Streptococcus pneumoniae Survey
2007 Antimicrobial Susceptibility Report

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Antimicrobial Susceptibility Report of *Streptococcus pneumoniae* Isolates from the Australian Group on Antimicrobial Resistance (AGAR)

2007 Surveillance Report

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1   Executive Summary

The Australian Group on Antimicrobial Resistance (AGAR) performs regular multicentre period-prevalence studies to monitor changes in antimicrobial resistance. In 2007, 20 laboratories participated in national surveillance of *Streptococcus pneumoniae* resistance. One thousand eight hundred and thirty one strains of *S. pneumoniae* were collected prospectively and tested by disc diffusion, Vitek2, Etest and/or agar dilution. Results were compared to five previous AGAR sponsored studies performed in 1989, 1994, 1999, 2002 and 2005. Three hundred and twelve (17.0%) were from blood cultures, which formed the majority of invasive isolates. Non-susceptibility to penicillin was present in 2.0% of isolates. Four of the 12 CSF isolates were resistant to penicillin (meningitis breakpoints); two of the penicillin resistant isolates were also non-susceptible to the third generation cephalosporins (at meningitis breakpoints). For β-lactam antibiotics, NSW/ACT had higher rates of non-susceptibility than the other regions. In non-invasive isolates resistance to macrolides (21.7%), tetracyclines (18.4%) and trimethoprim-sulphamethoxazole (28.8%) was higher than for invasive isolates (rates of 13.9%, 14.2% and 23.5% respectively). Clindamycin resistance was present in 72.9% of macrolide resistant strains (MLS_B resistance). Fluoroquinolone resistance remains rare with 0.6% of isolates demonstrating non-susceptibility to levofloxacin and 0.2% to moxifloxacin. For non-β-lactams, resistance was higher in Queensland and NSW/ACT than in other regions. This was also true for the number of multi-resistant strains. This may be due to higher numbers of multi-resistant serotypes circulating in these regions. Multi-resistant strains, defined as resistance to 3 or more antibiotic classes, was identified in 4.7% of invasive and 12.7% of non-invasive strains. Resistance rates for erythromycin, tetracycline and trimethoprim-sulphamethoxazole were higher among the elderly (≥65 years old). There was no significant age related difference in penicillin non-susceptibility. For all drugs resistance was higher amongst the inpatient population with differences reaching statistical significance for all except trimethoprim-sulphamethoxazole.

When compared to previous AGAR studies, penicillin non-susceptibility is increasing albeit at a slow rate. Strains with a penicillin MIC >2mg/L were 2% in 2007, in comparison these were largely absent from the 1989 and 1994 surveys (0.0% and 0.1% respectively), reaching just over 1% in the 1999 and 2002 surveys and reaching a high of 3.3% in the 2005 survey. Erythromycin resistance increased sharply from 1994 (8.7%) to 2002 (21.6%) but has decreased over the last two survey periods for invasive isolates. Rates were steady between 2002 and 2005 for non-invasive isolates and fell to 21.7% in this survey. No overall significant rise in tetracycline resistance was demonstrated between 1999 and 2007 however this was not true of the invasive isolates which increased from 6.3% resistance in 2005 to 14.2% in this survey. This increase was due to significant rises in two regions: NSW/ACT and Queensland. A decrease in resistance was observed for trimethoprim-sulphamethoxazole. As observed in the previous report (2005), the initial rapid rise in antibiotic resistance seen in the early 1990s, has been followed by a more gradual rise since 1999. Overall, the trends in susceptibility match trends seen in other developed countries although the rates seen in Australia in 2007 remain substantially lower than those seen in many areas in Europe and particularly the rates seen in many developing countries in Asia.

2 Introduction

2.2 Objective of the Programme

The objective of the 2007 surveillance program was to determine the prevalence of antimicrobial resistance in clinical isolates of *S. pneumoniae* throughout Australia, with particular emphasis on:

1. Obtaining accurate information on the minimum inhibitory concentrations to penicillin and third generation cephalosporins in order to ascertain whether beta-lactams are likely to remain effective therapy for *S. pneumoniae* infection in Australia.
2. To assess susceptibility to non β-lactam antibiotics and investigate any developing resistance to new fluoroquinolones.
3. Assess changes in resistance patterns over time in comparison to previous *S. pneumoniae* AGAR surveys.

AGAR commenced surveillance of *S. pneumoniae* in 1989.[1] Four similar surveys have been performed in 1994, 1999, 2002[2,3] and 2005[4] although the number of participating laboratories and testing methodologies have changed somewhat over this timeframe.

2.3 Importance of *Streptococcus pneumoniae*

Worldwide *S. pneumoniae* is the commonest bacterium causing pneumonia and meningitis. Invasive pneumococcal infection, (primarily bacteraemia and meningitis), occurs most commonly in young children <5 years of age and older adults ≥65 years of age. Bronchitis and sinusitis in adults and otitis media in children are frequently caused by *S. pneumoniae*, and these conditions are responsible for a significant proportion of the antibiotic prescriptions in the community. Otitis media is a particular problem as few antibiotics reach therapeutic levels in the middle ear particularly when *S. pneumoniae* and other bacterial pathogens have raised MICs. Community antibiotic use, in non-invasive infections is seen as an important driver for selection pressure of emerging resistance. Emergence of multi-drug resistance varies among pneumococcal serotypes and correlates with clonal spread. Subsequent to completion of this survey the 7-valent pneumococcal conjugate vaccine (7vPCV), first introduced in 2001 for children at high risk of invasive pneumococcal disease, was funded for all children as part of the Australian Vaccination Schedule commencing 2005. These surveys, along with serotype studies, will serve as important baselines to monitor changes that may occur in response to introduction of this vaccine.

2.4 Antimicrobials Tested and Resistance

2.4.1 β-lactams

This group of agents are the mainstay of treatment for *S. pneumoniae*, being the drugs of choice both for invasive infections (eg. meningitis), and non-invasive infections (eg. bronchitis, otitis media, sinusitis).[5]

Penicillin: Penicillin testing is used to predict resistance to penicillin, ampicillin and amoxycillin. Susceptibility reporting has conventionally been divided into susceptible (S), intermediate resistant (I) and resistant (R) [in this report intermediate and resistant are classed as non-susceptible (NS)]. In January 2008, the Clinical and Laboratory Standards Institute (CLSI) published new breakpoints for penicillin. The former S, I and R breakpoints (≤0.06, 0.12 – 1, ≥2mg/ L respectively) remain unchanged for patients without meningitis that can be treated with oral penicillin. The new breakpoints (≤2, 4, ≥8mg/L) apply to patients without meningitis that are treated with parenteral penicillin. Breakpoints for patients with meningitis are either susceptible (≤0.06mg/L) or resistant (≥0.12mg/L). For therapeutic use, penicillin and amoxycillin continue to be the preferred agents for infection caused by susceptible *S. pneumoniae*.

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Ceftriaxone/cefotaxime: The third-generation cephalosporin antibiotics are regarded as drugs of choice for pneumococcal meningitis, as attainable spinal fluid levels are approximately tenfold higher than for intravenous penicillin. When strains with raised penicillin MICs are or might be encountered, these β-lactams are often used as therapy for lower respiratory tract infections. However their benefit over penicillin has not been demonstrated for strains of *S. pneumoniae* with penicillin MIC <4 mg/L.[6]

For both ß-lactam classes, antibiotic resistance develops due to mutations to penicillin binding proteins, altering the binding affinity of β-lactam antibiotics. Although resistance to penicillins and cephalosporins may occur differentially, it is usual for MIC changes to increase in parallel, with third generation cephalosporin MIC results frequently only 1-2 dilutions below that of penicillin.

Laboratory definitions for penicillin and third generation cephalosporin resistance[7]:

	Susceptible	Intermediate	Resistant
Penicillin (oral penicillin V)	≤0.06mg/L	0.12 – 1mg/L	≥2mg/L
Penicillin parenteral (Non-meningitis)	≤2mg/L	4mg/L	≥8mg/L
Penicillin parenteral (Meningitis)	≤0.06mg/L	-	≥0.12mg/L
Cefotaxime/ceftriaxone (Non-meningitis)	≤1mg/L	2mg/L	≥4mg/L
Cefotaxime/ceftriaxone (Meningitis)	≤0.5mg/L	1mg/L	≥2mg/L

2.4.2 Other Antimicrobial Classes

Erythromycin and Clindamycin: Erythromycin is a macrolide antibiotic. In vitro, erythromycin is used to test for susceptibility to other macrolides (roxithromycin, clarithromycin) and azalides (azithromycin). In common with lincosamides and streptogramins, (MLS antibiotics) it shares an overlapping binding site on the 23S rRNA portion of the 50S ribosomal subunit. Changes in the target site, eg methylation due to acquisition of erythromycin ribosome methylase (*erm*) genes, result in high-level resistance to all MLS antibiotics (MLS$_B$ phenotype). Lincosamide (clindamycin) resistance may be constitutive or inducible. Inducible resistance is detected by the placement of an erythromycin disc adjacent to a clindamycin disc.

Genes that encode pumps that mediate macrolide efflux (*mef*) do not confer resistance to clindamycin (M phenotype). Resistance due to *ermB* is associated with higher erythromycin MICs (>64 mg/L) than when due to efflux (1-16 mg/L), and with a greater likelihood of failure of macrolide therapy. In bacteraemic patients however any resistance >1mg/L has been associated with failure of macrolide therapy[8]. Erythromycin resistance has co-evolved with penicillin and tetracycline resistance, and cross-resistance to two or more antibiotic classes occurs frequently.

