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PNEUMOCOCCAL DISEASE

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Streptococcus pneumoniae (pneumococcus) is a bacterial pathogen that affects children and adults worldwide. It is a leading cause of illness in young children and causes illness and death among the elderly and persons who have certain underlying medical conditions.

Bacteriology

Streptococcus pneumoniae are lancet-shaped, gram-positive, facultative anaerobic organisms. They are typically observed in pairs (diplococci) but may also occur singularly or in short chains. Some pneumococci are encapsulated, their surfaces composed of complex polysaccharides. Encapsulated organisms are pathogenic for humans and experimental animals, whereas organisms without capsular polysaccharides are not. Capsular polysaccharides are the primary basis for the pathogenicity of the organism. They are antigenic and form the basis for classifying pneumococci by serotypes.

Pneumococcal Serotypes The capsule of the *Streptococcus pneumoniae* bacterium consists of polysaccharides and constitutes a major virulence factor for the bacterium. Antibodies directed against the capsular polysaccharide protect against infection; type-specific antibodies bind capsular antigens; and opsonization facilitates phagocytosis. Currently, 90 serotypes of *S. pneumoniae* have been identified on the basis of antigenic differences in their capsular polysaccharides. The majority of serotypes cause serious disease, yet a relatively limited number of serotypes cause the majority of invasive pneumococcal infections. The 10 most common serotypes are estimated to account for approximately 62% of invasive disease worldwide. In the United States, the seven most common serotypes isolated from the blood or CSF of children aged <6 years (i.e., 14, 6B, 19F, 18C, 23F, 4, and 9V) account for 80% of infections and are the serotypes in the licensed vaccine PCV7. These same seven serotypes, by comparison, account for only 50% of isolates among persons aged >6 years in the United States.

Epidemiology

Asymptomatic nasopharyngeal carriage of pneumococcus is intermittent. Cross-sectional studies suggest that pneumococcus can be found among 15% of adults; in child care settings, up to 65% of children are colonized. Although pneumococcal carriage can lead to invasive disease (e.g., meningitis or bacteremia), AOM is the most common clinical manifestation of pneumococcal infection among children and the most common outpatient diagnosis resulting in antibiotic prescriptions among children.

Invasive Disease: Severe pneumococcal infections result from dissemination of bacteria to the bloodstream and the central nervous system. Data from community-based studies indicate that overall annual incidence of pneumococcal bacteremia in the United States is an estimated 10-30 cases per 100,000 population; the rate is higher for persons aged >65 years (50-83 cases per 100,000 population) and for children aged <2 years (160 cases per 100,000 population). In adults, 60%-87% of pneumococcal bacteremia is associated with pneumonia; in young children, the primary sites of infection are frequently not identified.

Lower Respiratory Tract infections: *S.pneumoniae* is the most common cause of community-acquired bacterial pneumonia, occurring most frequently among the elderly and young children. The precise incidence of pneumococcal pneumonia is difficult to ascertain because routine diagnostic tests are insufficiently specific and sensitive. *S. pneumoniae* accounts for approximately 25%-35% of cases of community-acquired bacterial pneumonia in persons who require hospitalization.

Acute Otitis Media and Other Upper Respiratory Tract Infections: *S.pneumoniae* is a substantial cause of acute otitis media (AOM) and other upper respiratory tract infections (e.g. sinusitis). Although these types of infections usually do not progress to invasive disease they cause considerable morbidity and medical cost. In the United States, AOM results in more than 24 million visits to pediatricians per year; approximately 30%-50% of AOM infections are caused by *S.pneumoniae*. AOM infection most often occurs in children aged <4 years. In the United States 62% of children experience an episode of AOM during their first year of life, and nearly half have had three or more episodes before their third birthday. In two prospective studies of community-acquired pneumonia among young children, 17%-28% of cases were diagnosed as pneumococcal. However, these and other studies probably underestimate the actual proportion of pneumococcal pneumonia cases as a result of low sensitivity of routine diagnostic testing. Studies using diagnostic tympanocentesis among children with AOM have found *S. pneumoniae* in 28%-55% of all middle ear aspirates. Otitis media is the most frequent reason for pediatric office visits in the United States, resulting in >15 million visits/year. By age 12 months, 62% of children have had at least one episode of AOM; peak incidence of AOM occurs during ages 6 months-1 year .

