

Annual report of the Australian Gonococcal Surveillance Programme, 2004

The Australian Gonococcal Surveillance Programme

Abstract

The Australian Gonococcal Surveillance Programme monitors the antibiotic susceptibility of *Neisseria gonorrhoeae* isolated in all states and territories. In 2004, the *in vitro* susceptibility of 3,640 isolates of gonococci from public and private sector sources was determined by standardised methods. Different antibiotic susceptibility patterns were again seen in the various jurisdictions and regions. Resistance to the penicillins nationally was 22 per cent and, with the exception of the Northern Territory, ranged between 12 and 30 per cent. Resistance to quinolones was found in all jurisdictions in a larger proportion of strains and with higher MICs. Nationally, 23 per cent of all isolates were ciprofloxacin-resistant, 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 again 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. *Commun Dis Intell* 2005;29:136–141.

Keywords: antibiotic resistance; disease surveillance; *Neisseria gonorrhoeae*

Introduction

Antimicrobial resistance (AMR) in *Neisseria gonorrhoeae* is a continuing and increasing problem in Australia, impacting adversely on disease control. Standardised treatment regimens for gonorrhoea utilise single dose treatments that seek to cure 95 per cent or more of cases. Surveillance of AMR can provide data on susceptibility patterns and provide guidance regarding optimal choice of standard treatments.¹ The increase in AMR in gonococci in most jurisdictions has necessitated changes in programmatic treatments away from oral agents such as the penicillins and latterly, the quinolones. Where these agents are retained for treatment, continuous monitoring is therefore required to ensure their ongoing effectiveness. Increasingly, the injectable third generation cephalosporin ceftriaxone has been introduced for treatment of gonorrhoea, and another injectable antibiotic, spectinomycin, is also available. There are however increasing numbers of reports of gonococcal isolates showing resistance to multiple antibiotics including decreased susceptibility to third generation cephalosporins such as ceftriaxone.^{2,3,4}

Monitoring of AMR in gonococci is conducted the Australian Gonococcal Surveillance Programme (AGSP) through a collaborative program conducted by reference laboratories in each state and territory. Data analysed by the AGSP 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 2004 calendar year.

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 thus provided in order to indicate the AGSP sample size.

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Gonococci isolated in and 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 (QA) program.⁷ Antibiotic sensitivity data were submitted quarterly to a coordinating laboratory which collated the results and also conducted the QA 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

Numbers of isolates

There were 3,640 gonococcal isolates referred to or isolated in AGSP laboratories in 2004, slightly less than the 3,772 examined in 2003. The source and site of infection with these isolates are shown in the Table. One thousand one hundred and thirteen gonococci (30% of the Australian total) were isolated in New South Wales, 854 (23.4%) in Victoria, 621 (17%) in Queensland, 515 (14.1%) in the Northern Territory, 329 (9%) in Western Australia, and 166 (4.5%) in South Australia with small numbers in Tasmania (22) and the Australian Capital Territory (20). Of the total, 3,542 remained viable for susceptibility testing.

Nationally, 132 (5%) fewer isolates were received in 2004 than in 2003. The number of isolates fell by 66 in Victoria, 61 in South Australia, but only in small numbers elsewhere. Numbers in Tasmania and the Australian Capital Territory, although small, rose substantially from 2003 levels.

Source of isolates

There were 3,077 strains from men and 559 from women, with a male to female (M:F) ratio of 5.5:1, slightly less than the 5.8:1 ratio for 2003. The number of strains from men decreased by 137 but rose by seven from women. The M:F ratio was again high in New South Wales (13.3:1) and Victoria (11.9:1) where strains were more often obtained from urban populations. The lower ratios in Queensland (4.3:1) Western Australia (4.8:1), and the Northern Territory (1.3:1) reflected the large non-urban component of gonococcal disease in those regions. Male rectal and pharyngeal isolates were most frequently found in Victoria (31% of isolates from men), New South Wales (30%) and South Australia (20%) These percentages approximate those recorded in 2003 but also may reflect clinical sampling practices in those States. About three per cent of isolates are shown as being isolated from 'other' or unknown sites. These included six cases of disseminated gonococcal infection in men (0.2%) and seven (1.2%) 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

