Prevalence of antimicrobial resistances in *Streptococcus pneumoniae* in Australia, 2005

Report from the Australian Group on Antimicrobial Resistance

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Abstract

In 2005 the Australian Group for Antimicrobial Resistance (AGAR) conducted a survey of the prevalence of antimicrobial resistance in unique clinical isolates of *Streptococcus pneumoniae*. Twenty laboratories from the 5 mainland states and the Australian Capital Territory collected 1,776 isolates prospectively and tested them by disk diffusion, Etest® and/or agar dilution against a range of antimicrobials. Data from this survey were compared with AGAR surveys conducted in 1989, 1994, 1999 and 2002. Non-susceptibility to penicillin was detected in 28.0% of isolates, 22.7% were erythromycin resistant, 15.6% clindamycin resistant, 18.4% tetracycline resistant and 31.0% trimethoprim-sulphamethoxazole resistant. Levofloxacin resistance was detected in only 4 of 1,775 (0.2%) isolates tested. Intermediate resistance to levofloxacin was detected in another 4 isolates. Moxifloxacin resistance was present in 2 isolates with minimum inhibitory concentrations of 3 mg/L and 4 mg/L. Seventeen point three per cent of isolates were multi-resistant (acquired resistance to more than 2 drug classes). Trend data show an increase in penicillin non-susceptible strains in each survey from 1989 to 2005. Between 1999 and 2005 the proportion of invasive strains with high-level resistance increased from 2.6% to 5.4%. After a rapid emergence and rise in resistance between 1989 and 1999, recent studies have documented a continuing rise in resistance to all non-ß-lactams except trimethoprim-sulphamethoxazole. *Commun Dis Intell* 2008;32:242–249.

Keywords: antibiotic resistance, epidemiology, *Streptococcus pneumoniae*

Introduction

Worldwide *Streptococcus pneumoniae* is the most common bacterium causing pneumonia and meningitis. Invasive pneumococcal infection, primarily bacteraemia and meningitis, occurs most commonly in young children aged less than 5 years and older adults aged over 65 years. Bronchitis and sinusitis in adults and otitis media in children are frequently caused by *S. pneumoniae*. 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* have raised minimum inhibitory concentrations (MICs). Community antibiotic use in non-invasive infections is seen as an important driver for selection pressure of emerging resistance.[1] 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. The Australian Group on Antimicrobial Resistance (AGAR) is a group of laboratories that conducts regular antimicrobial susceptibility studies with funding from the Australian Government Department of Health and Ageing. We report the results of the 2005 *S. pneumoniae* survey and compare the changes in susceptibility with those of previous studies. Ongoing surveys, along with serotype studies, will serve as important baselines to monitor changes that may occur in response to the introduction of this vaccine.

Methods

Twenty institutions from the 5 mainland states and the Australian Capital Territory participated in the *S. pneumoniae* AGAR survey. Starting from 1 January 2005, each laboratory collected up to 100 consecutive significant clinical isolates. Only 1 isolate per patient was tested. If *S. pneumoniae* was isolated from more than 1 site, then the isolate from the most significant clinical site was tested.

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 mm and 14 mm in CO_2 was tested for bile solubility.

Susceptibility testing methodology

Participating laboratories performed antimicrobial susceptibility tests according to each laboratory's routine standardised methodology[2–6] (CDS, CLSI or BSAC disc diffusion, Vitek2®, agar dilution or MIC testing). Clindamycin and erythromycin discs were placed side by side to look for clindamycin inducibility. Penicillin and moxifloxacin MICs were determined for all isolates using Etest® strips. Four hundred and seventy-one (95%) of the 497 isolates that were penicillin intermediate or resistant (MIC >0.064 mg/L) were also tested with either a ceftriaxone or cefotaxime Etest® strip.

Statistical analysis

P values were calculated using Fischer's Exact test (GraphPad® Prism Software).

Results

Source of isolates

The majority of isolates (54.9%) were from the respiratory tract. Invasive isolates (19.9%) include 341 isolates (19.2%) from blood cultures. Other common sites of isolation were ear and eye specimens (11.2% and 9.5% respectively). The ages of patients reflect the incidence of *S. pneumoniae* infection, with 25.1% of patients below the age of 5 years, and 27.4% in the elderly age group of ≥65 years.