Mortality: Pneumococcal infection causes an estimated 40,000 deaths annually in the United States (approximately 800 in Louisiana), accounting for more deaths than any other vaccine-preventable bacterial disease. Approximately half of these deaths potentially could be prevented through the use of vaccine. Case-fatality rates are highest for meningitis and bacteremia, and the highest mortality occurs among the elderly and patients who have underlying medical conditions.

The estimated yearly number of cases of diseases caused by pneumococci in Louisiana are 110,000 otitis media, 8,500 pneumonias, 850 bacteremias, and 50 meningitis.

Risk Factors

Children aged <2 years and adults aged >65 years are at increased risk for pneumococcal infection. Persons who have certain underlying medical conditions also are at increased risk for developing pneumococcal infection or experiencing severe disease and complications.

Adults at increased risk include those who are generally immunocompetent but who have

- chronic cardiovascular diseases (e.g., congestive heart failure or cardiomyopathy),
- chronic pulmonary diseases (e.g., chronic obstructive pulmonary disease [COPD] or emphysema),
- chronic liver diseases (e.g., cirrhosis).
- diabetes mellitus associated with cardiovascular or renal dysfunction
- asthma has not been associated with an increased risk for pneumococcal disease, unless it occurs with chronic bronchitis, emphysema, or long-term use of systemic corticosteroids.
- functional or anatomic asplenia (e.g., sickle cell disease or splenectomy)
- sickle cell disease: Before the widespread use of penicillin chemoprophylaxis for these patients, children with sickle cell disease were 600 fold more likely than children without this disease to develop pneumococcal meningitis.
- other sickle hemoglobinopathies (e.g., hemoglobin S-C disease or S-β-thalassemia), and those who are otherwise functionally or anatomically asplenic.
- splenectomy
- decreased responsiveness to polysaccharide antigens or increased rate of decline in serum antibody concentrations as a result of immunosuppressive conditions (e.g., congenital immunodeficiency)

ciency, human immunodeficiency virus [HIV] infection, leukemia, lymphoma, multiple myeloma, Hodgkins disease, or generalized malignancy); organ or bone marrow transplantation; therapy with alkylating agents, antimetabolites, or systemic corticosteroids, chronic renal failure or nephrotic syndrome

Children in Day Care: Out-of-home day care increases the risk for invasive pneumococcal disease and AOM among children. In a study of risk factors for invasive pneumococcal disease among children in the United States, attendance at a group day care center during the preceding 3 months was associated with an approximately 2.3-fold increase in invasive disease among children aged 12-23 months, and 3.2-fold increased risk among children aged 24-59 months. Moreover, in a recent population-based case-control study, non-elderly adults (i.e., persons aged 18-64 years) who lived in a household that included children who attended day care were at greater risk for acquiring invasive pneumococcal infections than adults who did not (multivariate odds ratio [OR] = 3.0).

In studies of otitis media resulting from all causes, risk for AOM was higher among children who attended day care outside the home compared with family day care, and risk for middle ear effusions increased with exposure to larger numbers of children in day care settings. Younger age when starting day care also increases risk for experiencing recurrent AOM. Day care attendance is also a risk factor for other acute upper respiratory tract infections among children aged <5 years.

Clinical Description

The organism colonizes the upper respiratory tract and can cause the following types of illnesses:

- disseminated invasive infections, including bacteremia and meningitis;
- pneumonia and other lower respiratory tract infections; and
- upper respiratory tract infections, including otitis media and sinusitis.