Table. Source and number of gonococcal isolates, Australia, 2004, by sex, anatomical site and state or territory

	Site	State or territory						Aust
		NSW	NT	Qld	SA	Vic	WA	
Male	Urethra	695	255	447	109	536	256	2,330
	Rectal	201	1	37	15	146	9	414
	Pharynx	118	1	14	13	102	4	253
	Other/NS	21	40	7	3	4	4	80
	Total	1,035	295	505	141	788	273	3,077
Female	Cervix	73	192	111	23	61	54	516
	Other/NS	5	24	5	25	5	2	43
	Total	78	216	116	25	66	56	559
Unknown	Total	0	4	0	0	0	0	4
Total*		1,113	515	621	166	854	329	3,640

* Includes isolates from Tasmania (22) and the Australian Capital Territory (20).

NS Not stated.

were probably from this source. There were a small number of isolates from the eyes (17) of both newborn and older infants and also adults, and from Bartholin's abscesses in women.

Antibiotic susceptibility patterns

In 2004, the AGSP reference laboratories examined 3,542 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

The categorisation of gonococci isolated in Australia in 2004 by penicillin MIC is shown in Figure 1. Infections unlikely to respond to the penicillin group of antibiotics (penicillin, ampicillin, amoxycillin, with or without clavulanic acid) are those caused by gonococci shown as 'penicillinase-producing' *N. gonorrhoeae* (PPNG) and 'RR – relatively resistant'. Resistance in the PPNG group results from the production of beta-lactamase and in those 'relatively resistant' by the aggregation of chromosomally-controlled resistance mechanisms⁸ – so-called CMRNG. Chromosomal resistance is defined by an MIC to penicillin of 1 mg/L or more. (The minimal inhibitory concentration in mg/L (MIC) is the least amount of antibiotic which inhibits *in vitro* growth under defined conditions.) Infections with gonococci classified as

fully sensitive (FS, MIC \leq 0.03 mg/L), or less sensitive (LS, MIC 0.06 – 0.5 mg/L) would be expected to respond to standard penicillin treatments.

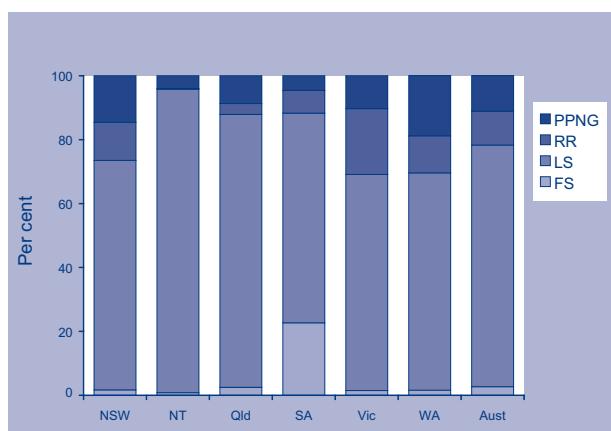
Nationally, 770 (21.7%) gonococci were penicillin resistant by one or more mechanisms in 2004 and 377 (10.6%) were CMRNG and 393 (11.1%) were PPNG. The number and proportion of CMRNG increased slightly in 2004 compared to the 333 (9%) seen in 2003. The national increase in the number of PPNG in 2004 was more substantial, up from 306 (9%) in 2003.

Penicillin resistant gonococci were a particularly large proportion of gonococcal isolates in Victoria (30.8%; PPNG 10.3%, CMRNG 20.5%), Western Australia (30.4%; PPNG 18.8%, CMRNG 11.6%), and New South Wales (26.5%; PPNG 14.5%, CMRNG 11.9%). In South Australia and Queensland penicillin resistance was also high at 11.7 per cent and 12.1 per cent respectively. PPNG were prominent in Queensland (8.7%) and CMRNG were prominent in South Australia (7.1%). Three PPNG were identified in the Australian Capital Territory and four in Tasmania where three CMRNG were also identified. In the Northern Territory there were 19 PPNG and a single CMRNG giving a total of 4.2 per cent of strains being penicillin resistant. Thirteen of the PPNG were from Darwin and where acquisition data were available, all PPNG were acquired overseas. No penicillin resistant isolates were identified among gonococci isolated in Alice Springs. Data on acquisition were available in only 106 (27%) infections with PPNG. Fifty-one infections with PPNG were acquired locally and 55 by contact in South or South East Asian countries.

