Invasive pneumococcal disease (*Streptococcus pneumoniae*)

Laboratory case definition

The Public Health Laboratory Network (PHLN) has developed standard case definitions for the diagnosis of key diseases in Australia. This document contains the laboratory case definition for *streptococcus pneumoniae*.

Authorisation: PHLN

1 PHLN Summary Laboratory Definition

1.1 Condition:

Invasive Pneumococcal Disease (IPD).

1.1.1 Definitive Criteria

- Isolation of *Streptococcus pneumoniae* from a normally sterile site;

  OR
- Detection of nucleic acid of *S. pneumoniae* from a normally sterile site.

1.1.2 Suggestive Criteria

- Detection of *S. pneumoniae* antigen from a normally sterile site (excluding urine);

  OR
- Gram positive diplococci consistent with *S. pneumoniae* in CSF.

1.1.3 Special Considerations / Guide for Use

Not applicable.

2 Introduction

Streptococcus pneumoniae is commonly carried in the nasopharynx of healthy people, particularly in young children.

It is also an important pathogen which causes:

- localised infection of the upper respiratory tract, such as otitis media and sinusitis;
- disseminated infection most commonly manifest as primary bacteraemia, pneumonia and/or meningitis. Less common sites of infection include septic arthritis, osteomyelitis, empyema, peritonitis and endophthalmitis.

Otitis media, of which *S. pneumoniae* is considered the commonest bacterial cause, is associated with significant morbidity in young children, including permanent hearing loss. However, in most cases the cause is rarely confirmed due to difficulty in acquiring a suitable specimen for culture. Similarly, pneumococcal pneumonia causes significant morbidity and mortality, predominantly in the elderly and immunocompromised, with a specific bacterial diagnosis confirmed in the minority in whom there is an associated bacteraemia and/or empyema. In addition, Gram stain and culture of respiratory tract specimens, such as sputum, conjunctiva and sinuses, cannot not reliably differentiate infection from colonising normal flora.

Due to these diagnostic problems, epidemiological studies generally define **invasive pneumococcal disease (IPD)** as isolation of *S. pneumoniae* by culture and/or detection of nucleic acid of *S. pneumoniae* from normally sterile sites. This results in underrepresentation of the total disease burden, however, the data still provides an objective measure of severe disease and is essential for continued surveillance to monitor vaccine efficacy.

The annual incidence of IPD in Australia has most recently ranged from 6.3-8.4/100,000, with variation seen among jurisdictions (ACT 5.1/100,000 and Northern Territory 22.2/100,000 (2018)). The incidence is significantly higher at the extremes of age - children under five and adults 70 years and over (19.4 and 15.2-41.3/100,000 (2018) respectively).[1,2] IPD is also significantly more common in indigenous Australians (34-58.6/100,000 (2006-2015)), accounting for 16% of cases of IPD in 2015 where the indigenous status was known.[1,2]

In children, primary bacteraemia is the commonest manifestation of IPD (70%), followed by pneumonia with bacteraemia and meningitis. Most adults with IPD have pneumonia with bacteraemia.[3]

The major virulence factor of *S. pneumoniae* is its polysaccharide capsule which protects it from phagocytosis and is the basis for serotyping. There are about 90 pneumococcal serotypes. Most disease is caused by a limited number of serotypes, the distribution of which varies across different geographic areas, with different disease manifestations and in different age groups. Host antibodies, either from natural exposure or immunisation, are directed against the capsular polysaccharides.

As of 2019, the 23-valent polysaccharide pneumococcal vaccine (introduced in 1999 for indigenous and in 2005 for non-indigenous adults) is currently recommended for all adults 65 years and over, all

Aboriginal and Torres Strait Islander 50 years and over, and all adults with medical conditions which put them at increased risk of IPD.[3]