Tetracycline: Tetracycline is used to test for susceptibility to doxycycline and minocycline, the most commonly used tetracycline agents. Until recently only oral tetracyclines have been available for therapy, and use has been primarily in upper respiratory tract infections. Because of discoloration of young teeth, tetracyclines are usually restricted to adults and children over the age of 8 years.

Trimethoprim-sulphamethoxazole: Trimethoprim-sulphamethoxazole (co-trimoxazole) is a folate synthesis (dihydrofolate reductase) inhibitor. This has been used in the past for treatment of *S. pneumoniae* and *H. influenzae* infections, however its use as a respiratory antimicrobial has declined over the past two decades, in part due to its adverse reaction profile and increased *S. pneumoniae* resistance.

Fluoroquinolones: Older generation fluoroquinolones such as ciprofloxacin demonstrate borderline MICs and have not traditionally been recommended for treatment of *S. pneumoniae* infection. Resistance is usually the result of modification

in the genes *gyrA* and *parC*, coding respectively for the target enzymes gyrase and topoisomerase IV. Mutations in *gyrB* and *parE* may also contribute to resistance. In addition an efflux mechanism has been described. The presence of acquired mutations lowers antibiotic affinity. The MICs increase sequentially as numbers of these quinolone resistance determining region (QRDR) mutations accumulate.

Different agents have varying enzyme affinity. The greater difficulty in selecting mutants to newer generation fluoroquinolones, such as moxifloxacin and gatifloxacin, suggests these agents act substantially through both target enzymes and two or three mutations may be required to develop clinical resistance. Clinical use of ciprofloxacin and levofloxacin antibiotics with less activity against *S. pneumoniae* due to lower enzyme affinity, may encourage selection of first step *gyrA* gene mutants, sufficient to result in high-level resistance. Sequential mutations lead to stepwise increases in resistance and cross-resistance to all fluoroquinolones. Unless the MICs of newer quinolones approach breakpoint levels, routine testing of these agents may not detect rising resistance. Because of potential cartilage damage, fluoroquinolone use is usually restricted to adults.

3 Methods

Twenty institutions from the 5 mainland states and the Australian Capital Territory (ACT) participated in the *S. pneumoniae* AGAR survey. Starting 1st September 2007, each laboratory collected up to 100 consecutive significant clinical isolates. Only one isolate per patient was tested. If *S. pneumoniae* was isolated from more than one site, then the isolate from the most significant clinical site was tested. For each isolate the following information was obtained: date of collection, age, sex, specimen site, and inpatient or outpatient status.

3.2 Species Identification

Alpha-haemolytic, optochin sensitive, and/or bile-soluble, Gram-positive cocci were identified as *S. pneumoniae*. Any strain with an optochin zone of inhibition of between 6 and 14mm in CO_2 was tested for bile solubility.

3.3 Susceptibility Testing Methodology

Participating laboratories performed antimicrobial susceptibility tests according to each laboratory's routine standardised methodology[9,10,11] (CLSI or BSAC disc diffusion, Vitek2, agar dilution or Etest).

3.3.1 Disc Tests

Antimicrobials tested included: oxacillin, erythromycin, clindamycin, tetracycline, levofloxacin and trimethoprim-sulphamethoxazole. Clindamycin and erythromycin discs were placed side by side to look for clindamycin inducibility (MLS_B phenotype).

3.3.2 MIC (Etest)

Penicillin and moxifloxacin MICs were determined using Etest® strips. Four hundred and seventy six (99.6%) of the 478 isolates with an MIC >0.06 mg/L were also tested with either a ceftriaxone or cefotaxime Etest® strip.

3.4 Quality Control

S. pneumoniae ATCC 49619 was the quality control strain for this survey.

3.5 Statistical Analysis

P values were calculated using Fisher's exact test (GraphPad® Prism Software).

4 Demographics

Both public (18) and private laboratories (2) participated in the study. Participants included New South Wales (6), Australian Capital Territory (1), Queensland (4), South Australia (3) Victoria (3) and Western Australia (3). There were 1,831 isolates from 20 institutions (Table 1). Isolates from New South Wales and Australian Capital Territory were combined.

The ages of patients reflect the incidence of *S. pneumoniae* infection, with 21.8% of patients below age 5, and 28.0% in the elderly age group ≥ 65 years) (Table 2). 881 (48.1%) of the patients were classified as hospital inpatients at time of collection, 899 (49.1%) were outpatients. Hospitalisation status was not available on 51 (2.8%).

4.2 Regional Source of Isolates

Table 1. Isolates by Region

Region	Number of Institutions	Total	%
New South Wales (NSW) Australian Capital Territory (ACT)	7	594	32.4
Queensland (Qld)	4	378	20.6
South Australia (SA)	3	291	15.9
Victoria (Vic)	3	284	15.5
Western Australia (WA)	3	284	15.5
Total	**20**	**1831**	**100**

4.3 Age

Table 2. Age of Patients

Age Range (years)	n	%
<2	283	15.5
2-4	116	6.3
5-14	102	5.6
15-29	159	8.7
30-64	658	35.9
≥65	513	28.0
Total	**1831**	**100**

5   Specimen Source

The majority of isolates (57.5%) were from the respiratory tract (Table 3). Invasive isolates (blood, CSF and sterile body cavity) accounted for 18.3% of the collection. Other common sites of isolation were from eye and ear specimens.

Table 3. Source of Isolates

Specimen Source	n	%
Respiratory	1053	57.5
Blood	312	17.0
Eye	187	10.2
Ear	170	9.3
Skin and soft tissue infection	41	2.2
Sinus	31	1.7
Urine	12	0.7
CSF	12	0.7
Sterile Body Cavity	11	0.6
Unknown	2	0.1
Total	**1831**	
Invasive	335	18.3
Non-Invasive	1494	81.6
Not Specified	2	0.1

6 Susceptibility Testing Results: 2007 Study

6.2 Penicillin

In this report, the combined penicillin intermediate and resistant categories are referred to as non-susceptible (NS). For the purposes of determining antibiograms and multi-resistance, NS has been treated as resistant. Overall 2.0% of isolates were penicillin NS using the parenteral breakpoints (Table 4). Higher rates were detected in NSW/ACT (3.7%): more than double that detected in Queensland which had the second highest rate at 1.6%. Differences between the regions reached significance when NSW/ACT was compared with Victoria and WA (p=0.002 and p=0.029 respectively).

Overall, there was a higher rate of non-susceptibility detected in non-invasive isolates compared with invasive isolates, although this did not reach statistical significance. One in three of the CSF isolates and almost one in five of the blood isolates were NS using the meningococcal breakpoints (Table 6).

Although penicillin non-susceptibility was higher in patients aged 65 or older, this did not reach statistical significance.

The highest penicillin MIC in this survey was 8mg/L. Isolated from the blood of an adult in NSW, the isolate was multi-resistant and belonged to serotype 19F.

Figures 2, 3 and 4 document trends in penicillin non-susceptibility between 1989 and 2007. Penicillin non-susceptibility increased from 1989 to 2005 albeit at a slow rate. Strains with a penicillin MIC >2mg/L were largely absent from the 1989 and 1994 surveys (0.0% and 0.1% respectively), reaching just over 1% in the 1999 and 2002 surveys and reaching a high of 3.3% in the 2005 survey. A significant (p=0.0148) decrease to 2.0% was observed in this survey. This was due to a decrease in the number of NS strains in non-invasive isolates. Rates of non-susceptibility in the invasive strains have remained constant at approximately 1% since 2002.

Table 4. Percentage and number of all isolates categorised as susceptible, intermediate and resistant by region (parenteral nonmeningitis breakpoints)

Region	S (≤2mg/L)	I (4mg/L)	R (≥8mg/L)
NSW/ACT	96.3% (572)	3.5% (21)	0.2% (1)
Qld	98.4% (372)	1.6% (6)	0% (0)
SA	98.6% (287)	1.4% (4)	0% (0)
Vic	99.6% (283)	0.4% (1)	0% (0)
WA	98.9% (281)	1.1% (3)	0% (0)
Aus	98.0% (1795)	1.9% (35)	0.1% (1)

Table 5. Percentage and number of isolates categorised as susceptible, intermediate and resistant by specimen type (parenteral nonmeningitis breakpoints)

Specimen	S (≤2mg/L)	I (4mg/L)	R (≥8mg/L)
Respiratory and sinus	97.4% (1056)	2.6% (28)	0% (0)
Blood and other sterile sites	99.1% (332)	0.6% (2)	0.3% (1)
Other	98.8% (405)	1.2% (5)	0% (0)
Unknown	100% (2)	0% (0)	0% (0)
Total	98.0% (1795)	1.9% (35)	0.1% (1)

Table 6. Percentage and number of CSF and blood categorised as susceptible, intermediate and resistant (parenteral meningitis breakpoints)

Specimen	S (≤0.06mg/L)	R (≥0.12mg/L)
Blood	80.8% (252)	19.2% (60)
CSF	66.7% (8)	33.3% (4)
Total	80.2% (260)	19.8% (64)