Ceftriaxone

Ceftriaxone is the third generation cephalosporin most used for treatment of gonorrhoea in Australia. The recommended dose for uncomplicated mucosal infection is 250 mg intramuscularly. To date there has been no instance of failure with ceftriaxone treatment attributable to decreased susceptibility described in Australia. Since 2001 however, low numbers of strains have been found with slightly raised ceftriaxone MICs. In 2002, there were 21 gonococci with ceftriaxone MICs > 0.03 mg/L isolated in Australia and 10 in 2003. In 2004, another 24 (0.7%) gonococci were seen with raised MICs. These were concentrated in New South Wales (22 of 24), with single isolates from the Northern Territory and Queensland. Isolates were usually also resistant to quinolones and penicillins, but spectinomycin sensitive. Recent Japanese data suggests that these strains are now more prevalent there, are multi-resistant and on occasion are associated with treatment failure with oral third generation agents not available in this country.^{2,3,5}

Figure 1. Penicillin resistance of gonococcal isolates, Australia, 2004 by region



FS	Fully sensitive to penicillin, MIC \geq 0.03 mg/L.
LS	Less sensitive to penicillin, MIC 0.06 – 0.5 mg/L.
RR	Relatively resistant to penicillin, MIC \leq 1 mg/L.
PPNG	Penicillinase producing <i>Neisseria gonorrhoeae</i> .

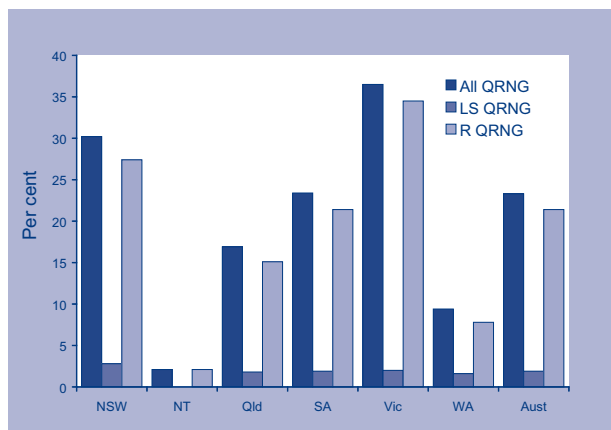
Spectinomycin

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

Quinolone antibiotics

Figure 2 shows the distribution of gonococci with altered susceptibility to quinolones, by region. Thus far 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 susceptibility 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, viz. 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 i.e. an MIC of 1 mg/L or more, rates of failed treatment rise rapidly. Currently, gonococci with MICs up to 16 and 32 mg/L are being seen in Australia.

Figure 2. Percentage of gonococcal isolates less sensitive to ciprofloxacin or with higher level ciprofloxacin resistance and all strains with altered quinolone susceptibility, Australia, 2004, by region



LS QRNG MIC 0.06 – 0.5 mg/L.

R QRNG MIC 1 mg/L or more.

Nationally in 2004, 825 (23.3%) gonococci had some level of resistance to quinolones (QRNG). This represents a further substantial rise in quinolone resistance. In 2003, a total of 529 (14.4%) isolates were QRNG and in 2002 there were 389 (10%) QRNG detected. However, the volatility of these rates is demonstrated when the 638 gonococci (17.5%) QRNG seen in 2001 are considered. Most QRNG in 2004, (757, or 92% of all QRNG) had resistance at a higher level, i.e. MICs \leq 1 mg/L.

The highest proportion of QRNG was seen in Victoria where the 309 QRNG represented 36 per cent of the total number examined. This is a further substantial increase in both the number (237) and proportion (26%) of QRNG seen in Victoria in 2003. In New South Wales, QRNG also increased markedly from 159 (14.4%) in 2003, to 331 (30%) in 2004. South Australia (36, 24%) and Queensland (103, 16.7%) also experienced increases in QRNG rates. In Western Australia, QRNG numbers were unchanged from 2003 and in other jurisdictions the numbers of QRNG were low (Northern Territory, 10; Tasmania, 3; Australian Capital Territory, 3).