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. Typically 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. Up to an estimated 175,000 hospitalized cases of pneumococcal pneumonia occur annually in the United States. Pneumococci account for up to 36% of adult community-acquired pneumonia and 50% of hospital-acquired pneumonia. It is a common bacterial complication of influenza and measles. The case-fatality rate is 5%-7%, and may be much higher in elderly persons. 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 50,000 cases of pneumococcal bacteremia occur each year. Bacteremia occurs in about 25%-30% of patients with pneumococcal pneumonia. The overall mortality rate for bacteremia is about 20%, but may be as high as 60% in elderly patients. Patients with asplenia who develop bacteremia may experience a fulminant clinical course.

Pneumococci cause 13%-19% of all cases of bacterial meningitis in the United States. An estimated 3,000 to 6,000 cases of pneumococcal meningitis occur each year. One-quarter of patients with pneumococcal meningitis also have pneumonia. The clinical symptoms, 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 mortality rate of pneumococcal meningitis is about 30%, but may be as high as 80% in elderly persons. Neurologic sequelae are common among survivors.

Pneumococcal Disease In Children

Bacteremia without a known site of infection is the most common invasive clinical presentation among children <2 years of age, 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. With the decline of invasive Hib disease, *S. pneumoniae* has become the leading cause of bacterial meningitis among children <5 years of age in the United States. Before routine use of pneumococcal conjugate vaccine, children <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, 62% 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. Before routine use of pneumococcal conjugate vaccine, the burden of pneumococcal disease among children <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 of 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 occur each year among children <5 years of age.

Despite appropriate antimicrobial therapy and intensive medical care, the overall case-fatality rate for pneumococcal bacteremia is 15%-20% among adults. Among elderly patients, this rate is approximately 30%-40%. An overall case-fatality rate of 36% was recently documented for adult inner-city residents who were hospitalized for pneumococcal bacteremia.

Among children, death from pneumococcal infection is relatively uncommon, except among those who

- have meningitis,
- are immunocompromised,
- have undergone splenectomy and have severe bacteremia.

Laboratory Tests

Detection of pneumococcal carriage is done with nasopharyngeal swabs inoculated into skim milk, tryptone, glucose, and glycerol medium (STGG).

A definitive diagnosis of infection with *Streptococcus 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 >25 white blood cells and <10 epithelial cells per 100-power field, and a predominance of gram-positive diplococci.

The quellung reaction (capsular swelling; capsular precipitation reaction) is a test that provides rapid identification of pneumococci in clinical specimens including spinal fluid, sputum, and exudates.

The procedure involves mixing loopfuls of bacteria in suspension, pneumococcal antiserum, and methylene blue on the surface of a glass slide and examination under oil immersion. If the reaction is positive, the organism will be surrounded by a large capsule. Several rapid tests for the detection of pneumococcal polysaccharide antigen in CSF and other body fluids are available. These tests generally lack sufficient sensitivity or specificity to assist in the diagnosis of invasive pneumococcal disease.

Treatment

Resistance to penicillin and other antibiotics is common. In some areas of the U.S. up to 40% of invasive pneumococcal isolates are resistant to penicillin. Treatment will usually include a broad spectrum cephalosporin, and often vancomycin.

Antimicrobial Resistance

Many penicillin-resistant pneumococci are also resistant to other antimicrobial drugs (e.g., erythromycin, trimethoprim-sulfamethoxazole and extended-spectrum cephalosporins). High-level penicillin resistance and multidrug resistance often complicate the management of pneumococcal infection and make choosing empiric antimicrobial therapy for suspected cases of meningitis, pneumonia, and otitis media increasingly difficult.

Penicillin Resistance: In the United States, decreased susceptibility to penicillin (i.e., a minimum inhibitory concentration [MIC] ≤ 0.12 mg/L) was relatively uncommon among *S. pneumoniae* until the late 1980s. Since that time, strains with decreased susceptibility have spread considerably; about 50% of strains now show decreased susceptibility to this agent (Figure 1).^[6,8-10] A significant proportion of these isolates show full resistance to penicillin (MIC ≤ 2.0 mg/L). These present a major problem to clinicians attempting to choose an appropriate treatment regimen. This is especially relevant when treatment begins empirically, as is often the case in the primary care setting. The problem highlights the need for health care professionals to be fully aware of local resistance patterns when prescribing antibiotics.