Table 7. Percentage and number of isolates categorised as susceptible, intermediate and resistant by specimen type (oral penicillin breakpoints)

Specimen	S (≤0.06mg/L)	I (0.12-1mg/L)	R (≥2mg/L)
Invasive	80.3% (269)	17.0% (57)	2.7% (9)
Non-invasive	72.6% (1084)	18.3% (274)	9.1% (136)
Unknown	0.0% (0)	100% (2)	0.0% (0)
Total	73.9% (1353)	18.2% (333)	7.9% (145)

Table 8. Percentage and number of isolates categorised as susceptible, intermediate and resistant by age range (parenteral nonmeningitis breakpoints)

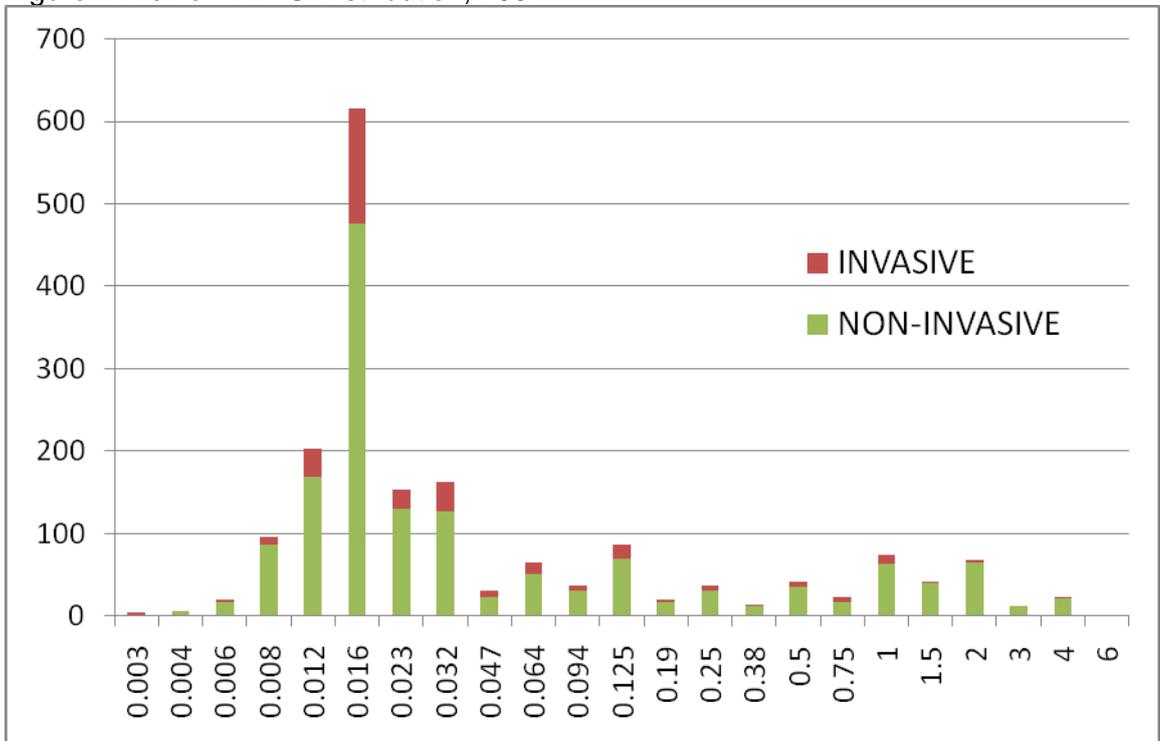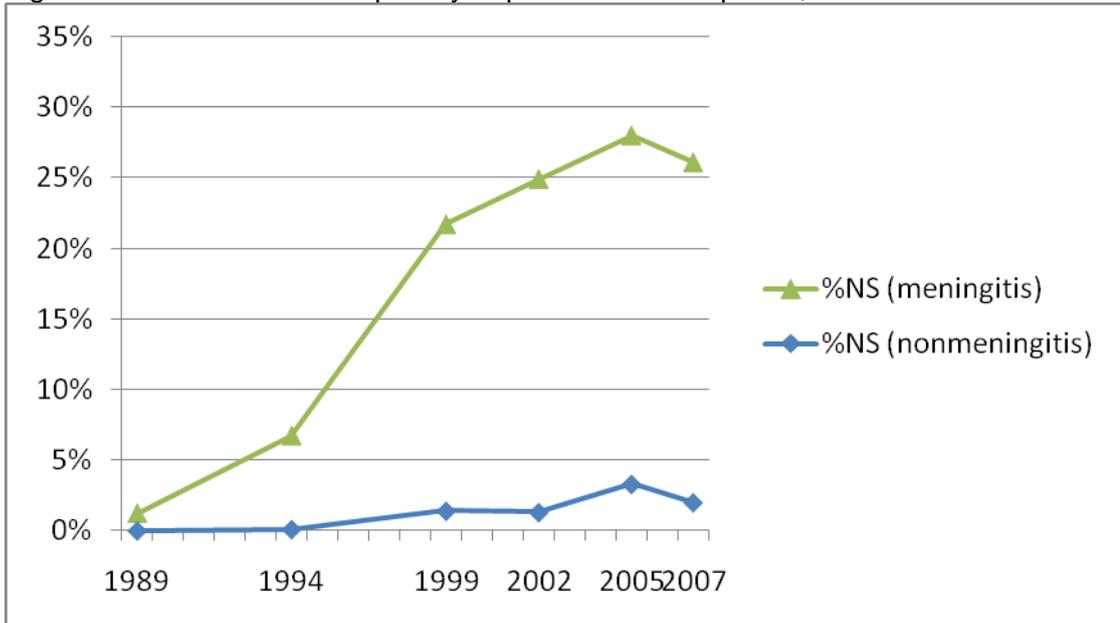| Age	S (MIC ≤2mg/L)	I (MIC 4mg/L)	R (MIC ≥8mg/L)
<5 years	98.5% (393)	1.5% (6)	0% (0)
5-64 years	98.3% (903)	1.6% (15)	0.1% (1)
≥65 years	97.3% (499)	2.7% (14)	0% (0)

Figure 1. Penicillin MIC Distribution, 2007

Figure 2. Percent non-susceptibility to parenteral breakpoints, all isolates 1989 to 2007

1989: n=1822, 1994: n=2385, 1999: n=1548, 2002: n=1009, 2005: n=1776, 2007: n=1831

Figure 3. Percent non-susceptibility to parenteral breakpoints, invasive isolates 1989 to 2007
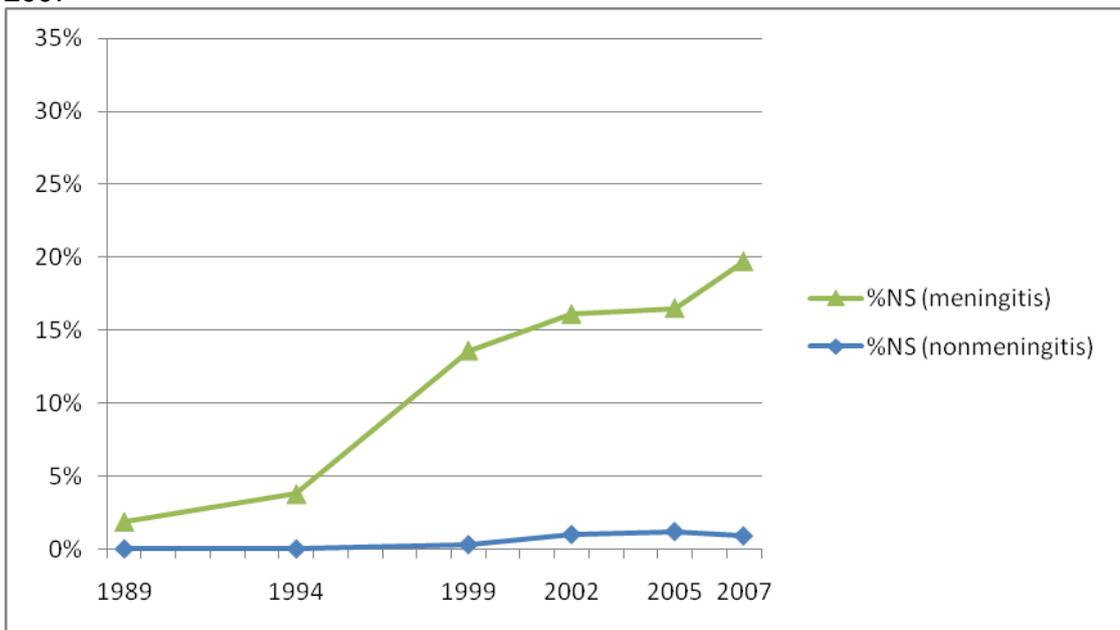
1989: n=105, 1994: n=509, 1999: n=381, 2002: n=291, 2005: n=347, 2009: n=335

