cardiovascular disease, pulmonary disease, diabetes, alcoholism, chronic liver disease, cirrhosis, cerebrospinal fluid leak, or a cochlear implant.

Immunocompromised persons 2 years of age and older who are at highest risk of pneumococcal disease or its complications should also be vaccinated. This group includes persons with splenic dysfunction or absence (either from disease or surgical removal), Hodgkin disease, lymphoma, multiple myeloma, chronic renal failure, nephrotic syndrome (a type of kidney disease), asymptomatic or symptomatic HIV infection, or conditions such as organ transplantation associated with immunosuppression. Persons immunosuppressed from chemotherapy or high-dose corticosteroid therapy (14 days or longer) should be vaccinated.

Pneumococcal vaccine should be considered for persons living in special environments or social settings with an identified increased risk of pneumococcal disease or its complications, such as certain Native American (i.e., Alaska Native, Navajo, and Apache) populations.

In 2010 ACIP added asthma and cigarette smoking to the list of indications for receipt of PPSV23 due to increased risk of invasive pneumococcal disease among these groups. Available data do not support asthma or cigarette smoking as indications for PPSV23 among persons younger than 19 years.

If elective splenectomy or cochlear implant is being considered, the vaccine should be given at least 2 weeks before the procedure. If vaccination prior to the procedure is not feasible, the vaccine should be given as soon as possible

after surgery. Similarly, there should also be a 2-week interval between vaccination and initiation of cancer chemotherapy or other immunosuppressive therapy, if possible.

Revaccination with PPSV23

Following vaccination with PPSV23, antibody levels decline after 5–10 years and decrease more rapidly in some groups than others. However, the relationship between antibody titer and protection from invasive disease is not certain for adults, so the ability to define the need for revaccination based only on serology is limited. In addition, currently available pneumococcal polysaccharide vaccines elicit a T-cell-independent response, and do not produce a sustained increase (“boost”) in antibody titers. Available data do not indicate a substantial increase in antibody level in the majority of revaccinated persons.

For immunocompetent adults 19 through 64 years of age with chronic heart disease, pulmonary disease (including asthma), liver disease, alcoholism, CSF leaks, cochlear implants, or those who smoke cigarettes only one dose of PPSV23 is recommended before the 65th birthday. Additionally those who received a dose of 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.

A second PPSV23 dose is recommended 5 years after the first PPSV23 dose for persons aged 19–64 years with functional or anatomic asplenia (e.g. from sickle cell disease or splenectomy) and for persons with immunocompromising conditions such as HIV infection, leukemia, lymphoma, Hodgkin disease, multiple myeloma, generalized malignancy, chronic renal failure, nephrotic syndrome, or other conditions associated with immunosuppression (e.g., organ or bone marrow transplantation) and those receiving immunosuppressive chemotherapy, including long-term corticosteroids. The above group includes the same conditions as those that are adult indications for PCV13, with the exception of CSF leak and cochlear implants. Persons with CSF leaks or cochlear implants should receive no additional doses of PPSV23 until age 65 years. Additionally, those who received 1 or 2 doses of 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.

Contraindications and Precautions to Vaccination

For both pneumococcal polysaccharide and conjugate vaccines, a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose is a contraindication

Pneumococcal Polysaccharide Vaccine Revaccination — Highest-risk Persons

- Persons 2 years of age or older with:
 - functional or anatomic asplenia
 - immunosuppression
 - transplant
 - chronic renal failure
 - nephrotic syndrome
- A revaccination dose 5 years after the first dose
- For those who receive 2nd dose prior to the 65th birthday, a third dose is recommended after the 65th birthday (and at least 5 years from the second dose)

Pneumococcal Vaccines Contraindications and Precautions

- Severe allergic reaction to vaccine component or following prior dose of vaccine
- Moderate or severe acute illness

Pneumococcal Conjugate Vaccine Adverse Events

- Events reported after PCV7 include
 - apnea
 - hypersensitivity reactions
 - dyspnea
 - bronchospasm
 - anaphylactic/anaphylactoid reactions
 - angioneurotic edema
 - erythema multiforme
 - injection site reactions

Pneumococcal Vaccines Adverse Reactions

- Local reactions
 - polysaccharide
 - 30%–50%
 - conjugate
 - 5%–49%
- Fever, myalgia
 - polysaccharide
 - <1%
 - conjugate
 - 24%–35%
- Febrile seizures
 - conjugate
 - 1.2–13.7/100,000
 - conjugate (with TIV)
 - 4–44.9/100,000
- Severe adverse reactions
 - polysaccharide
 - rare
 - conjugate
 - 8%

to further doses of vaccine. Such allergic reactions are rare. Persons with moderate or severe acute illness should not be vaccinated until their condition improves. However, minor illnesses, such as upper respiratory infections, are not a contraindication to vaccination.

The safety of PPSV23 vaccine for pregnant women has not been studied, although no adverse consequences have been reported among newborns whose mothers were inadvertently vaccinated during pregnancy. Women who are at high risk of pneumococcal disease and who are candidates for pneumococcal vaccine should be vaccinated before pregnancy, if possible.

