Pneumococcal infections case definition summary

Public Health Laboratory Network case definitions

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1. Introduction

Streptococcus pneumoniae is commonly carried in the nasopharynx of healthy people. It is an important pathogen, which causes a) localised infection associated with the respiratory tract, particularly otitis media and sinusitis and b) invasive disease that is most commonly manifest as unlocalised bacteraemia, pneumonia or meningitis. Otitis media, of which S. pneumoniae is the commonest bacterial cause, is associated with significant morbidity in young children, including permanent hearing loss. However, in individual cases the cause is rarely confirmed, since this requires invasive techniques that are usually only employed in special studies. Similarly, pneumococcal pneumonia causes significant morbidity and mortality, predominantly in the elderly and immunocompromised but a specific bacterial diagnosis is confirmed in the minority in whom there is an associated bacteraemia.

Because of these diagnostic problems, epidemiological data available from studies of invasive pneumococcal disease record only a small proportion of the total disease burden. However, they provide an objective measure of severe disease and an essential baseline for continued surveillance following the introduction of conjugate vaccines. In predominantly nonindigenous urban populations, the annual incidence of invasive pneumococcal disease is 8-15/100,000 overall, but significantly higher (50-100/100,000) at the extremes of age - children under two and adults over 65 years of age (1,2).

In children, unlocalised bacteraemia is the commonest manifestation but 10-15% of affected infants under two years develops meningitis. Most adults with pneumococcal bacteraemia have pneumonia. About half of the cases are associated with a recognised predisposing factor (eg. diabetes, cardiopulmonary, renal or liver disease, immunosuppression, alcoholism) but this varies from 4% in children under two to 60% or more of adults over 65. The case fatality rate is 12-14% overall, increasing with age to 23% the elderly (3).

Invasive pneumococcal disease is significantly more common in Aboriginal people, especially in Central Australia, where the incidence in children under two years (>1500/100,000/annum) is at least as high as that in developing countries or among native Americans. However the highest relative risk (RR), compared with nonaboriginal people, is in Aboriginal adults aged 15-64, particularly women, reflecting a high incidence of underlying disease in this group (4).
The major virulence factor of *Streptococcus pneumoniae* is its polysaccharide capsule, which protects it from phagocytosis. There are about 90 pneumococcal serotypes, many of which can cause disease. However, most disease is caused by a limited number of serotypes, the distribution of which varies in different geographic areas, with different disease manifestations and in different age groups. A 23-valent polysaccharide pneumococcal vaccine has been available for some years. It is relatively ineffective in young children and, contrary to current recommendations (3), has not been widely used in the elderly. Several new generation conjugate vaccines, which are immunogenic in young children, have recently become available and will soon be licensed for use in Australia. The number of polysaccharide antigens that can be included in conjugate vaccines is limited (currently 7-11). They will be used mainly in young children in whom they have been shown to be effective in preventing invasive disease due to vaccine serotypes. In the predominantly nonaboriginal urban Australian population (and that of other developed countries), 85-90% of isolates from children belong to serotypes included in these 7-11 valent conjugate vaccines and a similar proportion of those from adults in the 23-valent polysaccharide vaccine. However, only about two-thirds of isolates from Aboriginal children and Aboriginal adults belong to serotypes included in the 7-11 valent and 23-valent vaccines respectively (1;4).

Antibiotic resistance of *S. pneumoniae* has been increasing worldwide recently. In Australia, there has been an increase in penicillin resistance (intermediate and high level) from 1% in 1989 to 26% in 1997. The proportion is generally lower for invasive isolates (13% in 1997) but relatively high among the so-called “paediatric” serotypes that cause most childhood disease and are included in the conjugate vaccines (5). This is the basis of the hope that widespread childhood vaccination could reduce the prevalence of antibiotic resistant strains.