After introduction of the 7-valent conjugate pneumococcal vaccine (7vPCV) for infants in Australia in 2005, the notification rate of IPD due to 7vPCV serotypes decreased in all age groups.[4,5] However, rates of IPD caused by serotypes that were not contained in 7vPCV increased in Australia and several other countries.[6] It was particularly evident among non-Indigenous children aged <5 years, where infections due to non-vaccine serotypes increased by 168%. The current 13-valent conjugate pneumococcal vaccine (introduced in 2012) is recommended in Australia for all infants. By 2014, there was a 42% reduction in IPD due to 13vPCV-non-7vPCV serotypes (reduced to 1.8 per 100,000). Serotype 19A caused around 80% of 13vPCV-type disease in children and around 40% in adults before 13vPCV was introduced. Introducing 13vPCV reduced disease caused by serotype 19A by almost 70% overall.[5]

Systematic surveillance of IPD is important to continue to monitor changes in the incidence and serotype distribution following introduction of vaccines and antibiotic resistance of isolates. IPD is a *notifiable* disease in Australia.

3 Tests

3.1 Gram Stain and Culture

3.1.1 Methods

S. pneumoniae may be detected by Gram stain of specimens or centrifuged fluids. It typically appears as Gram positive, lancet shaped diplococci or cocci in chains. These features may be altered by antimicrobial treatment and over decolourisation, giving the appearance of Gram negative diplococci.

Blood is inoculated into highly nutrient, commercial blood culture media. Blood culture bottles with evidence of bacterial growth, and other specimens (sterile site and respiratory) are typically plated on blood agar with an optochin disc and incubated aerobically and in 5% CO_2, and on chocolate agar incubated in 5% CO_2. Following overnight incubation *S. pneumoniae* appears as optochin sensitive, small, greyish mucoid (i.e. capsule-producing) colonies with alpha-haemolysis. Typically, over the next 24-48 hours the colonies develop a central depression or "draughtsmen-like" shape.

S. pneumoniae is differentiated from other viridans-type streptococci by their susceptibility to optochin (ethylhydrocupreine) and, if necessary, bile solubility (autolysis in the presence of sodium deoxycholate).

Commercial biochemical identification systems are generally not necessary and may have difficulty in differentiating *S. pneumoniae* from other viridans-type streptococci.

Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) has the advantage over traditional phenotypic identification methods by providing more rapid identification. However, due to specificity concerns associated with misidentification of *S. mitis* species group as *S. pneumoniae*, MADLI-TOF MS identification is usually supplemented by optochin susceptibility.

3.1.2 Quality Assurance

3.1.2.1 Suitable specimens

Any sterile site specimen where infection with *S. pneumoniae* is suspected is suitable for Gram stain and culture. Sensitivity of culture is maximised when specimens are taken prior to antibiotics, however, this is not always clinically possible, particularly in the case of suspected bacterial meningitis. Centrifugation of fluid specimens is recommended to improve sensitivity for Gram stain and culture.

3.1.2.2 Test sensitivity

Pneumococcal meningitis is usually associated with CSF findings typical of bacterial meningitis - a predominant polymorphonuclear pleocytosis, high protein and low glucose levels. However, in fulminating cases there may be relatively few (occasionally no) polymorphonuclear cells 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.

CSF Gram stain has a sensitivity of 84% in detecting *S. pneumoniae,* however this is significantly reduced with prior administration of antibiotics.[8]

Sensitivity of culture depends on the clinical setting, volume of specimen cultured and whether or not antibiotics have been given prior to specimen collection. Processing a CSF specimen, as well as other clinical specimens, for culture as soon as possible is vital for optimal culture performance, because bacterial viability decreases over time. Blood cultures become negative soon after antibiotic therapy is started.

About 3-10% of untreated patients with pneumococcal pneumonia and >50% of those with meningitis have positive blood cultures.[7,9,10]

Resistance to optochin is reported among 10% of *S. pneumoniae* isolates. In circumstances of optochin resistance, where *S. pneumoniae* is highly suspected due to clinical and/or other laboratory features (i.e. Gram stain appearance and/or colony morphology), further testing is required for identification and differentiation from other viridans-type streptococci. Bile solubility is highly sensitive and specific for *S. pneumoniae*.

