Chapter 9: Pneumococcal Disease

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I. Disease description

Streptococcus pneumoniae infections are among the leading causes worldwide of illness and death for young children, persons with underlying debilitating medical conditions, and the elderly. The pneumococcus is the most commonly identified cause of bacterial pneumonia; since the widespread use of vaccines against *Haemophilus influenzae* type b, it has become the most common cause of bacterial meningitis in the United States.[1] The Centers for Disease Control and Prevention's (CDC) Active Bacterial Core Surveillance (ABCs) has tracked invasive pneumococcal disease (IPD) in selected regions of the United States since 1994. ABCs data suggest that individuals < 2 years of age and 65 years and older account for the highest percent of cases.[2]

Cross-sectional studies suggest that pneumococci can be found in the throats of 15% of well adults; in childcare settings, up to 65% of children are colonized. Although pneumococcal carriage can lead to invasive disease (e.g., meningitis or bacteremia), acute otitis media is the most common clinical manifestation of pneumococcal infection among children and the most common outpatient diagnosis resulting in antibiotic prescriptions in that group.[3]

Each year in the United States, pneumococcal disease accounts for a significant number of cases of meningitis, bacteremia, pneumonia, and acute otitis media (AOM), as shown in **Table 1** below.[2,4-6] Approximately 10% of all patients with invasive pneumococcal disease die of their illness, but case-fatality rates are higher for the elderly and patients with certain underlying illnesses.[5]

Table 1: Incidence of Pneumococcal infections in the United States

Type of Bacterial Infection	# cases/ year
Meningitis	3,000
Bloodstream infection	63,000
Pneumonia (hospitalized)	125,000
Ear Infections (AOM)	6,800,000

II. Background

A pneumococcal polysaccharide vaccine (PPV) targeting 23 of the most common serotypes of *S. pneumoniae* has been available since the early 1980s. The Advisory Committee on Immunization Practices (ACIP) recommends that it be administered to persons ≥ 2 years of age who have

any of several underlying medical conditions and to all persons 65 years of age or older.[4] Despite its availability and payment provided under Medicare, the vaccine is underutilized. In 1999 only 54.1% of persons ≥ 65 years of age had ever been vaccinated, with particularly low coverage among African-Americans and Hispanics.[7] There also has been very low PPV coverage among persons aged 18–64 years with medical conditions placing them at high risk for serious pneumococcal infection.[8]

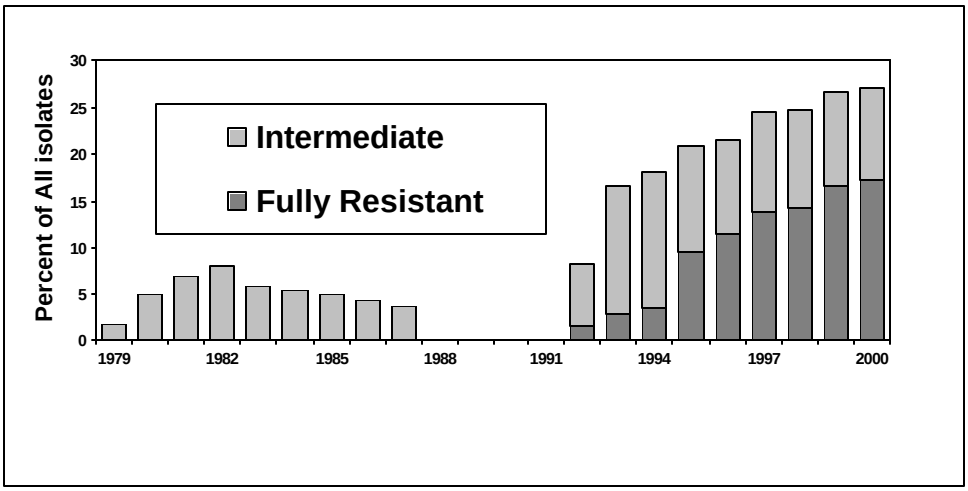
In February 2000, a 7-valent pneumococcal polysaccharide-protein conjugate vaccine (PCV7), Prevnar™, manufactured by Wyeth Lederle Vaccines, was licensed for use among infants and young children. PCV7 offers protection against the seven serotypes that most commonly cause invasive disease in children in the United States.[3] The efficacy of PCV7 is 97% for invasive pneumococcal disease caused by vaccine serotypes and 89% for all serotypes.[9] Although the efficacy of PCV7 against all AOM episodes is 6%–7%, the efficacy against AOM caused by serotypes in the vaccine is 57%.[9,10] In a large clinical trial, radiograph-positive pneumonia episodes were reduced 24.3% in the first year of life, 22.7% in the first two years, and 9.0% among children aged 2 years and older.[11]