Information on acquisition of QRNG was available in 179 of the 529 cases. One hundred and nine (60%) were acquired locally and the remainder overseas.

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 11.4 per cent of strains of this type were detected nationally with little further change in 2003. There was a further increase in TRNG in 2004 to 490 (13.8% of all gonococci).

TRNG were present in all jurisdictions with the highest proportion in Western Australia (27%, 86 isolates) and New South Wales (18%, 195 isolates). Victoria (12.65%, 107) and Queensland (1.3%, 63) also had high rates. Lower numbers were found in South Australia (12) and the Northern Territory (19) and four isolates of TRNG were found in Tasmania and the Australian Capital Territory.

Discussion

The 2004 AGSP data show a further reduction in Australia of the susceptibility of gonococci to antibiotics used for treatment of gonorrhoea. Because of the pronounced regional differences in patterns of AMR in gonorrhoea in Australia, programmatic and standard treatment regimens are best derived from a consideration of local patterns of susceptibility rather than aggregated national data. As a guide to interpretation of AGSP data, the World Health Organization recommends that once resistance to an antibiotic has reached a level of five per cent in a population, continuing use of that agent should be reconsidered.

Penicillin resistance continued at a high rate in urban centres in 2004 and penicillin resistance in New South Wales, Victoria, South Australia, Queensland and Western Australia ranged between 12 and 30 per cent. Different mechanisms were responsible for these rates in different jurisdictions. In Western Australia and Queensland PPNG remained prominent and PPNG increased New South Wales. In Victoria and South Australia most penicillin resistance was chromosomal. PPNG were found in all jurisdictions including Tasmania, the Australian Capital Territory and the Northern Territory. In the latter jurisdiction, most PPNG seemed to be confined to the Darwin area and were in the main, imported infections.

Further increases in quinolone resistance were observed in 2004. QRNG were found in all centres, in higher numbers and proportions and with MICs in higher ranges. Local spread was also common. Jurisdictional rates of resistance ranged from two per cent in the Northern Territory to 36 per cent in Victoria where high rates of QRNG continue. In New South Wales the rate of QRNG increased substantially in 2004. Alternative treatments to quinolones should now be used in most settings in Australia. QRNG are also widely distributed in countries close to Australia⁹ and antibiotics other than quinolones should be used for gonococcal infection acquired outside Australia.

The AGSP has for several years observed and reported the presence of low numbers of gonococci showing some decreased susceptibility to ceftriaxone, and by inference other third generation cephalosporins. A similar observation was made in 2004 and most of the isolates with decreased susceptibility to ceftriaxone were found in New South Wales. Japanese isolates with raised MICs have been shown to possess mosaic penicillin-binding protein 2 (PBP-2) genes⁵ possibly arising as a result of recombination events between *N. gonorrhoeae* and commensal *Neisseria*.¹⁰ Only continued surveillance will reveal if further alterations resulting in still higher levels of resistance occur. Cephalosporin less susceptible isolates in Australia and elsewhere usually display resistance to multiple antibiotics.⁴ All gonococci tested in Australia in 2004, including those with altered cephalosporin susceptibility, were susceptible to spectinomycin.

AMR surveillance conducted by the AGSP achieves consistently high technical standards through an on-going quality assurance program. For AMR surveillance it is necessary to obtain a sufficiently large and representative sample of isolates. The isolates obtained by the AGSP come from the pub-

lic and private sector and are currently in sufficient numbers to detect resistance rates at the five per cent level. However the increasing use of non-culture based methods for the diagnosis of gonorrhoea decreases the number of gonococcal isolates available for testing. Thus a continuing commitment to maintenance of culture-based systems is required for the purposes of AMR surveillance, and alternative methods based on targeted culture of high-risk groups require exploration. Every effort should be made to obtain a gonococcal isolate from patients in whom treatment failure is suspected.

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