

Annual report of the Australian Gonococcal Surveillance Programme, 2003

The Australian Gonococcal Surveillance Programme

Abstract

The Australian Gonococcal Surveillance Programme monitors the antibiotic susceptibility of *Neisseria gonorrhoeae* isolated in all Australian states and territories. In 2003 the *in vitro* susceptibility of 3,772 isolates of gonococci from public and private sector sources was determined by standardised methods. Antibiotic susceptibility patterns again varied considerably between jurisdictions and regions. Resistance to the penicillins nationally, was 17 per cent but ranged up to 27 per cent in larger urban centres. Quinolone resistance in gonococci (QRNG) remained widespread and increased in most states but most markedly in Victoria. Nationally, 14.4 per cent of all isolates were QRNG, and most of this resistance was at high MIC levels. All isolates remained sensitive to spectinomycin. A small number of isolates showed some decreased susceptibility to ceftriaxone (MIC 0.06 mg/L or more) and were concentrated in New South Wales. A high proportion of gonococci examined in larger urban centres were from male patients and rectal and pharyngeal isolates were common. In other centres and in rural Australia the male to female ratio of cases was lower, and most isolates were from the genital tract. In New South Wales, the number of available cultures decreased and represented 30 per cent of the national total. In Victoria, the number of isolates increased and was 25 per cent of all gonococci examined. *Commun Dis Intell* 2004;28:187–193.

Keywords: antibiotics, antimicrobial resistance, cephalosporin, *Neisseria gonorrhoeae*, gonorrhoea, penicillin, quinolone, spectinomycin

Introduction

Antimicrobial resistance (AMR) in *Neisseria gonorrhoeae* affects not only the individual patient who may fail to be cured by ineffective dosage regimens, but also compromises public health efforts aimed at control of gonococcal disease through use of programmatic treatments. Standardised treatment protocols for gonorrhoea utilise single dose treatments designed to cure 95 per cent or more of cases.⁵ The continuing increase in AMR in gonococci has led to the progressive loss of utility of different antibiotic classes in recent years. The effectiveness of the penicillins has long been compromised in much of Australia and quinolone-based treatment schedules have also been discontinued in some jurisdictions because of high levels of resistance to these agents. The net effect of increasing AMR in gonococci has been the decreased use of cheaper oral antibiotics and increased use of expensive injectable agents, most notably third generation cephalosporin antibiotics, as the agents of choice. Reports of treatment

failure from Japan with cepheems and monobactams were accompanied by evidence of raised MICs to cefixime (an oral agent not available in Australia) and ceftriaxone in gonococci already resistant to quinolones and penicillins.^{1,2,3} Gonococcal strains with these resistances have been detected in Australia.⁴

Laboratory analyses assist the control and treatment of gonorrhoea by confirmation of the diagnosis, application of typing for gonococcal strain differentiation and provision of antibiotic susceptibility data. Since 1979, the Australian Gonococcal Surveillance Programme (AGSP) has monitored the susceptibility to antibiotics of gonococci isolated throughout the country. The AGSP is a collaborative program conducted by reference laboratories in each state and territory. Data analysed by the program have been published quarterly from 1981 and annual reports have appeared in *Communicable Diseases Intelligence* since 1996. This report is based on data obtained during the 2003 calendar year.

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Methods

The AGSP is a component of the National Neisseria Network of Australia and comprises participating laboratories in each State and Territory (see acknowledgements). This collaborative network of laboratories obtains isolates for examination from as wide a section of the community as possible and both public and private sector laboratories refer isolates to regional testing centres. The increasing use of non-culture based methods of diagnosis has the potential to reduce the size of the sample of isolates available for testing. Details of the numbers of organisms examined are provided in order to indicate the AGSP sample size and not disease incidence and distribution, although some inferences on the latter may be also drawn from these data.