PCV7 is recommended for all children < 2 years and children 2–4 years with certain high-risk conditions.[3] Starting in August 2001, there were delays in delivery of PCV7 to some health departments and health-care providers, with increasing shortages continuing in 2002. The ACIP issued updated recommendations to health-care providers during the shortage, advising them to fully vaccinate high-risk children < 5 years and decrease the number of doses administered to healthy infants rather than to leave some infants unvaccinated.[12, 13]

Antimicrobial resistance trends

In the past, *S. pneumoniae* was almost uniformly susceptible to penicillin, allowing most physicians to treat persons with severe infections with penicillin alone, without testing for antibiotic resistance. However, since the early 1990's, resistance to penicillin and other antimicrobial agents has spread rapidly in the United States.[14,15] There is an increasing trend of invasive pneumococci resistant to 3 or more drug classes.[16] In some areas of the United States, over 30% of isolates are not susceptible to penicillin. The proportion of pneumococcal illnesses caused by drug-resistant *S. pneumoniae* (DRSP) among children may be higher than that among adults, and the incidence of drug-resistant infections can change rapidly.[17] Outbreaks due to susceptible *S. pneumoniae* and DRSP have been reported in childcare centers and among residents of long term care facilities in which pneumococcal vaccine coverage was low.[18-20]

Figure 1: Penicillin Resistance in *S. pneumoniae,* United States, 1979–2000



1979-1994: CDC Sentinel Surveillance System
1995-2000: CDC Active Bacterial Core Surveillance (ABCS) System, Emerging Infections Program[16]

The emergence of DRSP has made treatment of pneumococcal disease more difficult. Because of a lack of rapid, sensitive, and specific diagnostic tests, therapy for pneumonia and milder illnesses such as otitis media remains empiric. Groups of experts have made recommendations for treating infections commonly caused by pneumococcus, such as otitis media and pneumonia, because of the increasing prevalence of DRSP.[21, 22] Few communities remain in which resistance is not yet a problem and even in these communities, resistant infections can occur. For these reasons, clinicians and public health officials should follow national guidelines rather than attempt to create local treatment recommendations based on local resistance data.

Due to the limitations of current diagnostic testing, clinicians may prescribe therapy for suspected bacterial infections that is not indicated or is unnecessarily broad. Inappropriate antimicrobial use contributes to the development of DRSP. Principles have been developed to encourage appropriate use of antimicrobial agents for adults and children with upper respiratory infections.[23, 24]

III. Importance of surveillance

Goals of surveillance

Pneumococcal surveillance has several goals: to observe national and local trends in pneumococcal disease, to monitor the impact of PPV and PCV7 vaccines on disease, and to detect geographic and temporal changes in the prevalence of DRSP.

With the recent introduction of the 7-valent pneumococcal conjugate vaccine, surveillance for invasive pneumococcal disease among children aged < 5 years is particularly important for identifying populations that may not be receiving vaccination, observing trends during times of vaccine shortage, and monitoring the incidence of disease from non-vaccine serotypes for evidence of shifts in serotypes. Because PCV7 is a new vaccine, surveillance for possible vaccine failures is also important. Surveillance of invasive disease in persons ≥ 5 years is useful to monitor the impact of PPV vaccination, detect any herd immunity effects from PCV7 vaccination of young children, and identify changes in the distribution of serotypes of pneumococcal disease.

