Antimicrobial resistance in *Streptococcus pneumoniae*: a decade of results from south-western Sydney

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Abstract

We report the emerging drug-resistance in *Streptococcus pneumoniae* seen by the South Western Area Pathology Service (SWAPS) from 1 January 1990 to 31 July 2000. SWAPS performs all the pathology testing for the public hospitals in the South Western Sydney Area Health Service, which serves a population of 700,000; 120,000 separations occur at these hospitals annually. In all, 2,265 patients submitted specimens yielding *S. pneumoniae*. These included respiratory tract specimens, blood cultures, eye swabs and cerebrospinal fluid (CSF). Resistance to penicillin, cefotaxime, and non-β-lactam antibiotics, especially cotrimoxazole, has emerged over the 1990s. From 1997 onwards, around 10 per cent of CSF and blood culture isolates demonstrated penicillin-resistance and 5 per cent showed cefotaxime-resistance. In 2000, 35 per cent of pneumococci from sites other than CSF and blood exhibited resistance to penicillin and 15 per cent showed resistance to cefotaxime. Resistance to other agents also increased over the decade. In 2000, 76 per cent of all isolates were resistant to cotrimoxazole, 26 per cent to erythromycin and 24 per cent to tetracyclines. Rifampicin-resistance was negligible over the decade, and vancomycin-resistance was absent. Antibiotics currently used for empirical treatment of certain *S. pneumoniae* infections may now need to be reviewed. *Commun Dis Intell* 2000;24:340-343.

Keywords: Streptococcus pneumoniae*, antimicrobial resistance, blood cultures, cerebrospinal fluid, sputum*

Introduction

Streptococcus pneumoniae is a major bacterial pathogen. The emergence of resistance in the drugs used to treat infections with this organism is of major public health significance.

Penicillin-resistant *S. pneumoniae* (PRSP) was first isolated clinically in Australia in 1967.[1] In the two decades after this, PRSP isolates were reported from Papua New Guinea,[2] South Africa,[3] southern Europe,[4] and the United States.[5] PRSP has become common in Australia in the 1990s,[6-11] but there is considerable geographic variation.[8] PRSP isolates are often resistant to multiple classes of antibiotics, such as cephalosporins, macrolides, tetracyclines and folate antagonists.[8,12]

Treatment failures with penicillin and third generation cephalosporins are well described in meningitis due to PRSP.[13] The significance of PRSP in respiratory tract infections is less clear; perhaps only isolates with high level resistance are associated with treatment failure.[5] The outcome in pneumonia due to PRSP with intermediate resistance to penicillin is not significantly different if penicillin or third generation cephalosporin is used in treatment.[14] The presence of penicillin-resistance is associated with a poorer outcome in children with invasive pneumococcal disease.[11]

We report the emergence of drug-resistance in *S. pneumoniae* isolated from 1990 to the present from patients serviced by South Western Area Pathology Service.

Methods

The South Western Area Pathology Service performs all the pathology testing for public hospitals in the South Western Sydney Area Health Service, which serves a population of 700,000. All specimens from which *S. pneumoniae* was isolated for the period 1 January to 31 July 2000 were included. Specimens with duplicate hospital record numbers were deleted. Isolates were identified as *S. pneumoniae* on the basis of typical colonial morphology and sensitivity to optochin; atypical isolates were confirmed with the API 20 Strep biochemical strip and the Slidex Pneumo-Kit (bioMérieux Vitek, Australia, Pty Ltd).

Susceptibility testing was performed using the ATB Strep microbroth dilution strip (bioMérieux Vitek, Australia, Pty Ltd), using NCCLS interpretive criteria.[15] Oxacillin was used to screen for penicillin-resistance, in which case penicillin and cefotaxime Minimal Inhibitory Concentrations (MICs) were determined using the E-test (AB BIODISK Solna, Sweden). For penicillin, isolates with an MIC 0.12-1.0 mg/L were considered to show intermediate resistance, and isolates with an MIC 2 mg/L to exhibit high level resistance; for cefotaxime, isolates with an MIC = 1.0 mg/L were considered to show intermediate resistance, and isolates with an MIC 2 mg/L to exhibit high level resistance.[15]

Results

The number of non-duplicated specimens yielding *S. pneumoniae* per year is shown in Figure 1. Between 1 January 1999 and 31 July 2000, a total of 2,265 unique

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specimens yielded *S. pneumoniae.* The sites sampled were: respiratory tract n = 1,312 (expectorated sputum n = 908, ear swabs n = 131, endotracheal aspirates n = 124, bronchoscopy specimens n = 76, nose swabs n = 42, throat swabs n = 31), blood cultures n = 628, eye swabs n = 172, CSFs n = 16, and other types n = 138.