Figure 4: Percent non-susceptibility to parenteral breakpoints, non-invasive isolates 1989 to 2007
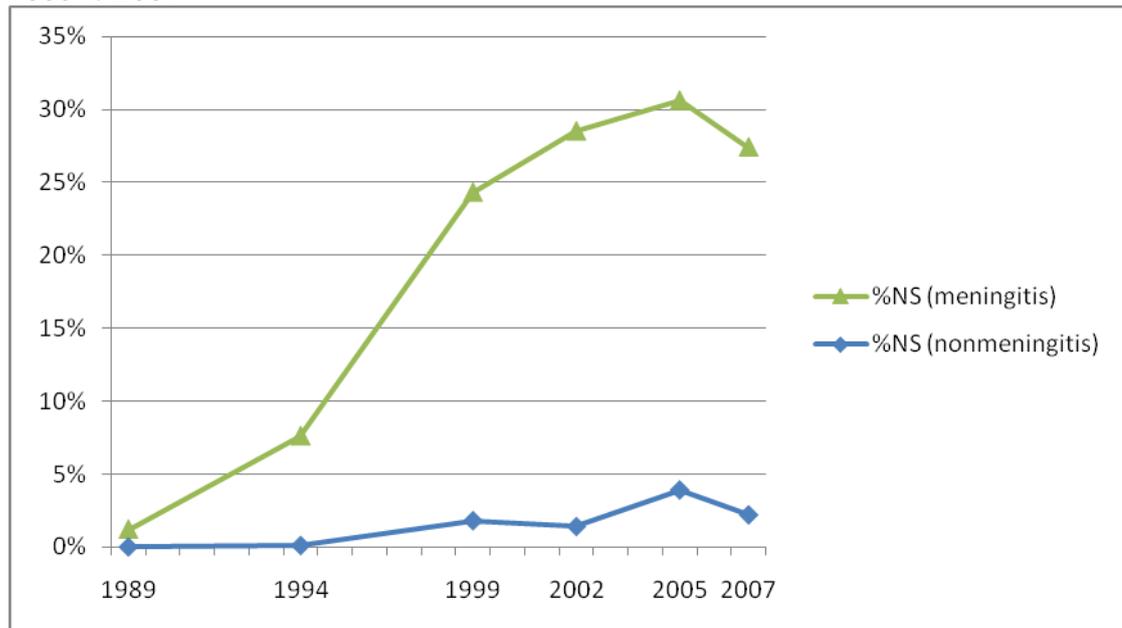
1989: n=1702, 1994: n=1858, 1999: n=1167, 2002: n=718, 2005: n=1420, 2007: n=1494

6.3 Cefotaxime/Ceftriaxone

Cefotaxime or ceftriaxone MIC was determined on 476 (99.6%) of penicillin isolates with an MIC >0.06mg/L. Non-susceptibility to the third generation cephalosporins was present in 12.0% of those strains tested (Figure 4). As the cephalosporin intermediate and resistant breakpoints are set at a higher level, compared with penicillin, a reading of overall proportion does not accurately reflect relationship between β-lactam MICs. Figure 5 confirms that for a majority of isolates, cephalosporin MICs present a similar distribution, one to two dilutions below that of penicillin. Of 57 cefotaxime/ceftriaxone NS isolates (MICs >1 mg/L), one was also resistant to penicillin (8 mg/L), and 21 had intermediate resistance. Two of the 12 CSF samples were ceftriaxone NS using the lower (<0.5 mg/L) meningitis breakpoint. Both isolates were also penicillin resistant.

Figure 4. Cefotaxime or Ceftriaxone MIC Distribution for 476 isolates with a penicillin MIC >0.06 mg/L
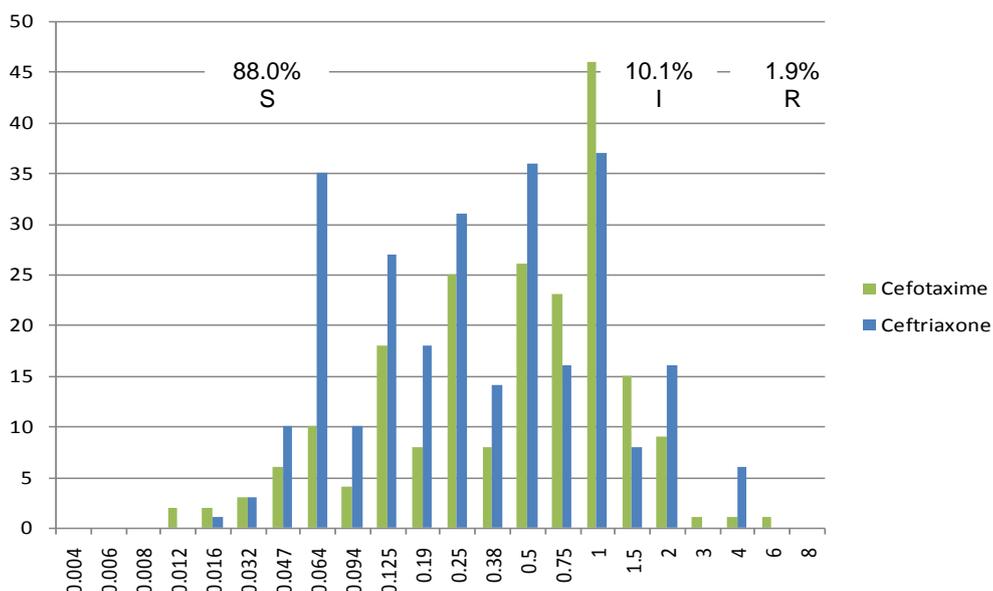
Cefotaxime/ceftriaxone non-meningitis breakpoints: Susceptible ≤1mg/L; Intermediate resistance MIC 2mg/L, Resistant MIC ≥4mg/L.

Figure 5. Penicillin, cefotaxime and ceftriaxone MIC distribution (where penicillin MIC >0.06mg/L)
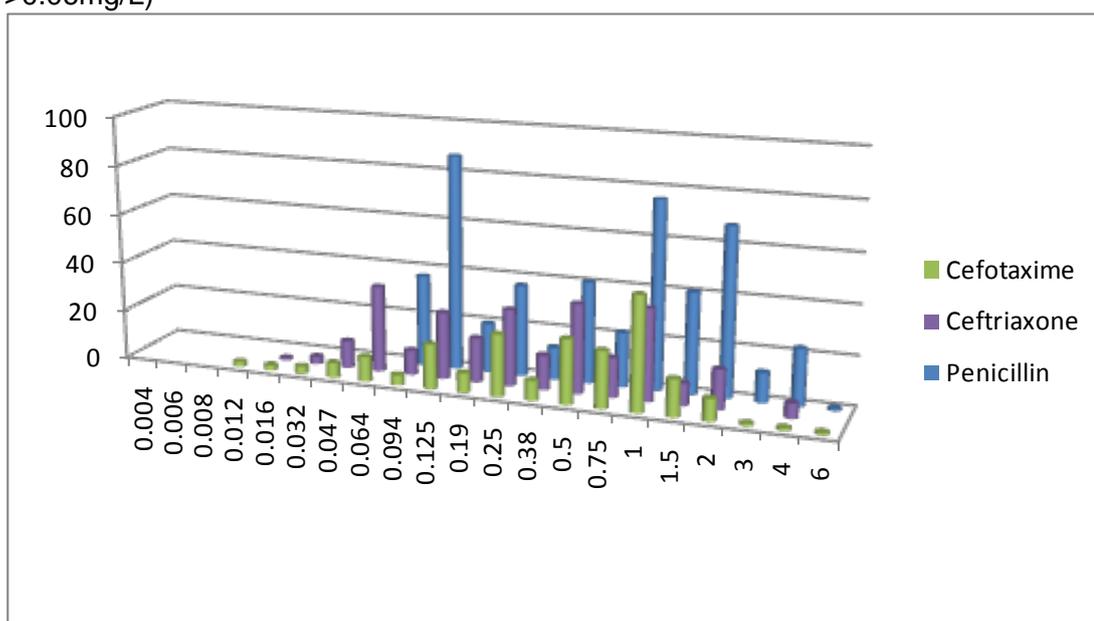
Table 9 : Ceftriaxone MICs

Penicillin	Ceftriaxone			Total
	S (≤1 mg/L)	I (2 mg/L)	R (≥4 mg/L)	
I (4 mg/L)	9 (39.1%)	10 (43.5%)	4 (17.4%)	23
R (≥8 mg/L)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0
	9	10	4	23

Table 10: Cefotaxime MICs

Penicillin	Cefotaxime			Total
	S (≤1 mg/L)	I (2 mg/L)	R (≥4 mg/L)	
I (4 mg/L)	5 (41.7%)	6 (50.0%)	1 (8.3%)	12
R (≥8 mg/L)	0 (0.0%)	0 (0.0%)	3 (100%)	3
	5	6	4	15

6.4 Erythromycin and Clindamycin

Erythromycin (macrolide) resistance was detected in 20.4% of isolates overall (Table 11). Resistance was significantly higher (p=0.001) in non-invasive (21.7%) compared with invasive strains (13.9%). The highest rates of resistance in invasive and non-invasive strains were seen in Queensland with rates of 28.9% and 29.1% respectively. The lowest rate of resistance for both invasive and non-invasive isolates was in WA (6.5% and 11.9% respectively). Resistance was lowest among the young and increased with age (Table 12).

Erythromycin resistance increased sharply from 1994 (8.7%) to 2002 (21.6%) but has decreased over the last two survey periods for invasive isolates. Rates were steady

between 2002 and 2005 for non-invasive isolates and fell to 21.7% in this survey (Figure 6).