Pneumococcal surveillance monitors emerging resistance concerns in communities by defining and monitoring the prevalence and geographic distribution of DRSP, enabling rapid recognition of new resistance patterns, and detecting the presence of rare resistance patterns. Surveillance information can be used on the national level for research and policy development and at the state or local level to raise awareness of DRSP among clinicians and the general public. Surveillance data also may be useful for tracking the impact of interventions aimed at reducing unnecessary use of antimicrobial agents.

Reportable conditions

In 1994, the Council of State and Territorial Epidemiologists (CSTE) recommended that states adopt mandatory reporting of invasive infections caused by DRSP.[25] While the CSTE case definition does not require reporting of all invasive isolates, this is desirable to calculate the prevalence of DRSP among all pneumococci causing invasive disease.

In 2000, the Council of State and Territorial Epidemiologists recommended national reporting of all invasive pneumococcal disease in children less than 5 years of age.[26] It also suggested surveillance of disease in all age groups, especially using mandatory laboratory reporting. Surveillance including all age groups would enable more complete analysis of the impact of the new PCV7 vaccine and of campaigns to increase the use of the 23-valent pneumococcal polysaccharide vaccine.

In September 2001, the Respiratory Diseases Branch of CDC began tracking cases of invasive pneumococcal disease among infants and young children who had received at least one dose of PCV7 and collecting isolates.[27] The goal of this voluntary surveillance is to identify factors associated with disease after receiving one or more vaccine doses, identify serotypes currently not included in the vaccine, or other factors. The CDC will serotype isolates to see if they are PCV7 serotypes, record host conditions to identify risk factors for vaccine failure, and monitor vaccine lots for decreased effectiveness.

IV. Disease reduction goals

With the introduction of the highly effective pneumococcal conjugate vaccine (PCV7) into the childhood immunization schedule in 2000 and substantial uptake in the first year, a significant decrease in invasive pneumococcal disease among infants and young children born after late 2000 is expected. The Healthy People 2010 goal for children under 5 years is to reduce the annual rate of invasive pneumococcal disease to 46 cases per 100,000 population from a baseline of 76 cases per 100,000 population in 1997.[28]

The 23-valent pneumococcal polysaccharide vaccine (PPV) has been underutilized. The new Healthy People 2010 objective calls for pneumococcal vaccination of 90% of adults aged 65 and older and 60% of those aged 18–64 years with medical conditions that place them at high risk for pneumococcal disease.[28] Methods such as the use of standing orders in clinics and hospitals, physician reminder systems, and simultaneous administration of pneumococcal vaccine with influenza vaccine have been shown to improve vaccine utilization.[4] The Healthy People 2010 goal for disease reduction for adults aged ≥ 65 years is 42 cases per 100,000 population from a baseline of 62 cases per 100,000 in 1997.[28]

Disease reduction goals also focus on minimizing complications of DRSP infections through prevention and control measures. In 1995, the CDC launched a national campaign to reduce antimicrobial resistance through promotion of appropriate antibiotic use. The control efforts initially targeted the pediatric population and later expanded to include adults.[23, 24]

CDC surveys have shown that there is a perception among providers that patient expectations may encourage overuse of antibiotics. To overcome this, patient education resources such as brochures in English and Spanish, parent question and answer sheets, "prescription pads" for symptomatic therapy, and a child care letter for daycare personnel describing the guidelines for a child with viral respiratory infection were developed and now available to aid in physician-patient communication. A curriculum for medical school residency training programs is reaching completion and older educational materials are currently being revised. The campaign includes numerous research projects funded by CDC to determine the impact of interventions promoting appropriate antibiotic use.

V. Case definitions

The following three case definitions are used for national surveillance of pneumococcal disease in the U.S. The first two definitions were approved by the Council of State and Territorial Epidemiologists (CSTE), for drug-resistant *S. pneumoniae* (DRSP) invasive disease in 1994, and for invasive pneumococcal disease in children less than five years of age in 2000.[25, 26]

Drug-resistant S. pneumoniae (DRSP) invasive disease

Clinical Description

S. 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 (CSF), or less commonly, joint, pleural, or pericardial fluid) AND

- "Non-susceptible" 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).[30]

  *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 *S. pneumoniae* isolates from patients with life-threatening infections should undergo susceptibility testing by using a quantitative MIC method acceptable for penicillin, extended-spectrum cephalosporins, and other drugs as clinically indicated.[29]

Case Classification

Confirmed DRSP case: A clinically compatible case caused by laboratory-confirmed culture of *S. pneumoniae* identified as "non-susceptible" according to laboratory criteria listed above.