The increase in the proportions of isolates of *S. pneumoniae* demonstrating intermediate and high-level resistance to penicillin is depicted in Figure 2 for blood culture and CSF isolates, and for other types of specimen in Figure 3. Around 10 per cent of blood culture and CSF isolates have demonstrated penicillin-resistance from 1997 onwards. Resistance to penicillin has steadily increased since the mid-1990s, and in 2000 just over 35 per cent of isolates from sites other than blood and CSF demonstrated resistance.

Corresponding data for cefotaxime are shown in Figures 4 and 5. Resistance was more evident in isolates from sites other than blood and CSF, and has risen since the mid-1999s to 15 per cent in 2000. A lesser degree of resistance was seen in blood and CSF isolates.

Increases in resistance to cotrimoxazole, erythromycin, and tetracycline are shown in Figure 6. Resistance to cotrimoxazole has risen sharply, to 76 per cent in 2000. Only seven isolates resistant to rifampicin were detected, none in 1999 or 2000. No isolate was resistant to vancomycin.

Tables 1 and 2 indicate the overall numbers and proportions of penicillin-sensitive, and intermediate and high-level penicillin-resistant, *S. pneumoniae* isolates which were resistant to one or more other antimicrobial agents.

Discussion

Antimicrobial resistance in *S. pneumoniae* is rapidly emerging in Australia[6-8] and our data show that over the 1990s there has been a substantial increase in resistance in isolates from all body sites. 'Invasive' (primarily blood culture and CSF) isolates are less likely to be resistant to penicillin than 'non-invasive' (primarily sputum) isolates,[8] as we report here (Figures 2 and 3). *S. pneumoniae* isolates that are resistant to penicillin are more likely to be resistant to other types of antimicrobials such as cefaclor, cefotaxime, macrolides, tetracyclines, and folate antagonists (Tables 1 and 2), a finding mirrored elsewhere.[5,8] The rise in resistance to cotrimoxazole was particularly striking (Figure 6). Rifampicin is rarely used in the community, so it is not surprising that resistance to this agent has been minimal.

What are the implications of the above? In the case of meningitis, treatment failures are well described, even with isolates of intermediate resistance.[13] For the empiric treatment of meningitis, the decision to add additional drugs (such as vancomycin) depends on the likelihood of penicillin resistance.[8] In our laboratory, 11 per cent of blood and CSF isolates now demonstrate resistance to penicillin. Smaller percentages are also resistant to cefotaxime. In this situation, it may be reasonable to add vancomycin to the empiric treatment. If PRSP is isolated from a patient with meningitis, modification of the drug regimen is not defined and specialist advice should be sought. A recent Australian paper reported that children with invasive penicillin-resistant pneumococcal infections, particularly meningitis, required longer hospitalisation, and it took longer for their fever to

Figure 1. Total isolates of *Streptococcus pneumoniae*, South Western Area Pathology Service, 1 January 1990 to 31 July 2000, by year

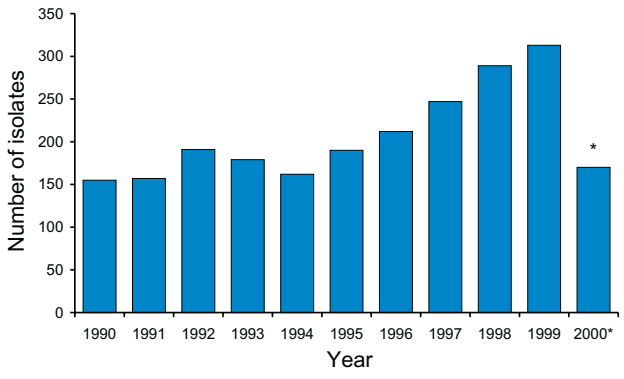


Figure 2. Penicillin-sensitivity of *Streptococcus pneumoniae* isolated from blood cultures and CSFs