The sensitivity of MALDI-TOF MS is high (92-100%).[11,12] The Vitek Compact system (bioMérieux) has slightly lower sensitivity (88.5%) associated with misidentification of *S. pneumoniae* as other viridans-type streptococci.[12]

3.1.2.3 Test specificity

The typical Gram stain appearance of *S. pneumoniae* in sterile site specimens has high specificity when observed by an experienced microscopist. The specificity for meningitis is 98%.[8] Accurate results are highly dependent on the operator's staining and interpretation skills.

Isolation of *S. pneumoniae* by culture from blood or other normally sterile specimens has 100% specificity for IPD. However, care must be taken not to mistake *Streptococcus pseudopneumoniae* for *S. pneumoniae* on the basis of optochin susceptibility when incubated in

ambient air and/or following streptococcal antigen positivity. *S. pseudopneumoniae* has intermediate susceptibility or resistance to optochin when incubated in 5% CO_2, is insoluble in bile and lacks a capsule.[14,15] The Vitek MS (bioMérieux) system has been shown to differentiate *S. pneumoniae* from *S. pseudopneumoniae*.[9]

Non-pneumococcal viridans-type streptococci, especially *S. mitis* and S. *oralis*, may be misidentified as *S. pneumoniae* by MALDI-TOF MS, *however the specificity of commercial systems appears to be improving.* The Vitek MS (bioMérieux) system has demonstrated a specificity of 100%.[11,12] The specificity of the MALDI-TOF Biotyper (Bruker Daltonics) system for *S. pneumoniae* identification was 92.4% (10 non pneumococcal isolates were misidentified as *S. pneumoniae*) after the January 2014 upgrade of the database, but only 49% with the precedent version (67 non pneumococcal isolates were misidentified as *S. pneumoniae*).[12,16] In the same analysis, the specificity of the VITEK Compact system (bioMérieux) for *S. pneumoniae* identification was 100%.[12]

3.1.2.4 Predictive values

For most populations, the positive predictive value of a positive culture from blood or sterile sites is near 100% due to the high specificity of culture.

The negative predictive value depends on the pre-test probability of IPD which is most influenced by risk factors (particularly age, indigenous status and co-morbidities such as human immunodeficiency virus, asplenia and hypogammaglobulinaemia), clinical features, supporting radiology and pathology testing (i.e. CSF microscopy, protein and glucose) and prior antibiotics (as reduces sensitivity). 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.

3.1.2.5 Suitable acceptance criteria

Isolation of a *S. pneumonia*e: typical Gram positive diplococci or cocci in chains growing as alpha haemolytic colonies on blood agar confirmed by optochin susceptibility +/- bile solubility.

3.1.2.6 Suitable internal controls

All media and tests should have properly documented, relevant quality control using ATCC or NCTC control strains.

3.1.2.7 Suitable test validation criteria

All tests performed need to be validated as per NPAAC criteria before reporting for clinical management purposes.

3.1.2.8 Suitable external QA program

Participation in a suitable external QA program, such as Royal College of Pathologist of Australasia Quality Assurance Program Pty. Ltd. (RCPA).

3.2 Nucleic Acid Amplification Tests (NAATs)

3.2.1 Methods

A number of in-house or commercial NAATs, mainly polymerase chain reaction (PCR), have been described to detect the presence of *S. pneumoniae* DNA. They include multiplex PCR for simultaneous detection of common causes of bacterial meningitis. The pneumolysin gene (*ply*), autolysin gene (*lytA*), pneumococcal surface adhesin A gene (*psaA*), *wzg/cpsA*, and the Spn9802 gene fragment have been used as PCR targets to detect *S. pneumoniae*.[10]

3.2.2 Quality Assurance

3.2.2.1 Suitable specimens

Clinical specimens used to detect invasive *S. pneumoniae* have included whole blood or serum,[17-19] CSF[20] and transthoracic needle aspirates.[21] However all specimen types may not necessarily be verified/validated against NPAAC standards for the detection of *S. pneumoniae* DNA, with their role in routine diagnosis across various specimens yet to be defined.