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

Comment: There are a variety of methods with which a laboratory can determine the antimicrobial susceptibility of *S. pneumoniae*, commonly including disk diffusion, testing by agar dilution or broth microdilution, and testing by antimicrobial gradient agar diffusion (E-test® method). When oxacillin disk screening is the only antimicrobial susceptibility method used, the antimicrobial susceptibility profile cannot be definitely determined. Oxacillin screening is highly sensitive and somewhat specific for detecting beta-lactam-resistant *S. pneumoniae*; however, resistance to non-beta-lactam antibiotics is not detected with this screening method (see Section VI, "Laboratory testing").

Invasive S. pneumoniae (Children < 5 years)

Clinical Description

S. pneumoniae causes many clinical syndromes, depending on the site of infection (e.g., 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).

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.[29]

Invasive pneumococcal disease in children < 5 who have received pneumococcal conjugate vaccine

Cases are limited to children less than five years of age with invasive pneumococcal disease, defined as *S. pneumoniae* isolated from a normally sterile body site, who have received at least one dose of PCV7. These cases are not nationally notifiable but are part of voluntary surveillance for possible vaccine failures (see Section VII, "Reporting").

VI. Laboratory testing

Definitive diagnosis of pneumococcal infection is confirmed by the recovery of *S. pneumoniae* from a normally sterile body site (e.g., blood, CSF, pleural fluid, or peritoneal fluid). Because pneumococci frequently colonize the upper respiratory tract in the absence of disease, the clinical significance of recovering the organism from nonsterile body sites (e.g., expectorated sputum, conjunctiva) is less certain. Gram strain may be helpful in interpreting cultures of expectorated sputum; finding a predominance of gram-positive diplococci and > 25 leukocytes with < 10 epithelial cells per high power field on microscopic examination supports the diagnosis of pneumococcal pneumonia.

Based on recommendations from the National Committee for Clinical Laboratory Standards (NCCLS), clinical laboratories should test all isolates of *S. pneumoniae* from CSF for resistance to penicillin, cefotaxime or ceftriaxone, meropenem, and vancomycin.[30] For organisms from other sources, laboratories should consider testing for resistance to erythromycin, penicillin, trimethoprim-sulfamethoxazole, clindamycin, cefepime, cefotaxime or ceftriaxone, a fluoroquinolone, meropenem, tetracycline, and vancomycin. Pneumococci resistant to vancomycin have never been described; a strain with a minimum inhibitory concentration of ≥ 2 µg/ml or zone diameter < 17 mm should be submitted to a reference laboratory for confirmatory testing, and if resistant, reported to the state health department. Because

pneumococci are fastidious organisms, some susceptibility testing methods used for other organisms are not appropriate for pneumococci; see the NCCLS document for testing recommendations.[30]

Currently licensed vaccines target a limited number of pneumococcal polysaccharide capsule serotypes. Identifying the serotypes of pneumococcal strains can be useful for evaluating episodes of pneumococcal disease occurring in vaccinated children or adults. Serotyping is currently performed in only a limited number of state health department laboratories, academic laboratories, or at CDC. CDC's Streptococcal Reference Laboratory will serotype pneumococcal isolates from blood, CSF or other sterile sites from episodes of bacteremia or meningitis occurring in children who have received pneumococcal conjugate vaccine as part of an effort to monitor the effect of the new vaccine (see discussion in Section VII, "Reporting").

VII. Reporting

Each state and territory has regulations and laws governing the reporting of diseases and conditions of public health importance.[31] These regulations and laws list the diseases that are to be reported, and describe those persons or institutions responsible for reporting, such as health-care providers, hospitals, laboratories, schools, daycare and childcare facilities, and other institutions. Contact the state health department for reporting requirements in your state.