Gonococci isolated in, or referred to the participating laboratories were examined for antibiotic susceptibility to the penicillins, quinolones, spectinomycin and third generation cephalosporins and for high-level resistance to the tetracyclines by a standardised methodology.⁶ The AGSP also conducted a program-specific quality assurance program.⁷ Antibiotic sensitivity data were submitted quarterly to a coordinating laboratory which collated the results and also conducted the quality assurance program. Additionally, the AGSP received data on the sex of the patient and site of isolation of gonococcal strains. Where available, data on the geographic source of acquisition of antibiotic-resistant isolates were included in analyses.

Results

Number of isolates

There were 3,772 gonococcal isolates referred to, or isolated in, AGSP laboratories in 2003. The source of and site of infection with these isolates are shown in the Table. One thousand one hundred and sixteen gonococci (30% of the Australian total) were isolated in New South Wales, 920 (24.5%) in Victoria, 637 (16.9%) in Queensland, 517 (13.8%) in the Northern Territory, 343 (9.1%) in Western Australia, and 227 (6%) in South Australia with small numbers in Tasmania (9) and the Australian Capital Territory (3). Of the total, 3,679 remained viable for susceptibility testing.

The site of isolation and sex of some infected patients was not known.

Nationally, 179 (5%) fewer isolates were received in 2003 than in 2002. The number of isolates fell by 509 in New South Wales and 48 in the Northern Territory but rose by 226 in Victoria, 95 in South Australia and 49 in Queensland. In Western Australia numbers were stable in 2003. Numbers in other centres remained low.

Table. Source and number of gonococcal isolates, Australia, 2003, by sex, anatomical site and state or territory

Sex	Site	State or territory						Aust*
		NSW	NT	Qld	SA	Vic	WA	
Male	Urethra	720	294	437	131	614	246	2,449
	Rectal	181	2	35	53	152	15	440
	Pharynx	101	0	12	28	94	5	240
	Other/NS	44	13	13	3	8	4	85
	Total	1,046	309	497	215	868	270	3,214
Female	Cervix	53	188	128	7	47	69	495
	Other/NS	14	17	12	5	5	4	57
	Total	67	205	140	12	52	73	552
Unknown	Total	3	3	0	0	0	0	6
Total*		1,116	517	637	227	920	343	3,772

* Includes isolates from Tasmania (9) and the Australian Capital Territory (3).

NS Not stated.

Source of isolates

There were 3,214 strains from men and 552 from women, with a male to female (M:F) ratio of 5.8:1, only slightly higher than the 5.6:1 ratio for 2002. The number of strains from men decreased by 121 and from women by 42. The M:F ratio was again high in New South Wales (15.6:1) and Victoria (16.7:1) where strains were more often obtained from urban populations. The lower ratios in Queensland (3.5:1) Western Australia (3.7:1), and the Northern Territory (1.5:1) reflected the large non-urban component of gonococcal disease in those regions. Male rectal and pharyngeal isolates were most frequent in South Australia (38% of isolates from men), New South Wales (27%) and Victoria (28%). These percentages are higher than in 2001 and 2002 but also may reflect clinical sampling practices in those States. About 2.5 per cent of isolates are shown as being isolated from 'other' or unknown sites. These included 14 cases of disseminated gonococcal infection in men (0.4%) and 10 (1.8%) in women. Although not all infected sites were identified, isolates from urine samples were regarded as genital tract isolates. Most of the other unidentified isolates were probably from this source. There were a small number of isolates from the eyes of both new-born and older infants and also adults, and from pelvic and Bartholin's abscesses in women.

Antibiotic susceptibility patterns

In 2003 the AGSP reference laboratories examined 3,677 gonococcal isolates for sensitivity to penicillin (representing this group of antibiotics), ceftriaxone (representing later generation cephalosporins), ciprofloxacin (representing quinolone antibiotics) and spectinomycin and for high level resistance to tetracycline (TRNG). As in past years the patterns of gonococcal antibiotic susceptibility differed between the various states and territories. For this reason data are presented by region as well as aggregated for Australia as a whole.