Adverse Events Following Vaccination Pneumococcal Conjugate Vaccine

Certain rare adverse events observed during PCV7 postmarketing surveillance included, apnea, hypersensitivity reaction including facial edema, dyspnea, bronchospasm, anaphylactic/anaphylactoid reaction including shock, angioneurotic edema, erythema multiforme, injection-site dermatitis, injection-site pruritus, injection-site urticaria, and lymphadenopathy localized to the region of the injection site. The causal relation of these events to vaccination is unknown.

Adverse Reactions Following Vaccination Pneumococcal Polysaccharide Vaccine

The most common adverse events following either pneumococcal polysaccharide or conjugate vaccine are local reactions. For PPSV23, 30%–50% of vaccinees report pain, swelling, or erythema at the site of injection. These reactions usually persist for less than 48 hours.

Local reactions are reported more frequently following a second dose of PPSV23 vaccine than following the first dose. Moderate systemic reactions (such as fever and myalgia) are not common (fewer than 1% of vaccinees), and more severe systemic adverse reactions are rare.

A transient increase in HIV replication has been reported following PPSV23 vaccine. No clinical or immunologic deterioration has been reported in these persons.

Pneumococcal Conjugate Vaccine

Local reactions (such as pain, swelling or redness) following PCV13 occur in up to half of recipients. Approximately 8% of local reactions are considered to be severe (e.g., tenderness that interferes with limb movement). Local reactions are generally more common with the fourth dose than with the first three doses. In clinical trials of pneumococcal conjugate

vaccine, fever (higher than 100.4°F [38°C]) within 7 days of any dose of the primary series was reported for 24%-35% of children. High fever was reported in less than 1% of vaccine recipients. Nonspecific symptoms such as decreased appetite or irritability were reported in up to 80% of recipients.

A study of 200,000 children 6 months through 4 years of age, conducted through the Vaccine Safety Datalink in 2010-2011, found that febrile seizures occurred in some children following receipt of inactivated influenza and PCV13 vaccines. Among children 6-59 months of age, the incidence rate ratio (IRR) for trivalent influenza vaccine (TIV) adjusted for concomitant PCV13 was 2.4 (95% CI, 1.2, 4.7) while the IRR for PCV13 adjusted for concomitant TIV was 2.5 (95% CI 1.3, 4.7); the IRR for concomitant TIV and PCV13 was 5.9 (95% CI 3.1, 11.3). Risk difference estimates varied by age due to the varying baseline risk for seizures in young children, with the highest estimates occurring at 16 months (12.5 per 100,000 doses for TIV without concomitant PCV13, 13.7 per 100,000 doses for PCV13 without concomitant TIV, and 44.9 per 100,000 doses for concomitant TIV and PCV13) and the lowest estimates occurring at 59 months (1.1 per 100,000 doses for TIV without concomitant PCV13, 1.2 per 100,000 doses for PCV13 without concomitant TIV, and 4.0 per 100,000 doses for concomitant TIV and PCV13). After evaluating the data on febrile seizures and taking into consideration benefits and risks of vaccination, ACIP made no change in its recommendations for use of TIV or PCV13.

Vaccine Storage and Handling

PCV13 and PPSV23 should be maintained at refrigerator temperature between 35°F and 46°F (2°C and 8°C). Manufacturer package inserts contain additional information and can be found at <http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093830.htm>. For complete information on best practices and recommendations please refer to CDC's Vaccine Storage and Handling Toolkit, <http://www.cdc.gov/vaccines/recs/storage/toolkit/storage-handling-toolkit.pdf>.

Goals and Coverage Levels

The *Healthy People 2020* goal is to achieve at least 90% coverage for pneumococcal polysaccharide vaccine among persons 65 years of age and older. Data from the 2005 Behavioral Risk Factor Surveillance System (BRFSS, a population-based, random-digit-dialed telephone survey of the noninstitutionalized U.S. population 18 years of age and older) estimate that 64% of persons 65 years of age or older

Pneumococcal Polysaccharide Vaccine Coverage

- Healthy People 2020 goal: 90% coverage for persons 65 years of age or older
- 2005 BRFSS: 64% of persons 65 years of age or older ever vaccinated
- Vaccination coverage levels were lower among persons 18-64 years of age with a chronic illness

Pneumococcal Polysaccharide Vaccine Missed Opportunities

- >65% of patients with severe pneumococcal disease had been hospitalized within preceding 3-5 years yet few had received vaccine

had ever received pneumococcal polysaccharide. Vaccination coverage levels were lower among persons 18–64 years of age with a chronic illness.

Opportunities to vaccinate high-risk persons are missed both at the time of hospital discharge and during visits to clinicians' offices. Effective programs for vaccine delivery are needed, including offering the vaccine in hospitals at discharge and in clinicians' offices, nursing homes, and other long-term care facilities.

More than 65% of the persons who have been hospitalized with severe pneumococcal disease had been admitted to a hospital in the preceding 3–5 years, yet few had received pneumococcal vaccine. In addition, persons who frequently visit physicians and who have chronic conditions are more likely to be at high risk of pneumococcal infection than those who require infrequent visits. Screening and subsequent immunization of hospitalized persons found to be at high risk could have a significant impact on reducing complications and death associated with pneumococcal disease.

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