	NCCLS: Otitis	Pneumonia
Resistant	MIC ≥ 2 μ g /mL	MIC ≥ 4 μ g /mL
Intermediate	$0.1 < \text{MIC} \leq 1$ μ g /mL	MIC ~ 2 μ g /mL
Sensitive	MIC ≤ 0.06 μ g /mL	MIC ≤ 1 μ g /mL

Macrolide Resistance: The problem of resistance among *S. pneumoniae* is not limited to penicillin and other β -lactam antibiotics. Indeed, resistance to the macrolides has increased sharply among *S. pneumoniae* in recent years, with 31% of isolates in a 1997 U.S. surveillance study showing resistance to azithromycin and clarithromycin.

Fluoroquinolone Resistance: The new fluoroquinolones with enhanced antipneumococcal activity provide an alternative option for treating lower RTIs in an era of increasing macrolide and penicillin resistance. Indeed, in the latest guidelines from the Infectious Disease Society of America for managing community-acquired pneumonia (CAP), the new fluoroquinolones are included as first-line therapies for outpatients. The Centers for Disease Control and Prevention, however, is more cautious about the use of such agents; it recommends that they be reserved for adults who have not responded to previous therapy, are allergic to preferred agents, or have documented infection with drug-resistant pneumococci. These recommendations reflect concern that pneumococcal resistance to fluoroquinolones will emerge rapidly with their more widespread use. Indeed, such concerns might be well founded, given the recent emergence of strains of *S. pneumoniae* with decreased susceptibility to fluoroquinolones (e.g., ciprofloxacin MIC ≤ 4 mg/L). Such strains appear with low frequency (approximately 5% in North America), but their prevalence seems to parallel increased use of these agents.

Risk factors associated with infection with penicillin-resistant pneumococci include younger age, attendance at a day care center, higher socioeconomic status, recent (i.e., <3 months) antibiotic use, and recurrent AOM. Recent day care attendance and recent antibiotic treatment are associated independently with invasive disease as a result of penicillin-resistant pneumococci. Penicillin resistance has been associated with treatment failures in AOM and meningitis; these failures could be because of difficulty in achieving high antimicrobial concentrations in middle ear fluid and cerebrospinal fluid (CSF). Additional research is

needed to determine the association between penicillin resistance and treatment failure in pneumococcal pneumonia or bacteremia among children.

Antimicrobial resistance is detected most frequently among serotypes included in PCV7. According to 1998 surveillance data from eight states, the PCV7 serotypes accounted for 80% of 312 penicillin-nonsusceptible isolates (MIC > 0.1 µg/ml) collected from normally sterile sites among children aged <6 years (ABCs/EIP Network, unpublished data, 1999). A similar serotype distribution of penicillin-nonsusceptible isolates was identified during a study of nasopharyngeal carriage among 216 children aged <6 years in Memphis, Tennessee; 78% of resistant isolates were of the same seven serotypes.

Treatment of DRSP is difficult.

- High dose amoxicillin 80-90 mg/kg
- Quinolones (levo, moxi, gati)
- Newer cephalosporins
- Vancomycin for serious infections

Surveillance

Streptococcus Pneumoniae, invasive infection penicillin resistant (DRSP) and Streptococcus Pneumoniae invasive infection in children < 5 years of age are reportable condition within 5 business days of diagnosis.

The purpose of the reports of invasive diseases in children less than 5 years of age is to track the effects of childhood vaccination against *S.pneumoniae*.

Case Definition

1. Streptococcus pneumoniae, Drug-Resistant Invasive Disease

Clinical description *Streptococcus pneumoniae* causes many clinical syndromes, depending on the site of infection (e.g., acute otitis media, pneumonia, bacteremia, or meningitis).

Laboratory criteria for diagnosis Isolation of *S. pneumoniae* from a normally sterile site (e.g., blood, cerebrospinal fluid, or, less commonly, joint, pleural, or pericardial fluid) and "Nonsusceptible" isolate (i.e., intermediate- or high-level resistance of the *S. pneumoniae* isolate to at least one antimicrobial agent currently approved for use in treating pneumococcal infection).