Clindamycin resistance overall was 15.4% but there were significant differences between regions. Whereas WA and SA had rates below 11%, Queensland had 23.0% which was significantly higher than the Australian average (p=0.0006). A presumptive assessment of resistance genotype was made based on clindamycin resistance and the clindamycin disc induction test among erythromycin resistant isolates (Table 14). Of 343 erythromycin resistant isolates, 240 (70.0%) had a MLS$_B$ constitutive resistant phenotype and 10 (2.9%) had inducible resistance. These results suggest the presence of an *ermB* mechanism of resistance, associated with higher erythromycin MICs than when due to efflux, in 72.9% of Australian macrolide resistant isolates. All clindamycin resistant isolates were also resistant to the macrolides.

Table 11: Erythromycin resistance: Number Resistant/Total Tested (%).

	NSW/ACT	Qld	SA	Vic	WA	Aus
All	132/594 **(22.2%)**	110/378 **(29.1%)**	45/277 **(16.2%)**	52/284 **(18.3%)**	32/284 **(11.3%)**	371/1817 **(20.4%)**
Invasive	21/147 **(14.3%)**	13/45 **(28.9%)**	3/39 **(7.7%)**	6/61 **(9.8%)**	2/31 **(6.5%)**	45/323 **(13.9%)**
Non-invasive	109/445 **(24.5%)**	97/333 **(29.1%)**	42/238 **(17.6%)**	46/223 **(20.6%)**	30/253 **(11.9%)**	324/1492 **(21.7%)**

Table 12: Erythromycin resistance by age range: Number resistant/total tested (%).

Age Range			Significance of Results		
<5yo	5-64	≥65	Between <5 and 5-64	Between 5-64 and ≥65	Between <5 and ≥65
55/394 (14.0%)	186/912 (20.4%)	130/511 (25.4%)	p=0.0064	p=0.0333	p<0.0001

Figure 6: AGAR surveys 1994 – 2007: Trends in erythromycin resistance
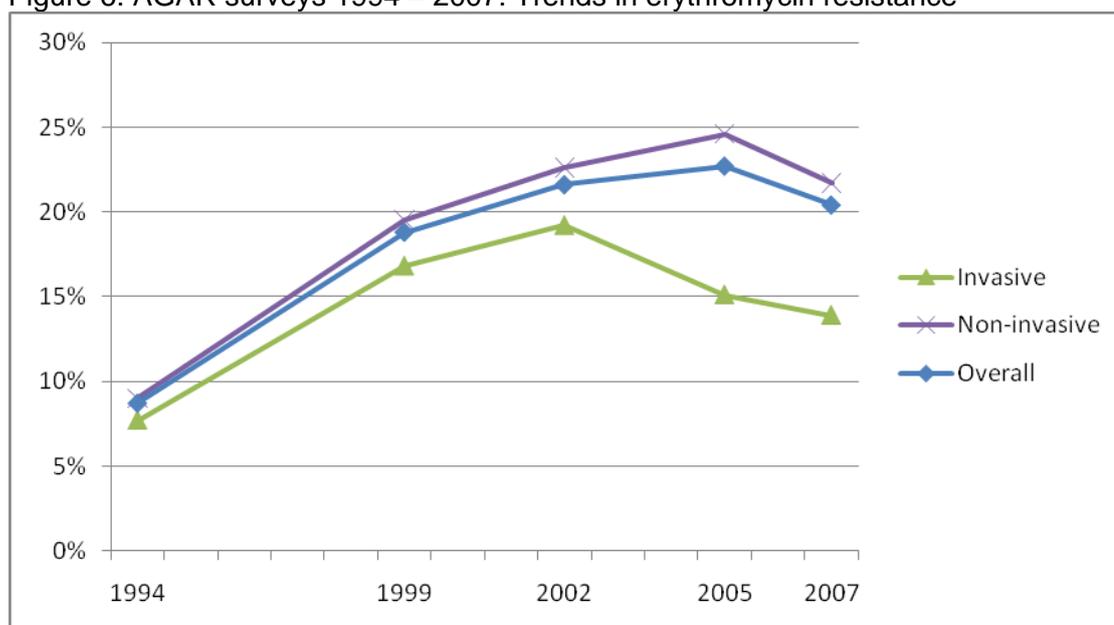
1994: Invasive n=505, non-invasive n=1858, overall n=2381. 1999: Invasive n=380, non-invasive n=1172, overall n=1552. 2002: Invasive n=312, non-invasive n=774, overall n=1086. 2005: Invasive n=347, non-invasive n=1420, overall n=1776. 2007: Invasive n=323, non-invasive n=1492, overall n=1817.

Table 13: Clindamycin resistance: Number Resistant/Total Tested (%).

	NSW/ACT	Qld	SA	Vic	WA	Aus
All	90/501 **(18.0%)**	87/378 **(23.0%)**	28/272 **(10.3%)**	23/184 **(12.5%)**	21/284 **(7.4%)**	249/1619 **(15.4%)**
Invasive	11/115 **(9.6%)**	12/45 **(26.7%)**	1/38 **(2.6%)**	1/35 **(2.9%)**	1/31 **(3.2%)**	26/264 **(9.8%)**
Non-invasive	78/384 **(20.3%)**	75/333 **(22.5%)**	27/234 **(11.5%)**	22/149 **(14.8%)**	20/253 **(7.9%)**	222/1353 **(16.4%)**

6.5 Clindamycin Genotype

Table 14: Presumptive genotype of erythromycin resistant strains

	Erythromycin R	%	Presumptive genotype
Clindamycin S	93	27.1%	*mef*
Clindamycin inducible resistance	10	2.9%	*erm*
Clindamycin R	240	70.0%	*erm*

6.6 Tetracycline

Tetracycline resistance among non-invasive (18.4%) and invasive (14.2%) strains was not significantly different. As with macrolide resistance, tetracycline resistance was lowest in WA and highest in Queensland. Rates for Queensland were significantly higher than the Australian average for both invasive and non-invasive strains (p=0.0169 and 0.0315 respectively). As for the macrolides, resistance increased with age. Tetracycline resistance increased from 1994-1999, all of the change being seen in non-invasive isolates (Figure 7). Resistance in invasive strains increased from 6.3% in 2005

to 14.2% in this survey (p=0.0008). All the change can be accounted for by the increase seen in two regions: NSW/ACT and Queensland. Resistance in NSW/ACT increased from 7.5% in 2005 to 17.0% in 2007 (p=0.0135) and resistance in Queensland increased from 7.5% in 2005 to 28.9% in 2007 (p=0.0135). No significant change in tetracycline resistance was demonstrated in non-invasive strains since 1999.

Table 15: Tetracycline resistance: Number Resistant/Total Tested (%).

	NSW/ACT	Qld	SA	Vic	WA	Aus
All	126/593 **(21.2%)**	92/378 **(24.3%)**	38/278 **(13.7%)**	43/284 **(15.1%)**	23/284 **(8.1%)**	322/1817 **(17.7%)**
Invasive	25/147 **(17.0%)**	13/45 **(28.9%)**	3/40 **(7.5%)**	4/61 **(6.6%)**	1/31 **(3.2%)**	46/324 **(14.2%)**
Non-invasive	99/444 **(22.3%)**	79/333 **(23.7%)**	35/238 **(14.7%)**	39/223 **(17.5%)**	22/253 **(8.7%)**	274/1491 **(18.4%)**

Table 16: Tetracycline resistance by age range: Number resistant/total tested (%).

Age Range			Significance of Results		
<5yo	5-64	>65	Between <5 and 5-64	Between 5-64 and >65	Between <5 and >65
57/394 (14.5%)	153/912 (16.8%)	112/511 (21.9%)	NS	p=0.0191	p=0.0045

Figure 7: AGAR surveys 1994 – 2007: Trends in tetracycline resistance
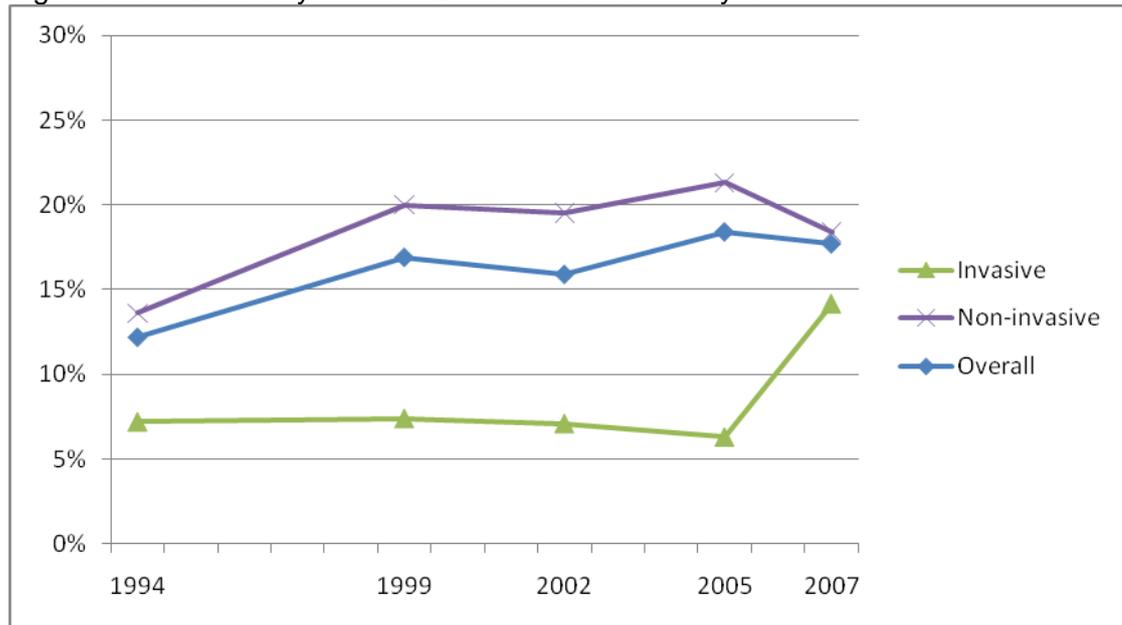
1994: Invasive n=402, non-invasive n=1582, overall n=2000. 1999: Invasive n=379, non-invasive n=1167, overall n=1546. 2002: Invasive n=312, non-invasive n=774, overall n=1086. 2005: Invasive n=347, non-invasive n=1419, overall n=1775. 2007: Invasive n=324, non-invasive n=1491, overall n=1817.