Susceptibility testing results

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 28% of isolates were non-susceptible to penicillin (Table 1). Higher rates were detected in Queensland (33.8%) and New South Wales/Australian Capital Territory (31.7%) than in the other states combined (21.4%).

Overall, there was a significantly higher rate of non-susceptibility detected in non-invasive isolates compared with invasive isolates ($p<0.001$). Queensland and New South Wales/Australian Capital Territory also had the highest rates of non-susceptibility demonstrated in non-invasive strains (>36%). Although Victoria had the lowest rates of non-susceptibility in non-invasive strains, it had the highest rate in invasive strains (21.9% and 20.8% respectively). Nationally, there were trends to higher rates of resistance among the young (<5 years), and the elderly (>65 years) (data not shown).

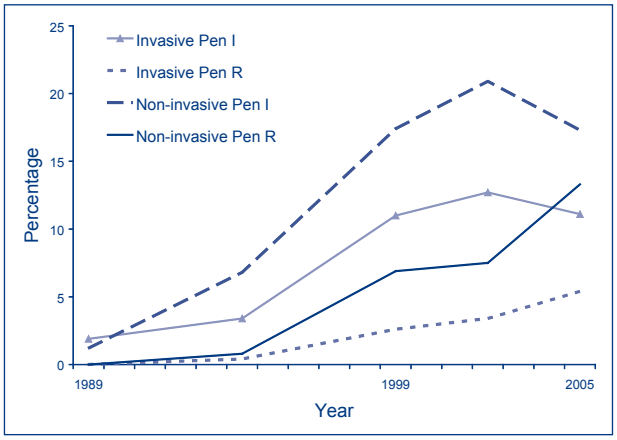
Penicillin 'high-level' resistance (MIC ≥2 mg/L) was present in 11.7% of isolates, with higher rates demonstrated in Queensland and New South Wales/Australian Capital Territory (range: 14.2%–17.3%) than in the other states (range: 7.1%–9.7%). Nationally, 29 isolates (1.6%) had a penicillin MIC ≥4 mg/L, a group that may better define the numbers that may fail penicillin treatment for non-meningeal infection. Overall, the most substantial rise in penicillin non-susceptibility was observed between 1994 and 1999, with a rise from 6.7% to 21.7%. Since 1999, this trend has continued, but less abruptly, with 28% non-susceptibility detected in the current study. Between the last 2 surveys, the rise seen has been predominantly in the proportion of strains demonstrating resistance (MIC ≥2 mg/L), rising from 6.8% to 11.7%, with a similar trend for both invasive (3.4% to 5.4%) and non-invasive (7.5% to 13.3%) isolates (Figure 1).

Because of changes in participating laboratories, these studies may not be fully comparable and hence p values have not been reported. However, an analysis of results for 8 core laboratories that have participated in all AGAR *S. pneumoniae* studies since 1994, have confirmed a similar trend to that described above. In the studies since 1994 a common methodology (Etest®) was used to measure penicillin MICs in all laboratories.

Table 1. Number and proportion of isolates non-susceptible to penicillin

Region	All Isolates		Invasive		Non-invasive	
	n	%	n	%	n	%
NSW/ACT	185/583	31.7	30/160	18.8	150/415	36.1
Qld	96/284	33.8	7/40	17.5	89/244	36.5
SA	101/392	25.8	9/73	12.3	92/319	28.8
Vic.	49/221	22.2	5/24	20.8	43/196	21.9
WA	66/296	22.3	7/54	13.0	59/242	24.4
Aus.	497/1,776	28.0	58/351	16.5	433/1,416	30.6

Figure 1. Trend in penicillin non-susceptible strains, AGAR surveys, 1989 to 2005



Pen I MIC 0.125–1 mg/L, Pen R MIC ≥2 mg/L

1989: Invasive n=105, non-invasive n=1,717, overall n=1,822.
1994: Invasive n=532, non-invasive n=1,835, overall n=2,385.
1999: Invasive n=381, non-invasive n=1,167, overall n=1,548.
2002: Invasive n=292, non-invasive n=717, overall n=1,009.
2005: Invasive n=351, non-invasive n=1,416, overall n=1,776