Limited data so far indicate that the conjugate vaccines can protect against invasive and mucosal (e.g. otitis media) disease due to, and reduce colonisation with, vaccine serotypes. However, there is concern and some evidence that widespread vaccination will lead to substitution in the normal flora and, potentially, to an increase in disease due to nonvaccine serotypes. Systematic surveillance of invasive pneumococcal disease is important to monitor changes in the incidence, serotype distribution and antibiotic resistance of isolates following introduction of vaccines.

2. Laboratory diagnosis

2.1 Gram stain and culture

Invasive pneumococcal infection is defined by isolation of *S. pneumoniae* from normally sterile sites such as blood, CSF or, less commonly, joint, pleural, ascitic/peritoneal fluids or tissue - e.g. pulmonary or vitreous - biopsy or aspirate. Isolation of *S. pneumoniae* from a specimen with normal flora such as sputum, conjunctiva, middle ear or sinus may provide supportive evidence but not proof of pneumococcal infection.

In Gram stained smears of normally sterile fluids or pus, Gram positive diplococci consistent with *S. pneumoniae* are significant, but their presence in specimens with normal flora should be interpreted with caution. In sputum, a predominance of such organisms, with numerous pus cells and few or no epithelial cells, is likely to be significant and to be confirmed by a predominant growth of *S. pneumoniae*. However, in the absence of bacteraemia, pneumococcal pneumonia is not included in the definition of invasive pneumococcal disease at present.
Blood is cultured in highly nutrient, commercial blood culture media. Other normally sterile specimens and blood cultures with evidence of bacterial growth, are plated on blood agar (incubated aerobically, in 5% CO2 and anaerobically) and chocolate agar (incubated in 5% CO2). After overnight (or up to 48 hours) incubation, colonies suggestive of *S. pneumoniae* - small alpha haemolytic colonies, with draughtsman-like shape; that are Gram positive diplococci on Gram stain – are further identified and differentiated from other viridans streptococci by their sensitivity to optochin and, if necessary additional tests such as bile solubility.

Pneumococcal meningitis is usually associated with CSF findings typical of bacterial meningitis - a predominantly polymorph pleocytosis, high protein and low glucose levels. However, in fulminating cases there may be relatively few (occasionally no) polymorphs but large numbers of bacteria, which can cause obvious turbidity, even in the absence of cells. The bacteria are usually obvious in the counting chamber (but can be overlooked), and their presence is confirmed by Gram stain of the centrifuged deposit.

Sensitivity of culture depends on the clinical setting, volume of specimen cultured and whether or not antibiotics have been given. Blood culture becomes negative soon after antibiotic therapy is started and, often, once the disease has become localised e.g. in the lungs or meninges. About 20% of untreated patients with pneumococcal pneumonia and 80% of those with meningitis have positive blood cultures. The specificity of a positive culture of a normally sterile specimen is 100%, since isolation of *S. pneumoniae* from such a specimen defines invasive pneumococcal infection. It can occur in someone, especially a child, with mild nonspecific, febrile illness, which may be self-limiting.

The predictive value of a positive culture is 100%. The negative predictive value varies depending on the clinical symptoms and age of the patient. Failure to isolate *S. pneumoniae* from blood of a patient with apparently typical pneumococcal pneumonia is common. Negative CSF culture does not exclude the diagnosis of pneumococcal meningitis, although this is less common.

### 2.2 Pneumococcal antigen test

Commercially available tests eg. latex agglutination, for pneumococcal antigen, are often used for supplementary rapid testing of abnormal CSF (showing a pleocytosis, consistent with bacterial meningitis). They may help to confirm a positive Gram stain or identify the cause of meningitis more rapidly than culture. Other body fluids, including serum, can also be tested, but pneumococcal urinary antigen tests are insensitive, and rarely helpful. The kit manufacturer’s instructions should be followed.

Generally antigen tests are no more sensitive than Gram stain and culture, but may remain positive for a longer period after antibiotic therapy has been started. They are highly specific, although false positive results can occur. The positive predictive value is reduced if tests are performed on CSF or other body fluids without other abnormalities suggesting sepsis.