6.7 Trimethoprim-sulphamethoxazole

Trimethoprim-sulphamethoxazole (TMP-SMX) resistance was 28.0% overall with higher rates seen in non-invasive (28.8%) compared to invasive (23.5%) isolates although this did not reach statistical significance. Over time, resistance has decreased in both non-invasive (37.1% in 1994 to 28.8% in 2007, $p < 0.0001$) and invasive strains (34.5% in 1994 to 23.5% in 2007, $p < 0.0001$). Nonetheless, high rates of resistance limit the use of TMP-SMX in infections caused by *S. pneumoniae* (Table 17).

Table 17: Trimethoprim-sulphamethoxazole resistance: Number Resistant/Total Tested (%).

	NSW/ACT	Qld	SA	Vic	WA	Aus
All	188/594 **(31.6%)**	117/378 **(31.0%)**	70/276 **(25.4%)**	74/284 **(26.1%)**	59/384 **(20.8%)**	508/1816 **(28.0%)**
Invasive	37/147 **(25.2%)**	13/45 **(28.9%)**	7/39 **(17.9%)**	12/61 **(19.7%)**	7/31 **(22.6%)**	76/323 **(23.5%)**
Non-invasive	149/445 **(33.5%)**	104/333 **(31.2%)**	63/237 **(26.6%)**	62/223 **(27.8%)**	52/253 **(20.6%)**	430/1491 **(28.8%)**

Table 18: Trimethoprim-sulphametoxazole resistance by age range: Number resistant/total tested (%).

Age Range			Significance of Results		
<5yo	5-64	>65	Between <5 and 5-64	Between 5-64 and >65	Between <5 and >65
109/394 (27.7%)	231/912 (25.3%)	168/510 (32.9%)	NS	p=0.0025	p=0.0945

Figure 8: AGAR surveys 1994 – 2007: Trends in trimethoprim-sulphamethoxazole resistance
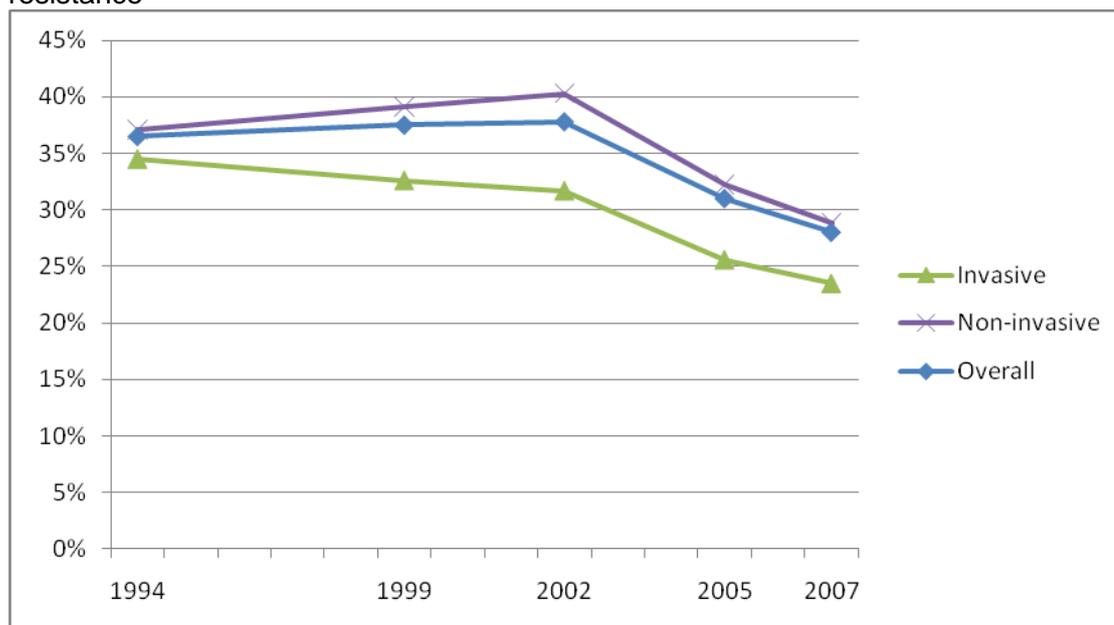
1994: Invasive n=440, non-invasive n=1630, overall n=2088. 1999: Invasive n=380, non-invasive n=1171, overall n=1551. 2002: Invasive n=312, non-invasive n=774, overall n=1086. 2005: Invasive n=347, non-invasive n=1419, overall n=1775. 2007: Invasive n=323, non-invasive n=1491, overall n=1816.

6.8 Fluoroquinolones

In 2007 fluoroquinolone resistance remains uncommon in Australia. By disc testing, levofloxacin resistance was detected in only eight of 1740 (0.5%) isolates tested. Intermediate resistance to levofloxacin was detected in another two isolates (Table 19). All ten were non-invasive isolates and were detected in Queensland (4), NSW (3), Victoria (2) and South Australia (1). Moxifloxacin resistance was present in four of the 1814 (0.2%) isolates tested. No isolates were detected with intermediate resistance. We are unable to confirm whether moxifloxacin resistance in these patients was acquired after pre-treatment with fluoroquinolones or if they had recently been overseas.

6.8.1 Levofloxacin

Table 19: Levofloxacin non-susceptibility (NS): Number NS/Total Tested (%).

	NSW/ACT	Qld	SA	Vic	WA	Aus
All	3/594 (0.5%)	4/378 (1.1%)	1/200 (0.5%)	2/284 (0.7%)	0/284 (0%)	10/1740 (0.6%)
Invasive	0/147 (0%)	0/45 (0%)	0/12 (0%)	0/61 (0%)	0/31 (0%)	0/296 (0%)
Non-invasive	3/445 (0.7%)	4/333 (1.2%)	1/188 (0.5%)	2/223 (0.9%)	0/253 (0%)	10/1442 (0.7%)

6.8.2 Moxifloxacin

Table 20: Moxifloxacin resistance: Number Resistant/Total Tested (%).

	NSW/ACT	Qld	SA	Vic	WA	Aus
All	2/594 (0.3%)	2/378 (0.5%)	0/274 (0%)	0/284 (0%)	0/284 (0%)	4/1814 (0.2%)
Invasive	0/147 (0 %)	0/45 (0%)	0/39 (0%)	0/61 (0%)	0/31 (0%)	0/323 (0%)
Non-invasive	2/445 (0.4%)	2/333 (0.6%)	0/235 (0%)	0/223 (0%)	0/253 (0%)	4/1489 (0.3%)

Figure 9: Moxifloxacin MIC Distribution
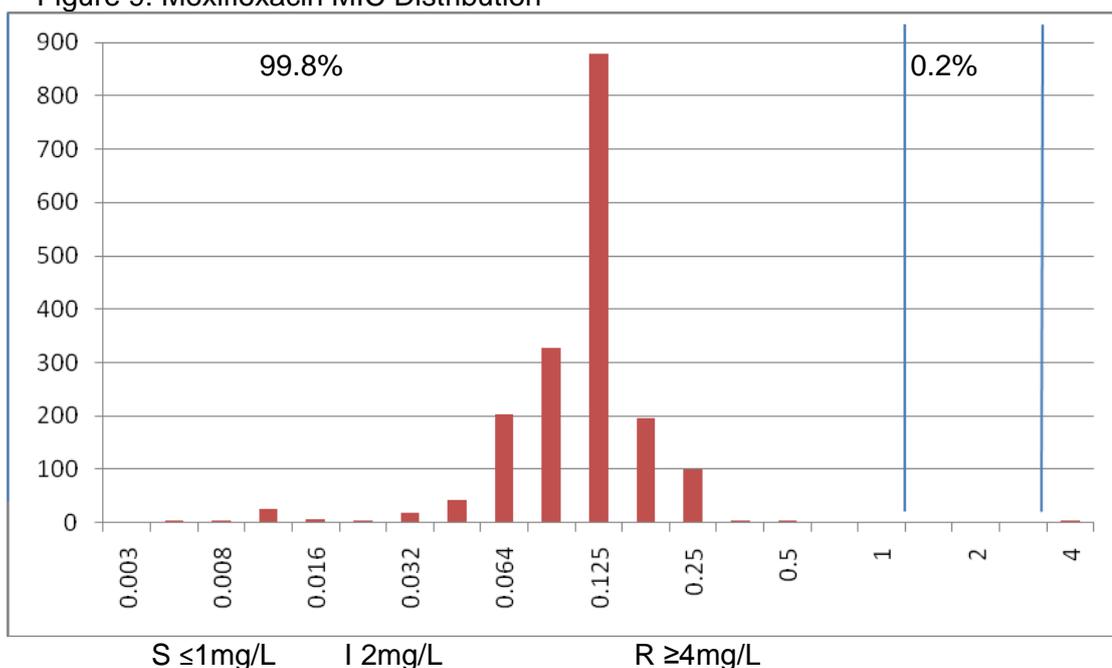
6.9 Resistance Rates – Invasiveness and Hospitalisation Status

Table 21 compares the difference in resistance rates for invasive and non-invasive isolates for all antibiotics, other than the fluoroquinolones. For all antibiotics except trimethoprim-sulphamethoxazole there are statistically significant higher levels of resistance among inpatient isolates compared with outpatient isolates. For erythromycin and clindamycin there are statistically significant higher levels of resistance in non-invasive isolates compared with invasive isolates.