Reporting to CDC

Reporting Invasive Pneumococcal Disease in Children aged < 5 years

Health-care providers or laboratories should report to their local or state health department all cases of invasive *S. pneumoniae* occurring in children less than 5 years of age. Some states also require reporting cases among those 5 years and older. The following date is recommended on the case report: patient's date of birth or age, the anatomic site of specimen collection, and type of infection. Other epidemiological information that is useful includes patient's gender, race and ethnicity, specimen collection date, whether the patient was hospitalized for the episode, clinical syndrome, antibiotic susceptibility, details of pneumococcal vaccination history, underlying medical conditions, daycare attendance, and outcome. Additional information may be collected at the direction of the state health department. The *S. pneumoniae* Surveillance Worksheet is included as Appendix 12. If your state is reporting through the National Electronic Telecommunications System for Surveillance (NETSS), use code 11700. If the isolate from a child < 5 years of age is also DRSP (see below), then report twice using both codes 11720 and 11700.

Reporting drug-resistant *Streptococcus pneumoniae*

Participating laboratories should report cases of DRSP to their local or state health department along with information on the patient's date of birth or age, the anatomic site of specimen collection, the date of specimen

collection, the antimicrobial susceptibility pattern, and unique identifiers for the laboratory and the specimen. To accurately calculate the prevalence of DRSP, it is highly desirable for the laboratory to report all cases of invasive pneumococcal infection along with the antibiogram of the *S. pneumoniae* isolate. Such a change in the case reporting requirements has been adopted or is under consideration in several states. An additional benefit of doing surveillance for all invasive pneumococcal disease is the ability to track the progress of vaccine efforts to reduce the incidence of *S. pneumoniae* infections. See Appendix 12 for the *S. pneumoniae* Surveillance Worksheet. If your state is reporting through NETSS, use code 11720. If the DRSP case is in a child < 5 years of age, report twice using both codes 11720 and 11700.

Reporting invasive pneumococcal disease in children who have received pneumococcal conjugate vaccine

Cases following PCV7 vaccination are to be expected, since vaccine efficacy has been reported to be 97% for invasive disease with pneumococcal serotypes included in the vaccine and 89% for all serotypes. There are over 90 serotypes of pneumococcus. The Respiratory Diseases Branch of CDC has developed a tracking system to determine the serotype of invasive pneumococcal isolates following receipt of PCV7, record host conditions that may contribute to PCV7 failure, and monitor for vaccine lots that may be associated with decreased protection. The tracking system is consistent with the 2000 CSTE position statement on invasive pneumococcal infections, which recommends that invasive pneumococcal disease in children less than 5 years old be placed under national surveillance.

The Pneumococcal Conjugate Vaccine Failure Case Report Form may be submitted when the following five conditions are met:

- The child is < 5 years old.
- The child has an invasive pneumococcal infection, defined as isolation of *S. pneumoniae* from a normally sterile site (e.g., CSF, blood, joint fluid, pericardial fluid).
- A pneumococcal isolate is available for serotyping.
- A vaccine history is available.
- The child has received at least one dose of PCV7.

If all five conditions are met, a completed PCV7 Failure Case Report Form, lab form and isolate should be sent to the CDC Streptococcus Laboratory through your State Health Department. The CDC disease reporting instruction sheet and case report forms are available on line at http://www.cdc.gov/nip/diseases/pneumo/PCV-survrpts/PCV7-instructions.htm. The case report form is included as Appendix 13. In addition, cases of suspected PCV7 failure may also be reported to the Vaccine Adverse Events Reporting System (VAERS) at http://www.vaers.org. Reporting through VAERS is not required. However, if a clinically significant adverse event occurs after vaccination with PCV7, it should be reported through VAERS. Isolates will be serotyped and results of the serotypes will be returned to the state health department and submitting physician or laboratory personnel.