Cefotaxime/ceftriaxone

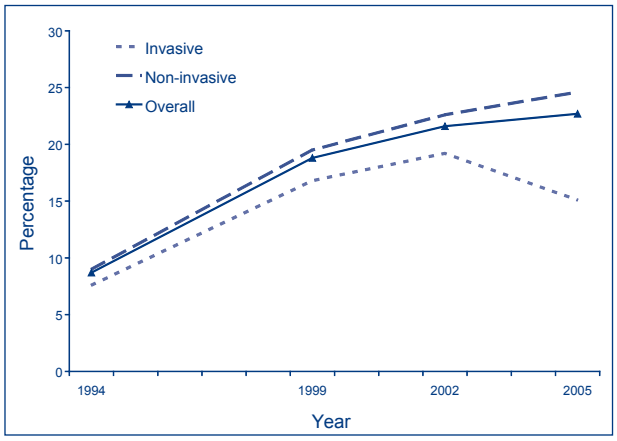
Cefotaxime or ceftriaxone MIC was determined on 471 (95%) penicillin non-susceptible isolates (MIC >0.064 mg/L). Non-susceptibility to the third generation cephalosporins was present in 14.9% of those strains tested. Of 14 cefotaxime/ceftriaxone resistant isolates (MIC >2 mg/L), 13 were also resistant to penicillin (2–8 mg/L), and 1 had intermediate resistance (0.38 mg/L). Of these, 13 were also resistant to macrolides, and 11 to tetracycline, but none were resistant to the fluoroquinolones. All 6 CSF samples were susceptible to ceftriaxone or cefotaxime using the lower (<0.5 mg/L) meningitis breakpoint.

Erythromycin and clindamycin

Macrolide (erythromycin) resistance was significantly higher ($p<0.001$) in non-invasive (24.6%) strains compared with invasive strains (15.1%) with the exception of Queensland, which had similar rates for both (28.3% and 27.5% respectively) (Table 2). The highest rate of resistance in non-invasive strains was seen in New South Wales/Australian Capital Territory, with a rate of 32%. The lowest rates of resistance for both invasive and non-invasive isolates were in Victoria (4.2% and 15.8% respectively). Resistance was highest among the elderly, and least in the 5–64 age range.

Erythromycin resistance increased from 1994 to 1999 for both invasive and non-invasive isolates. Comparison with the previous 2 studies revealed a rise in resistance for non-invasive isolates (from 19.5% to 24.6%), between 1999 and 2005, but this was not observed for invasive isolates (Figure 2).

Figure 2. Trends in erythromycin resistance, AGAR surveys, 1994 to 2005



1994: Invasive n=532, non-invasive n=1,835, overall n=2,385.
1999: Invasive n=381, non-invasive n=1,167, overall n=1,548.
2002: Invasive n=292, non-invasive n=717, overall n=1,009.
2005: Invasive n=351, non-invasive n=1,416, overall n=1,776

Clindamycin resistance was relatively uncommon among invasive strains (5.4% overall), with little variance across Australia (Table 3). A presumptive assessment of resistance genotype was made based

Table 2. Number and proportion of isolates with erythromycin resistance

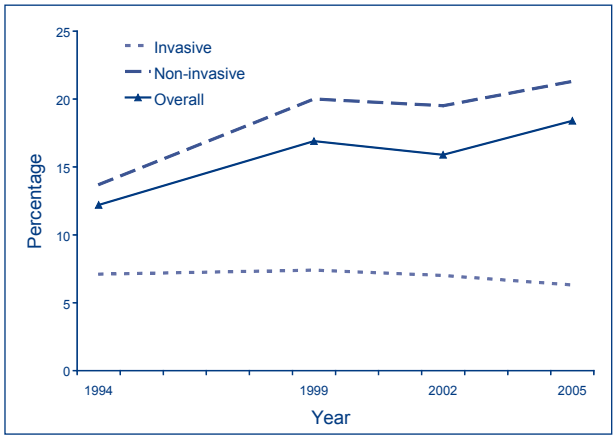
Region	All Isolates		Invasive		Non-invasive	
	n	%	n	%	n	%
NSW/ACT	162/583	27.8	26/160	16.2	133/415	32.0
Qld	80/284	28.2	11/40	27.5	69/244	28.3
SA	82/392	20.9	9/73	12.3	73/319	22.9
Vic.	35/221	14.5	1/24	4.2	31/196	15.8
WA	48/296	16.2	6/54	11.1	42/242	17.4
Aus.	404/1,776	22.7	53/351	15.1	348/1,416	24.6

on clindamycin resistance and the clindamycin disc induction test among erythromycin resistant isolates. Of 364 erythromycin resistant isolates, 222 (61%) had a MLS_B constitutive resistant phenotype and 6 (1.6%) had inducible resistance. These results suggest the presence of an *erm*B mechanism of resistance in 62.6% of Australian macrolide resistant isolates. All clindamycin resistant isolates were also resistant to erythromycin.