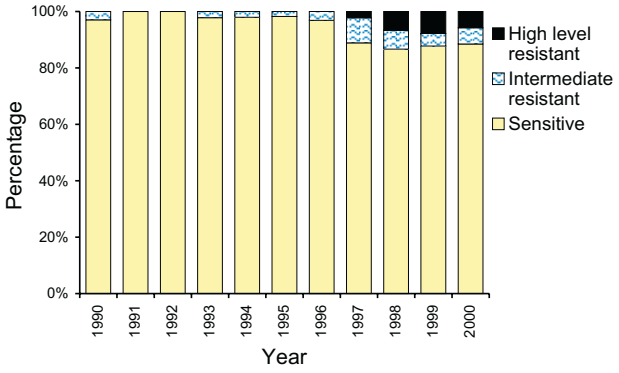
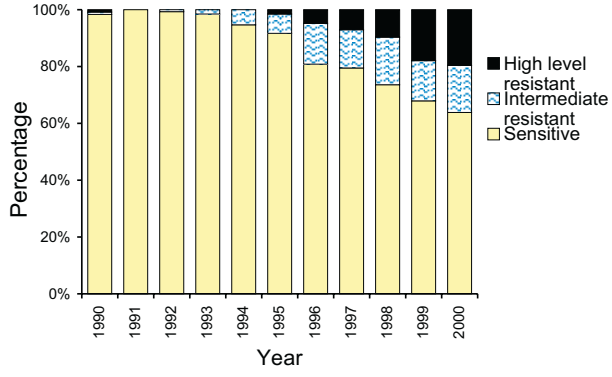


Figure 3. Penicillin-sensitivity of *Streptococcus pneumoniae* isolated from sites other than blood cultures and CSFs



* I January to 31 July only

abate.[11] Several regimens have been suggested for treating meningitis with penicillin-resistant pneumococci; these are vancomycin (possibly with rifampicin), very high doses of a third generation cephalosporin, or meropenem.[8]

Figure 4. Cefotaxime-sensitivity of *Streptococcus pneumoniae* isolated from blood cultures and CSFs

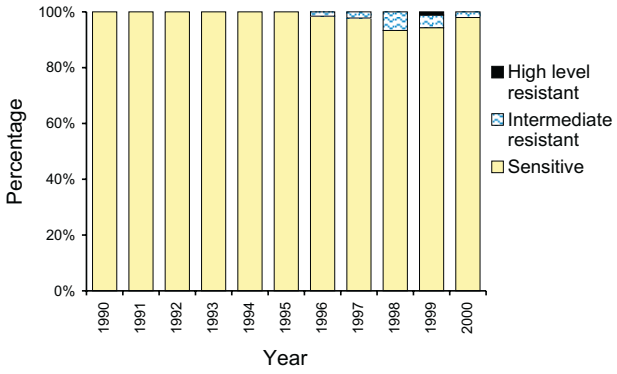


Figure 5. Cefotaxime-sensitivity of *Streptococcus pneumoniae* isolated from sites other than blood cultures and CSFs