Case classification

Probable: a clinically compatible case caused by laboratory-confirmed culture of *S. pneumoniae* identified as "nonsusceptible" (i.e., an oxacillin zone size of less than 20 mm) when oxacillin screening is the only method of antimicrobial susceptibility testing performed

Confirmed: a clinically compatible case that is laboratory confirmed

Resistance defined by National Committee for Clinical Laboratory Standards (NCCLS)-approved methods and NCCLS-approved interpretive minimum inhibitory concentration (MIC) standards (µg/mL) for *S. pneumoniae*. NCCLS recommends that all invasive *S. pneumoniae* isolates found to be "possibly resistant" to beta-lactams (i.e., an oxacillin zone size of less than 20 mm) by oxacillin screening should undergo further susceptibility testing by using a quantitative MIC method acceptable for penicillin, extended-spectrum cephalosporins, and other drugs as clinically indicated.

2. Streptococcus pneumoniae, Invasive, (Children <5 years)

Clinical description : Streptococcus pneumoniae causes many clinical syndromes, depending on the site of infection (e.g., acute otitis media, pneumonia, bacteremia, or meningitis). Starting in 2000, a conjugate pneumococcal vaccine is recommended for prevention of pneumococcal disease in the pediatric population.

Laboratory criteria for diagnosis Isolation of *S. pneumoniae* from a normally sterile site (e.g., blood, cerebrospinal fluid, or, less commonly, joint, pleural, or pericardial fluid)

Case classification

Confirmed: a clinically compatible case in a child less than 5 years of age caused by laboratory-confirmed culture of *S. pneumoniae* from a normally sterile site

Investigation

No investigation is necessary unless in outbreak situations.

Immunization

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 (PPV23) was licensed and replaced the 14-valent vaccine, which is no longer produced. PPV23 contains polysaccharide antigen from 23 types of pneumococcal bacteria which cause 88% of bacteremic pneumococcal disease. In addition, cross-reactivity occurs for several capsular types which account for an additional 8% of bacteremic 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.

Immunogenicity And Vaccine Efficacy: More than 80% of healthy adults who receive PPV23 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 less than 2 years of age, antibody response to most serotypes is generally poor. Elevated antibody levels persist for at least 5 years in healthy adults, but fall more quickly in persons with certain underlying illnesses. PPV23 vaccine efficacy studies have resulted in various estimates of clinical effectiveness. Overall, the vaccine is 60%-70% effective in preventing invasive disease. The vaccine appears to be less effective in preventing nonbacteremic pneumococcal pneumonia. The vaccine may be less effective in preventing pneumococcal infection in some groups, particularly those with significant underlying illness. Although the vaccine may not be as effective in some persons, especially those who do not have normal resistance to infections, it is still recommended for such persons because they are at high risk of developing severe disease. Studies comparing patterns of pneumococcal carriage before and after PPV23 vaccination have not shown clinically significant decreases in carrier rates among vaccinees. In addition, no change in the distribution of vaccine-type and nonvaccine-type organisms have been observed as the result of vaccination.

Vaccination Schedule And Use: Pneumococcal polysaccharide vaccine should be administered routinely to **all adults 65 years of age and older**. The vaccine is also indicated for **persons aged >2 years with a normal immune system who have a chronic illness**, including cardiovascular disease, pulmonary disease, diabetes, alcoholism, cirrhosis, or cerebrospinal fluid leak. **Immunocompromised persons aged >2 years** who are at increased 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's disease, lymphoma, multiple myeloma, chronic renal failure, nephrotic syndrome (a type of kidney disease), or conditions such as organ transplantation associated with immunosuppression. Persons immunosuppressed from chemotherapy or high dose corticosteroid therapy (>14 days) should be vaccinated. Persons aged >2 years with asymptomatic or symptomatic HIV infection 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 populations. If elective splenectomy is being considered, the vaccine should be given at least 2 weeks before the operation. If vaccination prior to splenectomy is not feasible, the vaccine should be given as soon as possible after surgery. Similarly, there should also be a two week interval between vaccination and initiation of cancer chemotherapy or other immunosuppressive therapy, if possible. Providers should not withhold vaccination in the absence of an immunization record or complete record. The patient's verbal history may be used to determine vaccination status. **Persons with uncertain or unknown vaccination status should be vaccinated.** The target groups for pneumococcal polysaccharide vaccine and influenza vaccine overlap. These vaccines should be given at the same time at different sites if indicated.