3.2.2.2 Test sensitivity

Nucleic acid amplification tests do not require viable bacteria for a positive result and are generally considered highly sensitive. PCR inhibitors in clinical specimens can compromise sensitivity. In the setting of pneumonia, NAATs have a sensitivity for detecting *S. pneumoniae* in blood samples ranging from 29% to 100%, although there is a tendency for the performance to be better in children than in adults.[7,10] NAATs using the autolysin gene (*lytA*) have been shown to have greater sensitivity over pneumolysin gene (*ply*).[9,10]

The sensitivity of NAATs applied to CSF samples for diagnosis of pneumococcal meningitis is 92%–100%.[7]

NAATs have also been successfully used with other samples obtained by invasive means, such as pleural fluid and lung aspirate specimens.[7,9]

3.2.2.3 Test specificity

As with all NAATs, care must be taken to prevent contamination. Pneumolysin gene (*ply)* can be detected in non-pneumococcal viridans-group streptococci, particularly *S. pseudopneumoniae* and *S. mitis*, which is thought to have contributed to positive pneumococcal NAAT results from blood in asymptomatic control subjects and poor performance in the detection of pneumococcal disease.[7,9,10] Other targets, including the autolysin gene (*lytA*), the pneumococcal surface adhesion gene (*psaA*), and the spn9802 gene fragment, appear to be more specific.[9]

The specificity of pneumococcal NAAT applied to CSF samples is reported at 100%.[7]

3.2.2.4 Predictive Values

The positive predictive and negative predictive values are influenced by the sensitivity and specificity of the test, and vary according to the pre-test probability of IPD. Results should always be correlated with the clinical features and results of other diagnostic tests.

Invasive pneumococcal disease – Laboratory case definition

3.2.2.5 Suitable acceptance criteria

General acceptance criteria for nucleic acid detection include:

- Absence of detectable contamination.
- Successful detection of positive control material.
- Absence of inhibition in the clinical material.

3.2.2.6 Suitable internal controls

Positive and negative control material should be included in the extraction stage and all subsequent amplification steps.

3.2.2.7 Suitable test validation criteria

Positive and negative control material should be included in the extraction stage and all subsequent amplification steps.

3.2.2.8 Suitable external QA program

Participation in a suitable external QA program.

3.3 Antigen Detection

3.3.1 Methods

There are two targets for antigen detection – the capsular polysaccharide and cell wall teichoic acid (C polysaccharide).

Capsular polysaccharide was first detected in the urine of patients with pneumococcal pneumonia in 1917, however levels in the urine of these patients were variable and dependent on the serotype. The latex agglutination test to detect urinary capsular polysaccharide of *S. pneumoniae*, was of limited usefulness because of limited sensitivity and specificity.[9,10]

C polysaccharide cell wall antigen is common to all strains of *S. pneumoniae* and is detected using a rapid immunochromatographic test (ICT) (Binax NOW *S. pneumoniae* urinary antigen test).[7]

3.3.2 Suitable specimens

While primarily designed and marketed as a urinary antigen test, studies have also shown the utility of the C polysaccharide antigen ICT in the identification of *S. pneumoniae* from CSF, pleural fluid, bronchoalveolar lavage (BAL), and blood culture media in both adult and pediatric patients. The use of antigen detection from sterile sites may be a better alternative than urine detection, especially in children.[9]

3.3.3 Test sensitivity

The C polysaccharide antigen ICT (Binax NOW) has reported sensitivity in urine for pneumonia in adults of 70-92% (higher for bacteraemic vs non-bacteraemic pneumonia), in pleural fluid for pneumococcal empyema of 71-96% and in CSF for meningitis of 95-100%.[7,10]

One advantage of the C polysaccharide antigen ICT (Binax NOW) is that prior antibiotic use has less influence on the diagnostic yield.[10]

3.3.4 Test specificity

In adults, the specificity of the C polysaccharide antigen ICT (Binax NOW) in urine for the diagnosis of community acquired pneumonia is 67-100%.[9] However, studies of urine samples from children have showed inadequate specificity (50-60%) due to the high rate of nasopharyngeal carriage in children, resulting in urinary excretion of teichoic acid.[10] False positives also occur following pneumococcal vaccination, due to cross reaction with other closely related streptococci (including *S. pseudopneumoniae*) or following resolved infection, as the test may remain positive several weeks after infection.[7,9] In addition, a positive urinary antigen test cannot distinguish pneumonia without invasive disease from IPD.