Table 21: Proportion of resistant isolates Australia-wide by source and hospitalisation

Antibiotic	Inpatient	Outpatient	Invasive	Non-invasive
Penicillin (I+R)	2.8%*	1.2%	0.9%	2.2%
Erythromycin	24.7%**	16.7%	13.9%	21.7%**
Clindamycin	18.4%**	13.2%	9.8%	16.4%**
Tetracycline	20.5%**	15.4%	14.2%	18.4%
Trimethoprim-sulphamethoxazole	30.1%	26.4%	23.5%	28.8%

*p<0.05
**p<0.01

7 Multi-resistance

The most problematic strains of *S. pneumoniae* are those with multiple acquired resistances. Although there is no agreed benchmark for the definition of multi-resistance in *S. pneumoniae*, we have chosen acquired resistance to > 2 drug classes to define multi-resistance in this survey. NSW/ACT and Queensland have significantly more multi-resistant strains than SA, Victoria or WA (p<0.05). Multi-resistance was more common in the elderly (≥65 years) than in the <5 years or 5-64 year age groups (p=0.0002 and p=0.0034 respectively; data not shown).

Table 22: Multi-resistance in *S. pneumoniae*

		Non-multiresistant				Multi-resistant			
Region	No	0	1	2	%	3	4	5	%
NSW/ACT	593	362	97	50	85.8%	65	18	1	14.2%
Qld	378	220	49	50	84.4%	54	5		15.6%
SA	200	140	34	8	91.0%	15	3		9.0%
Vic	284	188	46	26	91.6%	22	2		8.4%
WA	284	211	46	13	95.1%	10	4		4.9%
Australia	1739	1121	272	147	88.6%	166	32	1	11.4%
Invasive	296	197	56	29	95.3%	9	5		4.7%
Non-invasive	1441	924	216	118	87.3%	155	27	1	12.7%

Antibiotics included: penicillin (intermediate or resistant); erythromycin, tetracycline, trimethoprim-sulphamethoxazole, levofloxacin (intermediate or resistant). Only isolates with complete antimicrobial results included in table. Antibiotics excluded: clindamycin, cefotaxime, ceftriaxone.

8 Serotypes

Serotyping was not a requirement for this survey however a small subset of 149 (8.1%) isolates were serotyped as part of the laboratories' routine testing (Table 23). Although 31 serotypes were reported just over half (50.3%) belonged to just four serotypes: 19A (33), 19F (16), 22F (15) and 3 (11). Of the common serotypes, 19A and 19F were multi-resistant. 19F had the highest penicillin non-susceptibility with 22% of strains having a penicillin MIC >2mg/L. Two of the 28 isolates serotypes from children aged <5 years were of a type covered by the PCV7 vaccine (18C and 19F).

Table 23: Serotype of selected isolates

Serotype	NSW/ACT	Qld	SA	Vic	Aus
19A	16	10	4	3	33
19F	7	8		1	16
22F	6	3	1	5	15
3	8	2		1	11
23F	5	1		1	7
9V	4	2		1	7
6A	2	3		1	6
18C	4	1		1	6
6B	4	1			5
7F	1			3	4
4	2		1	1	4
11A	3				3
8	1	1		1	3
14	1			2	3
9N	2			1	3
Other	16	1	2	4	23
Total tested	82	33	8	26	149

9 Limitations of the Study

There have been changes in participating laboratories in the AGAR *S. pneumoniae* surveys over time from 1989 through to 2007 with the more recent inclusion of a number of private pathology laboratories.

10 Discussion

Internationally changes in susceptibility in *S. pneumoniae* have evolved rapidly in the past two decades for both β-lactam and other antibiotic classes, with potential to compromise treatment efficacy. Susceptibility rates have varied widely according to reporting countries, clinical site of infection (eg. invasive versus non-invasive infection), and according to pneumococcal serotype. Timely national surveillance studies that examine trends in antimicrobial resistance are essential for the formulation of appropriate, and up to date evidence-based therapeutic guidelines and in monitoring their ongoing relevance. This has implications for prescribing in situations where *S. pneumoniae* remains the major pathogen; primarily community acquired lower respiratory tract infections and upper respiratory tract infections, including sinusitis and otitis media, as well as the empiric treatment of community acquired meningitis. The Australian Group for Antimicrobial Resistance (AGAR), a network of Australian laboratories, has conducted studies in 1989, 1994, 1999, 2002, 2005 and 2007 to monitor changes in *S. pneumoniae* susceptibility.

In this article we report on the results of the 2007 survey conducted by 20 laboratories nationally. We have also briefly summarised overall trends in susceptibility compared to previous AGAR studies.

The slow increase in the rate of isolates with a penicillin MIC >2mg/L has reversed in this survey. In the current survey 2.0% of strains tested as non-susceptible, compared with 3.3% in 2005. Only one isolate had an MIC of >4mg/l (8mg/L). Isolated from an adult with bacteraemia, the isolate was serotype 19F, a so-called 'paediatric serotype', a multi-resistant clone that is commonly penicillin non-susceptible. Rates of penicillin non-susceptible pneumococcus (PNSP, MIC >0.06mg/L) in this study mirror those of the Australian isolates in the PROTEKT study (25.6%)[12]. Australia has lower rates than many countries in Asia (Hong Kong, Japan, Taiwan) where rates over 60% were recorded but less than some European countries (Austria, Germany, The Netherlands) where rates of PNSP are less than 10%. Prior antibiotic use, age

less than five years and attendance at day care centres were risk factors for colonisation with PNSP[13].

As has been noted previously, in 2007 higher rates of resistance were seen in strains causing non-invasive infection compared to invasive infection. This may be due to a number of contributing factors, including the differing serotypes that are involved in invasive and bloodstream infections and the selective pressure of frequent antibiotic use in upper respiratory tract and otic infections. As observed worldwide, such antimicrobial use appears to be the major factor involved in development of antibiotic resistance in *S. pneumoniae*. Cephalosporin, macrolide and more recently fluoroquinolone usage data have been linked with corresponding rises in penicillin, erythromycin and quinolone resistance respectively, and in multidrug resistance overall.

The changes in resistance rates should have little impact on empiric β-lactam therapy except for empiric therapy for meningitis. In non-invasive pneumococcal infection in Australia, the currently recommended antibiotic of choice for oral therapy is amoxycillin.[5] When higher doses are employed, amoxycillin achieves adequate tissue levels and is active against penicillin-intermediate strains. These ongoing changes require continuing observation but amoxycillin prescribed at the upper dosing range, still continues to be appropriate therapy for the vast majority of non-invasive infections occurring in Australia.

Similarly, for non-meningeal therapy, parenteral penicillin provides adequate levels for *S. pneumoniae* isolates encountered in Australia in the current survey. Third generation cephalosporins in combination with vancomycin are recommended as empiric therapy for meningitis.[5] Changes in therapy can be instituted once the MIC is available (usually about 48 hours after patient presentation). When isolates have cefotaxime or ceftriaxone MIC's ≥ 2 mg/L, cephalosporins may be less effective, leading to selection of alternate or combination drug therapy. In the 2007 study, one CSF isolate had an MIC of 2mg/L to ceftriaxone.

In 2007 erythromycin resistance was documented in 20.4% of isolates, a similar figure to previous AGAR surveys back to 1999. Of 343 erythromycin resistant isolates, 250 (72.9%) had a MLS_B phenotype suggestive of an *ermB* resistance mechanism, and associated with high level erythromycin resistance. This is consistent with published Australian data[14,15,16] and similar to European data for macrolide resistance, in which *ermB* resistance predominates. It differs to data from the USA[17,18] where up to 72% of macrolide resistance in the US was on the basis of macrolide efflux (*mef*) and in which macrolides may still be considered in some non-invasive infections. However it has now been clearly documented that there is an association between macrolide resistance and therapeutic failures in bacteraemic *S. pneumoniae* infection even when resistance is mediated by a macrolide efflux pump (*mef*) and MICs are lower (often between 1 to 16 µg/ml).[9,19] The AGAR study data suggests that if macrolides were used as sole empiric therapy for *S. pneumoniae* respiratory tract infections, many of these isolates (21.7% of non-invasive strains) are unlikely to respond to this class of antibiotics. The current Australian Antibiotic Guidelines[5] do not recommend macrolides as sole empiric therapy associated with otitis media, sinusitis, acute exacerbations of chronic bronchitis or as empiric therapy for community acquired pneumonia.