Penicillins

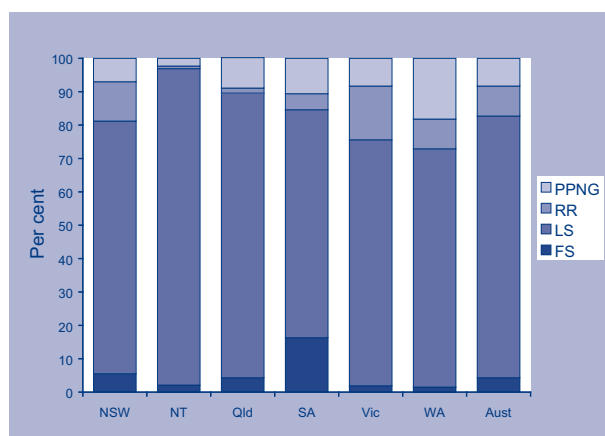
Resistance to the penicillin group (penicillin, ampicillin, amoxicillin) may be mediated by the production of beta-lactamase (penicillinase-producing *N. gonorrhoeae*—PPNG) or by chromosomally-controlled mechanisms (CMRNG).

Chromosomal resistance is expressed as the minimal inhibitory concentration (MIC) in mg/L which is the least amount of antibiotic which inhibits *in vitro* growth under defined conditions. The categorisation of strains in Australia in 2003 by penicillin MIC is shown in Figure 1. The MIC reflects the expression of multiple and different chromosomal changes present in an organism.⁸ These multiple changes result in

incremental increases in the MIC and strains are classified as fully sensitive (FS, MIC ≤ 0.03 mg/L), less sensitive (LS, MIC 0.06 – 0.5 mg/L) or relatively resistant i.e. CMRNG (RR, MIC ≥ 1 mg/L). PPNG are a separate (resistant) category. Infections with strains in the less sensitive or fully sensitive categories usually respond to therapy with standard treatment regimens with the penicillins. Infections caused by strains which are PPNG or in the relatively resistant category (CMRNG) usually fail to respond to treatment with the penicillins.

The number (333) and proportion (9%) of isolates resistant to penicillin by chromosomal mechanisms, CMRNG, in 2003 was lower than in 2002 (421, 10.9%) and 2001 (558, 15.3%). Strains of this type were concentrated in Victoria where 147 were detected (16.1% of all isolates) compared with 76 CMRNG, (11%) in 2002. A small increase in the proportion of CMRNG to 4.8 per cent was seen in South Australia in 2003. In Western Australia the number and proportion of CMRNG (29, 8.9%) was little changed from 2002. The number and proportion of CMRNG in Queensland (9, 1.5%) continued to decrease compared to 2002, (26 CMRNG, 4.6%) and 2001 (101, 17.3%). A large decrease in CMRNG was also seen in New South Wales in 2003 when 130 (11.8%) CMRNG were seen compared with 2002, (275 CMRNG, 17%). In the Northern Territory, four CMRNG strains represented 0.8 per cent of all isolates in 2003.

Figure 1. Penicillin resistance of gonococcal isolates, Australia, 2003, by region



- FS Fully sensitive to penicillin, MIC ≤ 0.03 mg/L.
- LS Less sensitive to penicillin, MIC 0.06 – 0.5 mg/L.
- RR Relatively resistant to penicillin, MIC ≥ 1 mg/L.
- PPNG Penicillinase producing *Neisseria gonorrhoeae*.