VIII. Vaccination

The Advisory Committee on Immunization Practices (ACIP) recommends that the pneumococcal conjugate vaccine (PCV7) be used for all children aged 23 months or younger and for children aged 24–59 months who are at increased risk for pneumococcal disease (e.g., children with sickle cell disease, CSF leak, human immunodeficiency virus infection, and other immunocompromising or chronic medical conditions).[3] ACIP also recommends that the vaccine be considered for all other children aged 24–59 months, with priority given to:

- children aged 24–35 months
- children who are of Alaska Native, American Indian, and African-American descent
- children who attend group daycare centers

The conjugate vaccine has not been studied sufficiently among older children or adults to make recommendations for its use among persons 5 years old or older who are at increased risk for serious pneumococcal disease. They should continue to receive 23-valent polysaccharide vaccine in accordance with previous ACIP recommendations.

During PCV7 vaccine shortages, the ACIP has revised recommendations to conserve vaccine and prioritize the delivery of vaccine to children at highest risk. Recommendations for use during the shortage include:

- the full recommended series for all high-risk children < 5 years
- a reduced number of doses dependent on age and severity of shortage for healthy infants under 24 months
- deferred vaccination for healthy children ≥ 2 years
- priorities for catch-up vaccination when the vaccine supply increases[13]

The 23-valent pneumococcal polysaccharide vaccine (PPV) is approximately 56%–75% efficacious for the prevention of invasive pneumococcal infection caused by vaccine serotypes.[32,33] A dose of vaccine should be administered to all persons aged ≥ 2 years at increased risk of serious pneumococcal infection because of underlying medical conditions and to all persons ≥ 65 years of age.[4] A single revaccination after at least 3–5 years (3 years if < 10 years old, 5 years if 10 or more years) should be considered for persons aged ≥ 2 to 64 years who are at highest risk or likely to have rapid declines in antibody levels. This includes those with functional or anatomic asplenia, HIV infection, leukemia, lymphoma, Hodgkin's disease, multiple myeloma, generalized malignancy, chronic renal failure, nephrotic syndrome or immunosuppression (e.g., organ transplants or receiving chemotherapy). Previously vaccinated persons should be revaccinated at 65 years of age or older, providing at least 5 years has passed since the first dose. Pneumococcal vaccine may be administered concurrently with influenza vaccine by separate injection in the opposite arm. Children 2–4 years of age with high-risk medical conditions should receive PPV at least 2 months after receiving recommended PCV7 doses.

IX. Enhancing surveillance

Several surveillance activities may improve the detection and reporting of pneumococcal disease and the quality of the reports.

Establishing reporting of all invasive pneumococcal disease in children < 5 years

At the recommendation of CSTE, a number of states have mandated reporting of all invasive pneumococcal disease in children < 5 years to monitor the impact of the pneumococcal conjugate vaccine for this age group.

Enhancing reporting of DRSP

Concern over increasing resistance to antibiotics has prompted many state health departments to institute reporting of resistant strains. Health departments are tracking DRSP using a variety of methods, including electronic laboratory-based reporting. CDC is working with state health departments to evaluate different surveillance methods to determine which methods would enhance the reliability of surveillance data, given certain goals and resource limitations.

Improving detection of DRSP in laboratories by promoting optimal techniques and appropriate interpretive standards

Because pneumococci are fastidious organisms, laboratory methods that are appropriate for some organisms are not appropriate for pneumococci. In addition, many laboratories are not monitoring resistance to some agents that are widely used for suspected pneumococcal infections, such as fluoroquinolone agents.[34] Universal adoption of optimal testing methods and testing for resistance to recommended antibiotics would improve our ability to detect and monitor resistant pathogens.

Streamlining reporting using electronic methods

Most surveillance systems still rely on paper and pencil for data collection; use of electronic data transfer directly from clinical laboratories would significantly improve reporting speed and data quality as well as reduce workload. Efforts are underway to move to electronic reporting.

X. Case investigations

As with most respiratory pathogens, rapid, sensitive, and specific diagnostic tests are not available; thus, early in the course of illness, diagnosis of *S. pneumoniae* infection is usually presumptive and the choice of antimicrobial therapy is nearly always empiric. However, once *S. pneumoniae* is isolated from a normally sterile body site, antimicrobial susceptibility testing is necessary for patient management. Case investigations are not usually warranted, except in outbreaks or as determined by the state health department.

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