Tetracycline resistance in Queensland (24.3%) and NSW/ACT (21.2%) was significantly higher than for the other Australian states. This was particularly true for invasive isolates and the reason for this is unclear. It is possible that multidrug resistant serotypes such as 19A and 19F are more common in these two regions.

A fall in resistance was demonstrated for trimethoprim-sulphamethoxazole which has fallen from 36.5% in 1994 to 28.0% in 2007. Whilst it is not recommended in empiric therapy of respiratory tract infection, the fall may reflect the reduction in antibiotic pressure due to a decline in prescribing of this drug in the community. It is notable that the tetracycline and folate synthesis inhibitor drugs were the two classes of antibiotics to show significant reduction in community prescribing over the past 14 years, 53% and 54% reduction respectively (unpublished data).[20]

The new "respiratory" fluoroquinolones, such as moxifloxacin are valuable drugs for the therapy of *S. pneumoniae* infections, particularly for infection by multi-drug resistant strains. However in countries where fluoroquinolones (particularly levofloxacin) have been used widely for respiratory tract infections, rising resistance levels are seen. Levels of 14% have been measured for levofloxacin in Hong Kong.[21] In some regions of France resistance levels of 3%

to levofloxacin have been observed[22]. In Europe and Canada a clear relationship is documented between the levels of fluoroquinolone use and rising resistance rates.[23,24,25] As for macrolides, quinolone resistance has been linked to failure of pneumonia therapy.[26] Because of the recent introduction of the new fluoroquinolones into clinical use, AGAR commenced an evaluation of resistance rates in 2005 using levofloxacin discs and moxifloxacin Etest MIC testing to detect early development of resistance. The results from the 2005 and 2007 surveys demonstrated extremely low levels of resistance. In 2005 only 2 of 1776 (0.1%) isolates tested and in 2007 4 of 1814 (0.2%) isolates were resistant to moxifloxacin. The low fluoroquinolone resistance levels are likely to be related to the relatively low volumes of these drugs that have so far been used in Australia, because of restrictions placed on their use (eg the need for an Authority prescription in the community and restricted formularies in most public hospitals). Australian guidelines have not endorsed fluoroquinolone use as first line therapy in community acquired pneumonia.

Total antibiotic prescriptions in the Australian outpatient community have shown a steady and progressive fall from 1994 through to 2003 i.e 24.2 to 19.3 DDD/1000 population/year. In the last three years 2004 through 2006 this figure has remained stable at 20.9, 21.3 and 20.9 DDD/1000 population/year.[20] This overall reduction in antibiotic prescribing in the Australian community is likely to be a contributing factor to the relatively lower resistance levels seen in Australia compared with other regions such as Eastern Europe and East Asia.

Although rising levels of antibiotic resistance are often regarded as inevitable, a number of studies have shown a decline in resistance trends after implementation of community prescribing restrictions. A study in Canberra involving young children showed that when not exposed to antibiotics for a period of 6 months or more, carriage rates of penicillin-resistant pneumococci fell to the rate seen in the general community.[27]

Immunisation has been effective not only in decreasing disease in children but also in their parents and grandparents.[28,29,30] In reducing disease burden it also has the potential to reduce antibiotic resistance rates by decreasing community driven antibiotic selection pressure.

Regular AGAR surveillance studies of *S. pneumoniae* resistance have allowed a much clearer picture of changing susceptibility in this important community pathogen. After a rapid emergence and rise in resistance between 1989 and 1999, recent studies have documented independent rises and decreases for non-β-lactam antimicrobial classes. Penicillin resistance slowly increased from 1989 to 2005 and has fallen to 2.0% in 2007. Ongoing surveillance is required to determine if levels will remain at these low rates. Overall, based on AGAR studies, Australia has lower rates of resistance in *S. pneumoniae* than many other countries. Introduction and maintenance of effective vaccination programmes as well as continuing promotion of prudent use of antibiotic prescribing in the community are crucial to maintaining effective control on resistance. If Australia can adopt these measures, there is an opportunity to curb this rise and to effect a reduction in resistance rates and preserve current antibiotics into the future. Ongoing surveillance studies such as the ones performed by the AGAR group are an important tool in measuring continuing trends in antibiotic resistance and as an indirect measure of the successes and failures of our health policies.

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12 Acknowledgements

Appendix 1   Trends in Resistance 1989-2007

Invasive	1989	1994	1999	2002	2005	2007
PEN	n=105	n=509	n=381	n=291	n=347	n=335
I (MIC 4mg/L)	0.0%	0.0%	0.3%	1.0%	1.2%	0.6%
R (MIC ≥8mg/L)	0.0%	0.0%	0.0%	0.0%	0.0%	0.3%
Ery	NT	n=505	n=380	n=312	n=347	n=323
		7.7%	16.8%	19.2%	15.1%	13.9%
Tet	NT	n=402	n=379	n=312	n=347	n=324
		7.2%	7.4%	7.1%	6.3%	14.2%
SXT	NT	n=440	n=380	n=312	n=347	n=323
		34.5%	32.6%	31.7%	25.6%	23.5%
Lev	NT	NT	NT	NT	n=284	n=296
					1.4%	0.0%
Mox	NT	NT	NT	NT	n=351	n=323
					0.0%	0.0%

Non-Invasive	1989	1994	1999	2002	2005	2007
PEN	n=1702	n=1858	n=1167	n=718	n=1420	n=1494
I (MIC 4mg/L)	0.0%	0.05%	1.7%	1.4%	3.4%	2.2%
R (MIC ≥8mg/L)	0.0%	0.05%	0.09%	0.0%	0.5%	0.0%
Ery	NT	n=1858	n=1172	n=774	n=1420	n=1492
		9.0%	19.5%	22.6%	24.6%	21.7%
Tet	NT	n=1582	n=1167	n=774	n=1419	n=1491
		13.6%	20.0%	19.5%	21.3%	18.4%
SXT	NT	n=1630	n=1171	n=774	n=1419	n=1491
		37.1%	39.1%	40.3%	32.2%	28.8%
Lev	NT	NT	NT	NT	n=702	n=1442
					0.7%	0.7%
Mox	NT	NT	NT	NT	n=1416	n=1489
					0.1%	0.3%

All Isolates	1989	1994	1999	2002	2005	2007
PEN	n=1822	n=2385	n=1548	n=1009	n=1776	n=1831
I (MIC 4mg/L)	0.0%	0.04%	1.4%	1.3%	2.9%	1.9%
R (MIC ≥8mg/L)	0.0%	0.04%	0.06%	0.0%	0.4%	0.1%
Ery	NT	n=2381	n=1552	n=1086	n=1776	n=1817
		8.7%	18.8%	21.6%	22.7%	20.4%
Tet	NT	n=2000	n=1546	n=1086	n=1775	n=1817
		12.2%	16.9%	15.9%	18.4%	17.7%
SXT	NT	n=2088	n=1551	n=1086	n=1775	n=1816
		36.5%	37.5%	37.8%	31.0%	28.0%
Lev	NT	NT	NT	NT	n=986	n=1740
					0.9%	0.6%
Mox	NT	NT	NT	NT	n=1416	n=1814
					0.1%	0.2%

NT: Not tested, pen: penicillin, ery: erythromycin, tet: tetracycline, SXT: trimethoprim-sulphamethoxazole, lev: levofloxacin, mox: moxifloxacin

Appendix 2   Antibiotic Profiles by Frequency

Table 1: All isolates excluding CSF

Profile	n	%
- - - - -	1114	64.5
- - - SXT -	215	12.4
- EryTetSXT -	159	9.2
- EryTet - -	74	4.3
- Ery - SXT -	41	2.4
- Ery - - -	41	2.4
- - TetSXT -	28	1.6
PenEryTetSXT -	27	1.6
- - Tet - -	13	0.8
- EryTetSXTLev	3	0.2
PenEry - SXT -	3	0.2
- - - - Lev	3	0.2
Pen - - SXT -	2	0.1
- - - SXTLev	1	0.1
PenEryTet - -	1	0.1
Pen - - SXTLev	1	0.1
PenEryTetSXTLev	1	0.1
- Ery - SXTLev	1	0.1
Total	1728	100

Antibiotics included: pen: penicillin (intermediate and resistant), ery: erythromycin, tet: tetracycline, SXT: trimethoprim-sulphamethoxazole, lev: levofloxacin (intermediate and resistant). Penicillin parenteral nonmeningitis breakpoints utilised. Only isolates with all antimicrobials tested appear in the table.
Antibiotics excluded: Ceftriaxone, Cefotaxime, Clindamycin, Moxifloxacin

Table 2: CSF isolates

Profile	n	%
- - - - -	7	63.6
PenEryTetSXT -	2	18.2
PenEryTet - -	1	9.1
- EryTet - -	1	9.1
Total	11	100

Antibiotics included: pen: penicillin, ery: erythromycin, tet: tetracycline, SXT: trimethoprim-sulphamethoxazole, lev: levofloxacin (intermediate and resistant). Penicillin parenteral nonmeningitis breakpoints utilised. Only isolates with all antimicrobials tested appear in the table.
Antibiotics excluded: Ceftriaxone, Cefotaxime, Clindamycin, Moxifloxacin