Revaccination: Following vaccination with PPV23, 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 (*i.e.*, higher antibody level does not necessarily mean better protection), 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-independent response, and do not produce a sustained increase ("boost") in antibody titers. Available data do not indicate a substantial increase in protection in the majority of revaccinated persons. Because of the lack of evidence of improved protection with multiple doses of pneumococcal vaccine, **routine revaccination of immunocompetent persons previously vaccinated with 23-valent polysaccharide vaccine is not recommended.** However, revaccination is recommended for persons 2 years of age and older who are at highest risk for serious pneumococcal infection and for those who are likely to have a rapid decline in pneumococcal antibody levels. **Only one PPV23 revaccination dose is recommended for high risk persons.** The second dose should be administered five or more years after the first dose. Revaccination 3 years after the previous dose may be considered for children at highest risk for severe pneumococcal infection who would be aged 10 years or less at the time of revaccination, including children who received PCV7. Persons at highest risk include all people >2 years of age with functional or anatomic asplenia (*e.g.*, sickle cell disease or splenectomy), HIV infection, leukemia, lymphoma, Hodgkins 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. Persons aged 65 years and older should be administered a second dose of pneumococcal vaccine if they received the vaccine more than 5 years previously, and were less than 65 years of age at the time of the first dose.

Adverse Reactions Following Vaccination : The most common adverse reactions following either pneumococcal polysaccharide or conjugate vaccine are **local reactions**. For PPV23, from 30% to 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 PPV23 vaccine than following the first dose. Moderate **systemic reactions** (such as fever and myalgias) are not common (<1% of vaccinees), and more severe systemic adverse reactions are rare. A transient increase in HIV replication has been reported following PPV23 vaccine. No clinical or immunologic deterioration has been reported in these persons.

Pneumococcal Conjugate Vaccine

The first pneumococcal conjugate vaccine (PCV7) was licensed in the United States in 2000. It includes purified capsular polysaccharide of 7 serotypes of *S. pneumoniae* (4, 9V, 14, 19F, 23F, 18C, and 6B) conjugated to a nontoxic variant of diphtheria toxin known as CRM197. The serotypes included in PCV7 accounted for 86% of bacteremia, 83% of meningitis, and 65% of acute otitis media among children <6 years of age in the United States during 1978-1994. Additional pneumococcal polysaccharide conjugate vaccines containing 9 and 11 serotypes of *S. pneumoniae* are being developed. The vaccine is administered intramuscularly. It does not contain thimerosal as a preservative, and is available only in single dose vials.

Immunogenicity And Vaccine Efficacy: After 4 doses of PCV7 vaccine, >90% of healthy infants develop antibody to all 7 serotypes contained in the vaccine. PCV7 has been shown to be immunogenic in infants and children, including those with sickle cell disease and HIV infection. In a large clinical trial, PCV7 was shown to reduce invasive disease caused by vaccine serotypes by 97%, and reduce invasive disease caused by all serotypes, including serotypes not in the vaccine, by 89%. Efficacy against pneumonia varied depending on the specificity of the diagnosis. The vaccine reduced clinically diagnosed pneumonia by 11%, but reduced pneumonia confirmed with X-ray with consolidation of >2.5 centimeters by 73%. Children who received PCV7 had 7% fewer episodes of acute otitis media and underwent 20% fewer tympanostomy tube placements than unvaccinated children. The duration of protection following PCV7 is currently unknown. The effect of PCV7 on nasopharyngeal carriage of pneumococci is not clear at this time.