The specificity for other fluids is high, including 100% for CSF, 71-100% for pleural fluid and 87% for BAL.[7,10]

3.3.5 Predictive Values

The positive predictive and negative predictive values are influenced by the sensitivity and specificity of the test for the specimen type, and vary according to the pre-test probability of IPD. A positive C polysaccharide antigen ICT (Binax NOW) from CSF with elevated polymorphonuclear cells has very high positive predictive value. Results should always be correlated with the clinical features and results of other diagnostic tests.

3.3.6 Suitable acceptance criteria

Presence of control line for each test using the C polysaccharide antigen ICT (Binax NOW).

3.3.7 Suitable internal controls

Positive and negative controls supplied in the kit; or human urine containing *S. pneumoniae* antigen (positive control) and normal human urine (negative control).

3.3.8 Suitable test validation criteria

Positive and negative controls supplied in the kit; or human urine containing *S. pneumoniae* antigen (positive control) and normal human urine (negative control).

3.3.9 Suitable external QA program

Participation in a suitable external QA program, such as Royal College of Pathologist of Australasia Quality Assurance Program Pty. Ltd. (RCPA).

3.4 Antibody Detection

Use of antibody tests for the routine diagnosis of acute *S. pneumoniae* infection is not recommended due to suboptimal sensitivity and specificity, and time taken to demonstrate seroconversion. In addition, antibody detection is unable to differentiate IPD from non-invasive pneumococcal disease.

4 Agreed Typing & Subtyping Methods

S. pneumoniae is divided into at least 90 serotypes, based on differences in capsular polysaccharide antigens. The Quellung reaction is the gold standard method for pneumococcal capsular serotyping. The method involves testing a pneumococcal cell suspension with pooled and specific antisera directed against the capsular polysaccharide. Serotyping is not required for individual patient management but may sometimes be useful for investigation of case clusters and recurrent invasive disease. However, with the widespread use of conjugate vaccines, routine surveillance of isolates from all cases of invasive pneumococcal disease, and potentially selected clinically significant isolates from respiratory sites, will be required to monitor changes in serotype distribution.

In 2015 serotypes 19A, 3, 22F, 19F, 9N and 7F caused 43% of IPD. All but 22F and 9N are included in the 13-valent pneumococcal conjugate vaccine. The remainder of cases were due to 36 different serotypes.[1]

The serotypes are grouped on the basis of antigenic similarities. On exposure of pure culture to specific anticapsular antiserum, the capsule becomes enhanced and bacterial cell appears surrounded by a halo, as observed under the light microscope. Standard antiserum pools are available for the main serogroups and individual serotypes (Table 1). As of 2019, serotyping is currently performed in four Australian laboratories (Microbiological Diagnostic Unit, Victoria; Institute of Clinical Pathology and Medical Research (ICPMR)-NSW Health Pathology, New South Wales; Queensland Forensics and Scientific Services, Queensland; and PathWest Laboratory Medicine WA, Queen Elizabeth II Medical Centre, Western Australia).

As up to 10% of IPD is diagnosed on the basis of nucleic acid detection in the absence of culture. Direct molecular typing is also available (Microbiological Diagnostic Unit, Victoria; Institute of Clinical Pathology and Medical Research (ICPMR)-NSW Health Pathology; Queensland Forensics and Scientific Services). The molecular typing currently covers all serotypes in the conjugate 13-valent vaccine and some additional types, however is not always able to distinguish a single factor type, therefore multiple results may be given (e.g. 15B/C, 11A/D/18F, 47F/35F). In a significant number of cases where molecular typing is attempted, a serotype is unable to be determined, mainly due to the insufficient amounts of *S. pneumoniae* DNA present in those samples.