The number of PPNG isolated in 2003 (306) was 32 more than in 2002 and the proportion of all isolates (9%), was also more than the previous year (7.1%). Again the distribution of PPNG differed significantly by region. Western Australia once again had the highest proportion of PPNG, (59 PPNG representing 18.2% of all gonococci). South Australia had 24 PPNG (10.6%), Queensland 56 (9.1%) and Victoria 76 (8.3%). New South Wales had the highest number of PPNG (78, 7%) The 11 PPNG in the Northern Territory represented 2.3 per cent of all isolates there. Two PPNG were found in Tasmania but none in the Australian Capital Territory. Information on the geographic location of the acquisition of PPNG was available for only 80 of the 306 infections and most data were from New South Wales and Western Australia. In Western Australia, local acquisition was prominent (30 of 39 cases) and in New South Wales overseas acquisition was recorded in 26 of 40 cases. Cambodia, China, Fiji, Hong Kong, Indonesia, Papua New Guinea, the Philippines, Thailand, Viet Nam, the United States of America and the United Kingdom were identified as countries of PPNG acquisition.

Ceftriaxone

No instance of treatment failure following a 250 mg dose of ceftriaxone and attributable to altered MICs has been described in Australia to date. However in 2001, a small number of strains in a few states showed a small increase in ceftriaxone MICs. In 2002, there were 21 gonococci with ceftriaxone MICs > 0.03 mg/L isolated in Australia. In 2003, this number declined to a total of 10 with seven of these in New South Wales, two in South Australia and one in Queensland. Isolates were usually also resistant to quinolones and penicillins, but spectinomycin sensitive.

Spectinomycin

All isolates were susceptible. Resistance most often occurs as a result a single step ribosomal change.

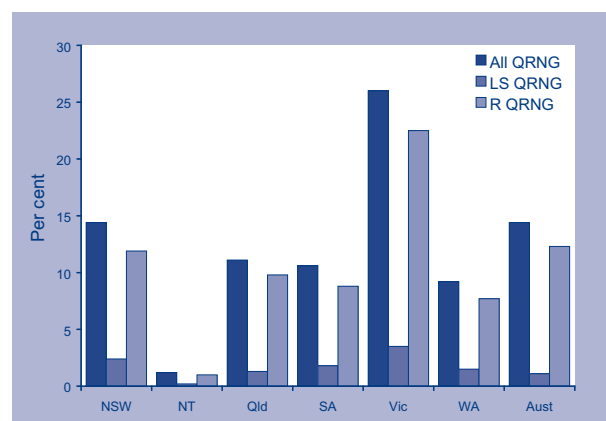
Quinolone antibiotics

Gonococcal resistance to the quinolone antibiotics is mediated only by chromosomal mechanisms so that incremental increases in MICs are observed. The AGSP uses ciprofloxacin as the representative quinolone and defines altered resistance as an MIC of 0.06 mg/L or more. Treatment with currently recommended doses of 500 mg of ciprofloxacin is effective for strains with a lower level of resistance, (0.06 – 0.5 mg/L) in about 90 per cent of cases, but lower doses of the antibiotic will more often result in treatment failure. At higher levels of resistance (1 mg/L or more), treatment failure occurs in about 60 per cent of cases. The proportion of treatment fail-

ures increases exponentially as MICs rise, even if higher dose regimens are used. Currently gonococci with MICs up to 16 and 32 mg/L are being seen in Australia.

In 2003, a total of 529 (14.4%) gonococci had some level of resistance to quinolones (QRNG) (Figure 2) an increase over the 389 (10%) recorded in 2002 but less than the 638 (17.5%) seen in 2001. Most QRNG (452, 85%) had resistance at a high level (MICs \geq 1 mg/L).

Figure 2. Percentage of gonococcal isolates which were less sensitive to ciprofloxacin or with higher level ciprofloxacin resistance and all strains with altered quinolone susceptibility, by region, Australia, 2003



LS QRNG MIC 0.06 – 0.5 mg/L.

R QRNG MIC 1 mg/L or more.