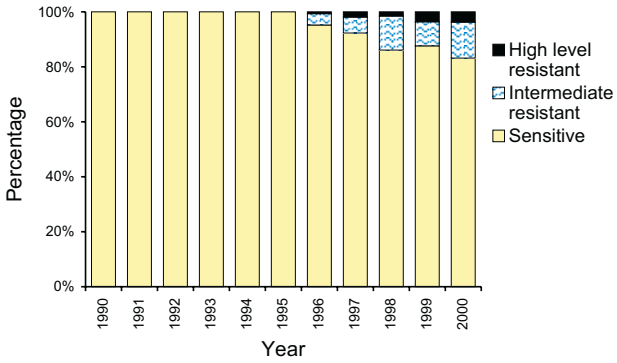
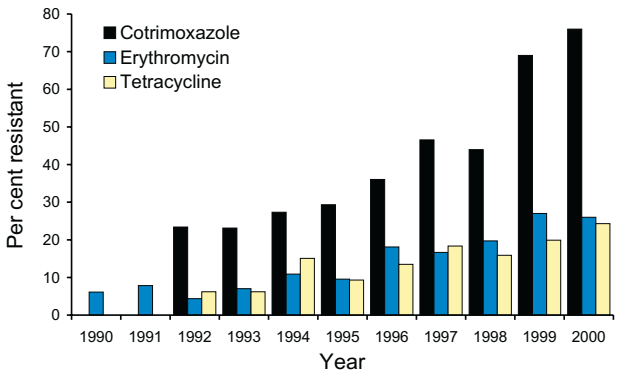


Figure 6. Resistance of *Streptococcus pneumoniae* isolates to non-β-lactam antibiotics



The treatment of the much more common respiratory infections is more difficult. Treatment of pneumococcal respiratory infections with -lactams is unlikely to fail unless the isolate has high level resistance (MIC 2 mg/L).[16] In one study of pneumonia due to *S. pneumoniae*, treatment of PRSP (mainly of intermediate resistance) with penicillin or third generation cephalosporin did not result in a significantly different mortality.[14] Many strains of PRSP are multi-drug resistant,[8,16] as was the case in our study, which makes the choice of a non- -lactam antimicrobial agent problematic. However, newer quinolones may be useful.[17]

It is essential that medical practitioners be informed of developing patterns of resistance in common organisms.[8] This information can influence their prescribing patterns, both in terms of prevention of the emergence of resistant organisms and treatment of infections by them. Most respiratory infections are viral, and many prescriptions for antimicrobials are therefore superfluous. The emergence of PRSP is driven partially by selection pressure of antimicrobial use.[18] When patients present with infections which may be due to PRSP, diagnostic specimens should be obtained for culture whenever possible.[8,19]

Penicillins may paradoxically remain the drugs of choice to treat PRSP infections, as resistance to penicillin is only relative and is less than to the other classes of anti-microbials, in particular oral cephalosporins.[8,20] In addition penicillins (amoxycillin in particular) will reach levels in respiratory secretions above the MIC of many strains of PRSP, which is not the case with oral cephalosporins.[16,19,20]

PRSP isolates are usually of one of the polysaccharide types incorporated into the available 23-valent pneumococcal vaccine.[5] Adults at risk of invasive pneumococcal infection (those over age 65 years, Aboriginals and Torres Strait Islanders over 50 years of age, asplenic or immunocompromised individuals, or those with chronic medical disease or CSF leaks) should be vaccinated as per the Australian Standard Immunisation Schedule.[21] Unfortunately, children under 2 years of age, who are at high risk of pneumococcal disease and are also more likely to harbour PRSP, do not respond to the currently available vaccine.[22] Conjugated pneumococcal vaccines will probably

Table 1. Number and proportions of penicillin-sensitive and penicillin-resistant *Streptococcus pneumoniae* resistant to other antimicrobial agents

Other antimicrobial	Sensitive n = 1966 %	Intermediate resistant n = 180 %	High level resistant n = 119 %
Cotrimoxazole	37.0	88	95
Cefotaxime			
Intermediate 1mg/L	0.0	26	63
High 2mg/L	0.0	0	21
Erythromycin	8.8	45	59
Tetracycline	7.6	45	58
Rifampicin	0.5	0	0

Table 2. Number and proportions of β-lactam-sensitive and β-lactam-resistant pneumococcal isolates resistant to no, or up to three, other classes of antimicrobial agent

		Resistance to non- -lactam antimicrobials*				
Penicillin susceptibility	n	0 (%)	1 (%)	2 (%)	3 (%)	4 (%)
Sensitive	1966	62	25	4	3	0
Intermediate	180	17	31	23	28	0
High level resistant	119	9	28	22	41	0

* Cotrimoxazole, erythromycin, tetracycline, and rifampicin.

confer a higher response, particularly in children, and with the emergence of PRSP are now urgently needed.

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