Table 1: List of serotypes

1	9V	15B	23F	35A
2	10F	15C	23A	35B
3	10A	16F	23B	35C
4	10B	16A	24* (24F, 24A, 24B)	36

Invasive pneumococcal disease – Laboratory case definition

5	10C	17F	25* (25F,25A)	37
6A	11F	17A 18F	27	38
6B	11A	18A	28* (28F,28A)	39
6C	11B	18B	29	40
6D	11C	18C	31	41* (41F, 41A)
7F	11D	19F	32*(32F,32A)	42
7A	12F	19A	33F	43
7B	12A	19B	33A	44
7C	12B	19C	33B	45
8	13	20	33C	46
9A	14	21	33D	47
9L	15F	22F	34	48
9N	15A	22A	35F	

Grouping sera only are kept in Australia for these rare serogroups.

5 Antimicrobial Susceptibility

Changes in *S. pneumoniae* antimicrobial susceptibility evolved rapidly internationally from the 1990s, with penicillin non-susceptibility (intermediate and resistant) of particular concern. Susceptibility has varied according to geographical location, site of infection and pneumococcal serotype. Australian data from 2007 demonstrated stabilisation or reduction in non-susceptibility rates (following alarming

increases around the late 1990s/early 2000s) for parenteral penicillin (25% using meningitis breakpoints and <5% using non-meningitis breakpoints), erythromycin (20.4%), clindamycin (15.4%), tetracycline (17.7%) and trimethoprim-sulphamethoxazole (28%).[22] Moxifloxacin non-susceptibility was rare (0.3%).[22] Non-susceptibility rates were higher for non-invasive isolates compared to invasive isolates.

Three main standards for reporting antimicrobial susceptibility are used in Australian laboratories – European Committee on Antimicrobial Susceptibility Testing (EUCAST),[23] Clinical and Laboratory Standards Institute (CLSI)[24] and Calibrated Dichotomous Susceptibility (CDS).[25] Reporting and interpretation of penicillin susceptibility for *S. pneumoniae* is complicated by different breakpoints for non-meningitis vs meningitis isolates and oral vs parenteral agents, and variable dosing recommendations based on the minimum inhibitory concentration (MIC). From 2019, EUCAST has recommended that "Intermediate" breakpoints (traditionally regarded as non-susceptible) are reported and interpreted as "Susceptible – Increased Exposure", recognising that favourable clinical outcomes may be achieved when adequate drug concentrations are maintained at the site of infection. CLSI continues with an "Intermediate" classification, to also account for variability in laboratory performance, whilst CDS uses the terminology "Decreased Susceptibility". Tables 2-4 compare the breakpoints of the three methods for the antibiotics commonly used.

Resistance to beta lactam antibiotics (such as penicillin) is associated with changes to one or more of the penicillin binding proteins (PBP 1A, 1B, 2A, 2b and 2X). There are currently no genotypic resistance assays for beta-lactam or other classes of antibiotics used routinely in clinical laboratories.

Table 2: Beta-lactam antibiotic susceptibility interpretations for *S.pneumoniae* based on MIC (mg/L) breakpoints* according to EUCAST[23] and CLSI[24] standards (July 2019)

Antibiotic	Susceptible (S)		Intermediate (CLSI) Susceptible Increased Exposure (EUCAST)		Resistant (R)	
	EUCAST	CLSI	EUCAST	CLSI	EUCAST	CLSI
Benzylpenicillin (non-meningitis)	≤0.06	≤2	0.12-2	4	>2	≥8
Benzylpenicillin (meningitis)	≤0.06	≤0.06	-	-	>0.06	≥0.12
Phenoxymethylpenicillin	Oxacillin 1ug disc >=20mm	≤0.06	-	0.12-1	Oxacillin 1ug disc <20mm	≥2

Antibiotic	Susceptible (S)		Intermediate (CLSI) Susceptible Increased Exposure (EUCAST)		Resistant (R)	
	EUCAST	CLSI	EUCAST	CLSI	EUCAST	CLSI
Amoxicillin/ampicillin (intravenous)	≤0.5	-	1-2	-	>2	-
Amoxicillin (non-meningitis)	-	≤2	-	4	-	≥8
Amoxicillin (oral)	≤0.5	-	1	-	>1	-
Ceftriaxone/cefotaxime (non-meningitis)	≤0.5	≤1	1-2	2	>2	≥4
Ceftriaxone/cefotaxime (meningitis)	≤0.5	≤0.5	1-2	1	>2	≥2

NOTE: medium, inoculum and incubation requirements may vary between the two methodologies. Breakpoints for disc diffusion also available for some antibiotics.