The highest proportion of QRNG was seen in Victoria where the 237 QRNG were 26 per cent of the total number examined. This is a substantial increase in both the number (98) and proportion (14%) of QRNG seen in Victoria in 2002. In New South Wales there were 159 QRNG (14.4%), in South Australia 24 (10.6%), Western Australia 30 (9.2%) and in Queensland 69 (11.1%). In other jurisdictions the numbers of QRNG were low (Northern Territory, 6; Tasmania, 3; Australian Capital Territory, 1).

Information on acquisition of QRNG was available in 110 of the 529 cases. In New South Wales, 41 infections were acquired locally and 41 overseas, but in Western Australia only seven of 28 cases were acquired locally. Overseas acquisition was from many sources. In addition to the countries listed above for PPNG acquisition, QRNG were acquired from contacts in Malaysia and Singapore.

High level tetracycline resistance

The spread of high level tetracycline resistance in *N. gonorrhoeae* (TRNG) is examined as an epidemiological marker even though tetracyclines are not a recommended treatment for gonorrhoea. There was an upsurge in TRNG isolation in 2002 when 442 (11.4%) strains of this type were detected nationally. In 2003, the number (411) and proportion (11.2 %) of TRNG detected throughout Australia was little changed. Most TRNG were found in New South Wales (125, 11.3% of isolates). Western Australia (79, 24%) again had the highest proportion of TRNG. The proportion of TRNG in Queensland (69 isolates, 11.1%) and Victoria (106 isolates, 11.6%) was similar to that in New South Wales. Lower numbers were found in South Australia (17) and the Northern Territory (11) and single isolates of TRNG were found in Tasmania and the Australian Capital Territory.

Discussion

The examination of the susceptibility of gonococci is undertaken principally to determine the patterns of susceptibility of prevalent gonococci to those antibiotics currently recommended for single-dose treatment. The WHO recommends that once resistance to an antibiotic has reached a level of five per cent, then use of that agent should be discontinued. Before surveillance can be reliably performed, a number of technical obstacles that arise from the fastidious nature of the gonococcus need to be overcome. These include the need for specialised isolation and testing methods and that a sufficient number of isolates are examined. The AGSP adopted standardised methods from its inception and conducts a program-specific quality assurance survey. The number of isolates available in Australia in 2003 remained sufficient for the purpose of detecting resistance at the five per cent level. The limitations of culture-based diagnosis, especially in remote settings, decreases the number of gonococci available for testing so that the AGSP currently examines all isolates available to its members, rather than a sample of these isolates. The increasing use of non-culture based methods for the diagnosis of gonorrhoea also decreases the number of gonococcal isolates available for testing. A continuing commitment to maintenance of culture-based systems is required for the purposes of AMR surveillance, while molecular methods for gonococcal susceptibility testing remain problematic.⁹

The wider introduction of nucleic acid amplification testing for diagnostic purposes has also meant that analysis of comparative rates and trends in gonorrhoea, is now more difficult. However some important inferences can be drawn from ancillary information obtained by the AGSP, most notably that on sites of infection and the ratio of disease in men and women. In 2003, although the overall number of isolates was little altered from previous years, a change in the number of isolates in New South Wales and Victoria was notable. While the number of isolates from New South Wales, which had progressively increased over a number of years, declined in 2003 to 1,100 from a peak of 1,600 in 2002, in Victoria the number of gonococci examined increased to 900 from the 700 seen in both 2002 and 2001. As a consequence, the New South Wales gonococci decreased as a proportion of all Australian isolates from 40 per cent in 2002 to 30 per cent in 2003 while the Victorian percentage increased from 18 per cent to 25 per cent. The reasons for these alterations in numbers in New South Wales and Victoria remain uncertain. In both States, gonorrhoea continued to be concentrated in homosexually active males. In New South Wales the ratio of isolates from men and women was unaltered and rectal and pharyngeal isolates from men were again prominent—27 per cent of all male isolates in both 2003 and 2002. In Victoria, the ratio of isolates from men and women increased to 16.7:1 from 10.5:1 in 2002 and the proportion of rectal and pharyngeal isolates in men also increased from 23 per cent to 28 per cent.