Vaccination Schedule And Use: All children <24 months of age and children age 24-59 months with a high risk medical condition should be routinely vaccinated with PCV7. The primary series beginning in infancy consists of three doses routinely given at 2, 4, and 6 months of age. A fourth (booster) dose is recommended at 12-15 months of age. PCV7 should be administered at the same time as other routine childhood immunizations, using a separate syringe and injection site. For children vaccinated at <12 months of age, the minimum interval between doses is 4 weeks. Doses given at >12 months of age should be separated by at least 8 weeks. Unvaccinated children 7 months of age and older do not require a full series of 4 doses. The number of doses a child needs to complete the series depends on the child's current age. Unvaccinated children aged 7-11 months should receive two doses of vaccine, at least 4 weeks apart, followed by a booster dose at age 12-15 months. Unvaccinated children aged 12-23 months should receive two doses of vaccine, at least 8 weeks apart. Previously unvaccinated healthy children aged 24-59 months should receive a single dose of PCV7. Unvaccinated children aged 24-59 months with sickle cell disease, asplenia, HIV infection, chronic illness, or immunocompromising conditions should receive 2 doses of PCV7 separated by at least 8 weeks. ACIP recommends that healthcare providers consider PCV7 for all children aged 24-59 months, with priority given to children aged 24-35 months, children of Alaskan Native, American Indian or African American descent, and children who attend group daycare (defined as any setting outside the home where a child regularly spends >4 hours per week with >2 unrelated children under adult supervision). PCV7 is not routinely recommended for persons >59 months of age. Few data are available on the use of PCV7 among children previously vaccinated with PPV23. Children 24-59 months of age who have already received PPV23 and who are at high-risk of invasive pneumococcal disease (sickle cell disease, asplenia, HIV infection or other immunocompromising conditions or chronic diseases) could benefit from the immunologic priming induced by PPV23. ACIP recommends these children receive 2 doses of PCV7 separated by at least 8 weeks. The first dose of PCV7 should be given no sooner than 2 months after PPV23. Similarly, children 24-59 months of age who have already received one or more doses of PCV7 and who are at high risk of invasive pneumococcal disease will benefit from the additional serotypes included in PPV23. Vaccination with PPV23 should be considered for these high risk children. PPV23 should be given no sooner than 2 months after the last dose of PCV7. Routine administration of PPV23 to healthy children 24-59 months of age is not recommended.

Revaccination after an age-appropriate primary series with PCV7 is not currently recommended.

Adverse Reactions Following Vaccination: Local reactions following PCV7 occur in 10%-20% of recipients. Fewer than 3% of local reactions are considered to be severe (e.g., tenderness that interferes with limb movement). Local reactions are more common with the fourth dose than with the first 3 doses. In clinical trials of pneumococcal conjugate vaccine, fever >38°C within 48 hours of any dose of the primary series was reported in 15%-24% of children. However, in these studies, whole-cell pertussis vaccine was administered simultaneously with each dose, and some or most of the reported febrile episodes may be attributable to the DTP. In one study acellular pertussis vaccine (DTaP) was given at the same visit as the

booster dose of PCV7. In this study, 11% of recipients had a temperature >39°C. No severe adverse events attributable to PCV7 have been reported.

Contraindications And Precautions To Vaccination

For both pneumococcal polysaccharide and conjugate vaccines, a **serious allergic reaction** to a vaccine component or following a prior dose is a contraindication 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 PPV23 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.

Vaccine Storage And Handling

Pneumococcal polysaccharide vaccine should be shipped in an insulated container with coolant packs. Although pneumococcal polysaccharide vaccine can tolerate room temperature for a few days, CDC recommends that the vaccine be stored at refrigerator temperature (2°C-8°C [35°F-46°F])

Pneumococcal conjugate vaccine should be stored at refrigerator temperature. **Pneumococcal vaccines must not be frozen.** Opened multidose vials may be used until the expiration date printed on the package if not visibly contaminated.

Hospital precaution and isolation: Droplet precautions.