Tetracycline

There was a significant difference in tetracycline resistance among non-invasive (21.3%) and invasive (6.3%) strains ($p<0.001$). Compared with ß-lactam and macrolide resistance, tetracycline resistance in invasive isolates was consistently less than 10% across all Australian states (Table 4). Queensland and New South Wales/Australian Capital Territory had the highest rates of resistance demonstrated in non-invasive strains (24.6% and 25.5% respectively). Unlike rates for penicillins and macrolides, resistance was not higher in the young (<5 years), as would be predicted by lack of tetracycline use in this age group. Rates were again highest in the elderly. Tetracycline resistance increased from 1994 to 1999, all of the change being seen in non-invasive isolates (Figure 3). No significant rise in tetracycline resistance was demonstrated between 1999 and 2005 (16.9% and 18.4% respectively).

Figure 3. Trends in tetracycline resistance, AGAR surveys, 1994 to 2005



1994: Invasive n=532, non-invasive n=1,835, overall n=2,385.
1999: Invasive n=381, non-invasive n=1,167, overall n=1,548.
2002: Invasive n=292, non-invasive n=717, overall n=1,009.
2005: Invasive n=351, non-invasive n=1,416, overall n=1,776

Trimethoprim-sulphamethoxazole

Unlike other antibiotic classes, trimethoprim-sulphamethoxazole (TMP-SMX) resistance appears to have peaked in the previous decade. TMP-SMX resistance decreased from 1999 to 2005 for both invasive and non-invasive isolates (Figure 4). Nonetheless, rates of resistance of 25.6% for invasive and 32.2% for non-invasive strains limit the use of TMP-SMX in infections caused by *S. pneumoniae* (Table 5).

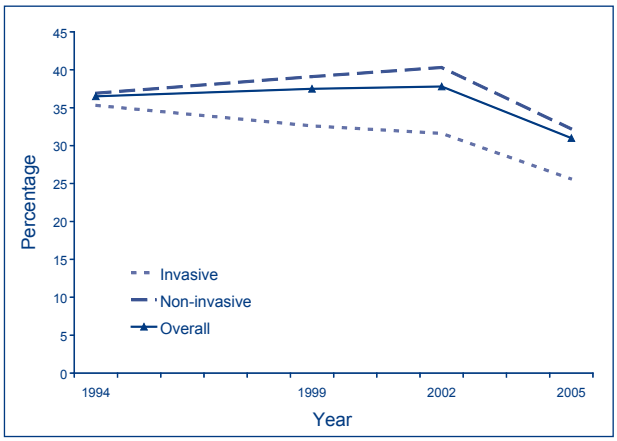
Table 3. Number and proportion of isolates with clindamycin resistance

Region	All Isolates		Invasive		Non-invasive	
	n	%	n	%	n	%
NSW/ACT	88/522	16.9	7/143	4.9	80/376	21.3
Qld	52/284	18.3	5/40	12.5	47/244	19.3
SA	53/309	17.2	2/67	3.0	51/242	21.1
Vic.	10/51	19.6	1/9	11.1	9/42	21.4
WA	25/296	8.4	2/54	3.7	23/242	9.5
Aus.	228/1,462	15.6	17/313	5.4	210/1,146	18.3

Table 4. Number and proportion of isolates with tetracycline resistance

Region	All Isolates		Invasive		Non-invasive	
	n	%	n	%	n	%
NSW/ACT	121/583	20.8	12/160	7.5	106/415	25.5
Qld	63/284	22.2	3/40	7.5	60/244	24.6
SA	60/391	15.3	2/73	2.7	58/318	18.2
Vic.	38/221	17.2	2/24	8.3	36/196	18.4
WA	44/296	14.9	3/54	5.6	41/242	16.9
Aus.	326/1,775	18.4	22/351	6.3	301/1,415	21.3

Figure 4. Trends in trimethoprim-sulphamethoxazole resistance, AGAR surveys, 1994 to 2005



1994: Invasive n=532, non-invasive n=1,835, overall n=2,385.
1999: Invasive n=381, non-invasive n=1,167, overall n=1,548.
2002: Invasive n=292, non-invasive n=717, overall n=1,009.
2005: Invasive n=351, non-invasive n=1,416, overall n=1,776

Fluoroquinolones

In 2005, fluoroquinolone resistance remained uncommon in Australia. By disc testing, levofloxacin resistance was detected in only 4 of 1,775 (0.2%) isolates tested. Intermediate resistance to levofloxacin was detected in another 4 isolates. All 8 were non-invasive isolates and were detected in New South Wales (4), South Australia (3) and Queensland (1). Moxifloxacin resistance was present in 2 isolates with MICs of 3 mg/L and 4 mg/L.