#### 2.2.1 Suitable and unsuitable specimens

#### 2.2.2 Test details

#### 2.2.3 Test sensitivity

#### 2.2.4 Test specificity

#### 2.2.5 Predictive values and relevant populations
2.2.6 Suitable test acceptance criteria
2.2.7 Suitable internal controls
2.2.8 Suitable original test validation criteria
2.2.9 Suitable external Quality Assurance Program(s) (QAP)
2.2.10 Special considerations
2.2.11 References

2.3 Nucleic acid tests (NAT)

A number of nucleic acid tests, mainly PCR, have been described to detect the presence of pneumococcal DNA in clinical specimens including whole blood or serum (6-8), CSF (9) and transthoracic needle aspirates (10). They include multiplex PCR (11) for simultaneous detection of common causes of bacterial meningitis. Specific pneumococcal DNA targets include the pneumolysin (7,8), autolysin, 16S rRNA (11), psaA (121) and penicillin binding protein (13) genes. Nested PCR, targeting penicillin binding protein genes allows direct detection of penicillin resistant pneumococcus in specimens (12).

PCR is generally more sensitive than culture and antigen tests for diagnosis of pneumococcal pneumonia (8,10), meningitis and other types of invasive pneumococcal disease, especially in children (6,7). However there is variation according to the configuration of the test and the target. So far there has been limited clinical evaluation of the use of these tests and their role in routine diagnosis remains to be defined (8,10).

As with all NAT, care must be taken to prevent contamination and, if so, the specificity of NAT for S. pneumoniae is high. A positive result indicates the presence of pneumococcal DNA, not necessarily viable organisms. In studies including healthy controls, results have varied. In one, pneumolysin PCR was negative in all healthy controls and all children with positive PCR results had other evidence of pneumococcal infection. In another, PCR was positive in 17% (all children) of healthy controls presumably because of nasopharyngeal carriage (5). Results must be interpreted with caution and the test should be applied only to patients with clinically compatible disease.

2.3.1 Suitable and unsuitable specimens
2.3.2 Test details
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3. Typing & Subtyping Methods

3.1 Typing (Subtyping) Method

*S. pneumoniae* is divided into at least 90 serotypes, based on differences in polysaccharide antigens, which are grouped on the basis of antigenic similarities (see attached list). Standard antiserum pools are available for the main serogroups and individual serotypes. Serotyping is currently performed in Australia in three laboratories. It is not required for individual patient management and rarely, if ever, for investigation of case clusters. However, with the imminent release and widespread use of conjugate vaccines, routine surveillance of isolates from all cases of invasive pneumococcal disease and selected clinically significant isolates from respiratory sites will be required to monitor changes in serotype distribution and antibiotic susceptibility.

Multilocus sequence typing (MLST) is most used for more discriminatory subtyping of isolates to track the spread of highly invasive or antibiotic resistant clones (14,15).

3.1.1 Utility

3.1.2 Test acceptance criteria

3.1.3 Suitable internal controls

3.1.4 Suitable external Quality Assurance Program(s) (QAP)

3.1.5 Special considerations

3.1.6 International reference focus

3.1.7 References

4. Laboratory Nomenclature for National Data Dictionary

List of serotypes (provided by John Bates, Queensland Health Scientific Services)

* Grouping sera only are kept in Australia for these rare serogroups. If any was identified they could be sent to the States Serum Institute for factor typing.

4.1 Organism Name(s) List

4.2 Typing/Subtyping Nomenclature List(s)

5 PHLN Summary Laboratory Definition

5.1 Condition: Invasive pneumococcal disease

5.1.1 Definitive Criteria
Isolation of *Streptococcus pneumoniae* from normally sterile site; OR Positive nucleic acid test for *S. pneumoniae*.

5.1.2 Suggestive Criteria
*S. pneumoniae* antigen in CSF in meningitis; OR Gram positive diplococci in CSF in meningitis.

5.1.3 Guide for Use

5.1.4 Parent PHLN Document Number (0020)

6 Revision History

Draft 0.1, 20 October 2000, L. Gilbert

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7. References