Considerable regional variation in susceptibility of gonococci to antibiotics was again observed in Australia in 2003. Previous AGSP data has demonstrated that antibiotic resistant gonococci are more prevalent in larger urban centres than in rural centres.⁴ Because of these pronounced regional differences in patterns of AMR in gonorrhoea in Australia, standard treatment regimens are best derived from a consideration of local patterns of susceptibility rather than aggregated national data.

Oral penicillins remain the mainstay of treatment in rural settings in a number of jurisdictions and patterns of resistance to the penicillins altered little in 2003. In the Northern Territory, both CMRNG and PPNG rates were low. In contrast, penicillin resistance continues at a high rate in urban centres in 2003 and penicillin resistance in New South Wales, Victoria, South Australia, Queensland and Western Australia ranged between 10 and 27 per cent. In Victoria and New South Wales, most of this resistance was chromosomally mediated, but in Western Australia, South Australia and Queensland PPNG were prominent.

Patterns of quinolone resistance have shown considerable volatility over a number of years. Until 1999, QRNG were particularly concentrated in homosexually active males in New South Wales and Victoria and the QRNG were predominantly in the lower MIC range (0.06–0.5 mg/L). In 2001 QRNG were more widely dispersed through all centres in Australia, had higher MICs and heterosexual spread was more pronounced. This trend to higher levels of MICs in QRNG continued in 2002 and about 80 per cent of all QRNG, equivalent to eight per cent of all gonococci in Australia, had MICs in the higher range (1–32 mg/L). In 2003, a further upward shift in quinolone resistance in gonococci was observed. More QRNG were detected (14.5% of all gonococci examined) and one in eight of all gonococci in Australia were resistant at an MIC of 1 mg/L or more of ciprofloxacin. Most of this increase in QRNG occurred in Victoria. The number of QRNG there increased from 98 to 237 and QRNG as a proportion of all gonococci doubled in 2003. Smaller increases in the numbers of QRNG detected occurred in South Australia, New South Wales and Queensland, with a slight decline in Western Australia. Acquisition data on QRNG were difficult to obtain, but sustained domestic transmission remained important in New South Wales. There was a significant rate of acquisition of QRNG from countries close to Australia where rates of QRNG remain very high.¹⁰ Use of quinolones, including more recently available members of this group, are unsuitable for the treatment of individuals who acquire gonorrhoea overseas.

Repeated attention has been drawn to the appearance of gonococci with decreased susceptibility to third generation cephalosporin antibiotics in recent AGSP reports. While it is emphasised that no treatment failures have been documented in Australia with gonorrhoea treated with ceftriaxone when a 250 mg dose was used, reports from Japan have confirmed treatment failures with other oral third generation agents including cefixime.¹¹ Laboratory data indicated that these treatment failures in Japan were accompanied by increased MICs with mosaic *penA* genes in the gonococci.³ These gonococci were also resistant to penicillins and quinolones and their presence has been reported in regional surveys and elsewhere.^{10,12} The AGSP uses the Japanese isolates for comparative purposes. Gonococci encountered in Australia have characteristics similar to those reported in Japan. In 2003 these isolates were 10 in number from apparently sporadic cases and MICs did not increase over the values seen in 2001 and 2002. If treatment failure of any type of gonorrhoea with any cephalosporin antibiotic is suspected, intense efforts should be made to obtain cultures of the organism for formal susceptibility testing in a National Neisseria Network laboratory.

All gonococci tested in Australia in 2003, including those with altered cephalosporin susceptibility, were susceptible to spectinomycin.

There is little cause for complacency in the current AGSP data. The incidence of antibiotic resistance in *N. gonorrhoeae* shows no evidence of a decline, and resistance to commonly used agents is at levels that require continuing surveillance to ensure that optimal antibiotic treatment is available for both individual case management and disease control.

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