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 greater than 2 drug classes to define multi-resistance in this survey (Table 6). By this definition, 17.3% of isolates were multi-resistant.

Limitations of the study

There have been changes in participating laboratories in the AGAR *S. pneumoniae* surveys over time from 1989 through to 2005, with the more recent inclusion of a number of private pathology laboratories.

Table 5. Number and proportion of isolates with trimethoprim-sulphamethoxazole resistance

Region	All Isolates		Invasive		Non-invasive	
	n	%	n	%	n	%
NSW/ACT	198/583	34.0	43/160	26.9	151/415	36.4
Qld	101/284	35.6	8/40	20.0	93/244	38.1
SA	122/391	31.2	22/73	30.1	100/318	31.4
Vic.	65/221	29.4	7/24	29.2	58/196	29.6
WA	64/296	21.6	10/54	18.5	54/242	22.3
Aus.	550/1,775	31.0	90/351	25.6	456/1,415	32.2

Table 6. Multi-resistance in *Streptococcus pneumoniae*

Region	Number tested	Non-multi-resistant				Multi-resistant		
		0	1	2	%	3	4	%
NSW/ACT	583	307	90	62	78.7	42	82	21.3
Qld	284	144	48	31	78.5	13	48	22.5
SA	392	223	75	40	86.2	5	49	13.8
Vic.	221	140	31	16	84.6	15	19	15.4
WA	296	191	46	24	88.2	12	23	11.8
Australia	1,776	1,005	290	173	82.7	87	221	17.3
Invasive	351	216	77	37	94.0	12	9	6.0
Non-invasive	1,416	786	211	135	79.9	75	209	20.1

Antibiotics included: penicillin (intermediate or resistant); erythromycin, tetracycline, trimethoprim-sulphamethoxazole, levofloxacin.
Antibiotics excluded: clindamycin, cefotaxime, ceftriaxone.

Discussion

Internationally, changes in susceptibility in *S. pneumoniae* have evolved rapidly in the past 2 decades for both ß-lactam and other antibiotic classes, with potential to compromise treatment efficacy. 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 and upper respiratory tract infections, including sinusitis and otitis media, as well as the empiric treatment of community-acquired meningitis. The AGAR has conducted studies in 1989, 1994, 1999, 2002 and 2005 to monitor changes in *S. pneumoniae* susceptibility.

In AGAR sponsored studies, penicillin non-susceptibility has continued to increase, albeit at a slower rate than first observed in the early 1990s, reaching a national level in this survey of 28%. This increase has occurred in both the penicillin intermediate and resistant categories. In 1989, only 1% of strains tested were penicillin non-susceptible and only intermediate resistance to penicillin was detected.[7] In 1994, 6.7% of isolates were non-susceptible, the majority with intermediate resistance. From 1999 to 2005, the rate of *S. pneumoniae* resistance doubled from 5.9% to 11.7%.[8,9]

Monitoring of invasive isolates is also performed by the Enhanced Surveillance Pneumococcal Working Group of the Communicable Diseases Network Australia and published yearly in *Communicable Diseases Intelligence*. In the 2005 report,[10] of 1,481 isolates tested, 11.9% had reduced susceptibility to penicillin, similar to but lower than the 16.5% reported in this survey. Monitoring of invasive strains is important in determining the burden of invasive infection and potential impact of this on vaccination strategies. The AGAR data also include non-invasive isolates. This provides a better estimate for the reservoirs and drivers of increasing community antibiotic resistance and for potential antibiotic prescribing failures in respiratory tract infections.

Increasing resistance rates will impact on empiric ß-lactam therapy but mainly for meningitis. In non-invasive pneumococcal infection in Australia, the currently recommended antibiotic of choice for oral therapy is amoxicillin.[11] When higher doses are employed, amoxicillin achieves adequate tissue levels and is active against penicillin-intermediate strains. Between 1999 and 2005 there was an almost twofold increase in the number of non-invasive isolates with a MIC ≥2 mg/L from 6.9% to 13.3%. These ongoing changes require continuing observation but amoxicillin prescribed at the upper dosing range, still continues to be appropriate therapy for the vast majority of non-invasive infections occurring in Australia.