Table 3: Antibiotic susceptibility interpretations for *S.pneumoniae* according to CDS[25] standards (July 2019)

Antibiotic	Susceptible (S)	Decreased Susceptibility	Resistant (R)
Benzylpenicillin (non-meningitis)	0.5u disc ≥6mm	0.5u disc <6mm AND Ampicillin 5ug disc ≥4mm	0.5u disc <6mm AND Ampicillin 5ug disc <4mm
Benzylpenicillin (meningitis)		-	0.5u disc < 6mm

Antibiotic	Susceptible (S)	Decreased Susceptibility	Resistant (R)
Amoxicillin/ampicillin (non-meningitis)	5ug disc ≥4mm	5ug disc ≥4mm-AND 0.5u benzylpenicillin disc <6mm	5ug disc < 4mm
Ceftriaxone/cefotaxime (non-meningitis)	0.5ug disc ≥4mm	0.5ug disc <4mm AND 5ug disc ≥4mm	5ug disc <4mm
Ceftriaxone/cefotaxime (meningitis)		-	0.5ug disc < 4mm

Table 4: Antibiotic susceptibility interpretations for *S.pneumoniae* based on MIC (mg/L) breakpoints* according to EUCAST[23] and CLSI[24] standards, and CDS[25] standards (July 2019)

Antimicrobial	CDS Disc Strength Angular radius S ≥6mm R <6mm	Susceptible (S)		Intermediate (CLSI) Susceptible Increased Exposure (EUCAST)		Resistant (R)	
		EUCAST	CLSI	EUCAST	CLSI	EUCAST	CLSI
Erythromycin	5ug	≤0.25	≤0.25	0.5	0.5	>0.5	≥1
Clindamycin#	2ug	≤0.5	≤0.25	-	0.5	>0.5	≥1
Tetracycline^	10ug	≤1	≤1	2	2	>2	≥4
Moxifloxacin	2.5ug	≤0.5	≤1	-	2	>0.5	≥4

Antimicrobial	CDS Disc Strength Angular radius S ≥6mm R <6mm	Susceptible (S)		Intermediate (CLSI) Susceptible Increased Exposure (EUCAST)		Resistant (R)	
		EUCAST	CLSI	EUCAST	CLSI	EUCAST	CLSI
Trimethoprim-sulphamethoxazole	1.25/23.75ug	≤1	≤0.5	2	1-2	>2	≥4

NOTE: medium, inoculum and incubation requirements may vary between the two methodologies. Breakpoints for disc diffusion also available for some antibiotics.

 # If inducible resistance then report as resistant

^ Organisms susceptible to tetracycline are susceptible to doxycycline however doxycycline resistance cannot be inferred from tetracycline

6 Laboratory Nomenclature for National Database Dictionary

6.1 Organism Name(s) List

SNOMED CT concept	Code
Invasive pneumococcal disease (disorder)	406617004
Pneumococcal infectious disease	16814004
Streptococcus pneumoniae (organism)	9861002
Multiple drug-resistant Streptococcus pneumoniae (organism)	409806004
Streptococcus pneumoniae serotype 3 (organism)	103497003

SNOMED CT concept	Code
Streptococcus pneumoniae serotype 19A (organism)*	415611002
Streptococcus pneumoniae DNA (substance)	708447006
Streptococcus pneumoniae antigen (substance)	120985002
Streptococcus pneumoniae pneumonia (finding)	717216007
Streptococcus pneumoniae antigen assay (procedure)	122120003
Bacterial serotyping (procedure)	57906000

*specific codes for other serotypes can be accessed from SNOMED-CT browsers

7 References

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