Despite lower rates compared with non-invasive strains, increasing numbers of invasive strains also demonstrate high-level resistance to penicillin. The rates in invasive strains rose from 2.6% to 5.4% between 1999 and 2005. Reviews of the literature on the clinical implications of penicillin resistance[12,13] suggest that failures of therapy in non-meningeal infections are not predicted until MIC levels are ≥4 mg/L. As strains with MICs ≥4 mg/L are rare (1.6%) in Australia, data from the most recent AGAR study support current recommendations for high dose parenteral penicillin in non-meningeal invasive *S. pneumoniae* infection. Third generation cephalosporins in combination with vancomycin are recommended as empiric therapy for meningitis. When isolates have cefotaxime or ceftriaxone MICs ≥2 mg/L, even cephalosporins may be ineffective. However, of note in the 2005 study, all cerebrospinal fluid isolates were susceptible to the third generation cephalosporins using the CLSI meningeal breakpoints.

In 2005, erythromycin resistance was documented in 22.7% of isolates, a rise of 5% since 1999. Increases were primarily in non-invasive isolates. Of 364 erythromycin resistant isolates, 228 (62.6%) had a MLS_B phenotype suggestive of an *erm*B resistance mechanism, and associated with high-level erythromycin resistance. It has now been clearly documented that there is an association between macrolide resistance and therapeutic failures in bacteraemic *S. pneumoniae* infection.[14,15] The AGAR study data suggest that if macrolides are used as sole empiric therapy for respiratory tract infections when pneumococci may be implicated, many of these isolates (24.6% of non-invasive strains) are unlikely to respond to this class of antibiotics. The current Australian Antibiotic Guidelines[11] do not recommend macrolides as empiric therapy associated with otitis media, sinusitis, acute exacerbations of chronic bronchitis or as empiric therapy for community-acquired pneumonia except where additional cover for atypical organisms is required.

Tetracycline resistance in invasive isolates was below 10% across all Australian states. This may reflect the restricted use of oral tetracyclines for non-invasive infections in adults, and its restricted use for all infections in children.

A fall in resistance was demonstrated for trimethoprim-sulphamethoxazole from 37.8% in 2002 to 31.0% in 2005. Whilst it is considered an unsuitable drug for use in 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 2 classes of antibiotics to show significant reduction in community prescribing over the past 14 years, 53% and 54% reduction respectively (unpublished data – Drug Utilisation Subcommittee, Australian Government Department of Health and Ageing).

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.[16–18] As for macrolides, quinolone resistance has been linked to failure of pneumonia therapy.[19] Because of the recent introduction of the new fluoroquinolones into clinical use, the AGAR 2005 *S. pneumoniae* study undertook an evaluation of resistance rates using levofloxacin discs and moxifloxacin Etest® MIC testing to detect early development of resistance. Of 1,776 isolates tested, only 2 moxifloxacin resistant non-invasive isolates were detected (0.1%). Both isolates were multi-resistant. The low fluoroquinolone resistance levels are likely to be related to the relatively low volume of these drugs that have so far been used in Australia because of restrictions placed on their use. Australian guidelines do not endorse 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. 25.6 to 19.8 DDD/1,000 population/day. In the last 2 years, this trend has reversed but still remains 15% below 1994 levels i.e. 21.7 DDD/1,000 population/day (unpublished data – Drug Utilisation Subcommittee, Australian Government Department of Health and Ageing). 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.

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 a gradual rise or decrease for non-ß-lactam antimicrobials. Rates of 'high-level' penicillin resistance and multi-resistance continue to rise. Overall, based on AGAR studies, Australia has lower rates of resistance in *S. pneumoniae* than many other countries. Introduction and maintenance of effective vaccination programs 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.

A full detailed report of this study may be found under 'AMR surveillance' on the Australian Group on Antimicrobial Resistance web site: http://www.antimicrobial-resistance.com/

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South Australia

Gribbles Pathology, Institute of Medical and Veterinary Science, SouthPath, Women's and Children's Hospital

Victoria

Alfred Hospital, Austin Hospital, St Vincent's Hospital

Western Australia

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