

Annual report of the Australian Gonococcal Surveillance Programme, 2001

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 2001 the *in vitro* susceptibility of 3,641 isolates of gonococci from public and private sector sources was determined by standardised methods. Antibiotic susceptibility patterns again varied considerably between regions. Resistance to the penicillins remained high in larger urban centres and warrants close attention in those rural centres where treatment with the penicillins continues. Quinolone resistance in gonococci (QRNG) became more widespread in Australia in 2001 and MICs increased. Nationally, 17.5 per cent of all isolates were QRNG. Endemic cycles of transmission of QRNG in homosexually active men declined further, but heterosexual transmission increased substantially. All isolates remained sensitive to spectinomycin. A small number of isolates in a number of jurisdictions again showed some decreased susceptibility to ceftriaxone. 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* 2002;26:242-247.

Keywords: Surveillance, Neisseria gonorrhoeae, antimicrobial resistance, gonorrhoea, antibiotics, quinolones, penicillins, spectinomycin, cephalosporins

Introduction

The Australian Gonococcal Surveillance Programme (AGSP) was established in 1979 to monitor the susceptibility to antibiotics of gonococci isolated throughout the country. The need for such a program is arguably now more important than ever as both the rates of gonococcal disease and levels of antibiotic resistance in *Neisseria gonorrhoea* continue to increase.

The AGSP is a long-term collaborative program conducted by reference laboratories in each State and Territory. Data from this program were published in *Communicable Diseases Intelligence* (CDI) from 1981 and annual reports have been produced since 1996. Prior to 1996, consolidated data were published elsewhere. This report is based on data obtained during the 2001 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 acknowledgments). 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. Although the sources of isolates remained relatively unchanged in 2001, the increasing use of non-culture based methods of diagnosis reduces the number of cultures available for susceptibility testing, and the details of the numbers of organisms examined are provided in order to indicate sample size and not disease incidence.

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.¹ The AGSP also conducted a program-specific quality assurance (QA) program.² 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. The geographic source of acquisition of resistant strains was ascertained whenever possible.

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Results

Numbers of isolates

There were 3,725 gonococcal isolates referred to or else isolated in AGSP laboratories in 2001. The number and percentage of isolates from each State and Territory (except for the Australian Capital Territory and Tasmania, n=19) for 1999 to 2001 are shown in Table 1.

The source and site of infection of these isolates are shown in Table 2. Of these 3,641 remained viable for susceptibility testing.

Compared with data from the same sources in recent years, there were decreases in the number of isolates tested from Victoria (from 744 in 1999 and 802 in 2000 to 701) and in Western Australia. Increases were recorded in South Australia (124) and New South Wales (1,505). The number of isolates available from the Northern Territory and Queensland was stable. Numbers in other centres were low.

Table 1. Trends in sample size of gonococcal isolates analysed by the AGSP, Australia (except the Australian Capital Territory and Tasmania) 1999 to 2001, by State or Territory

Jurisdiction	Number (% of annual total) gonococcal isolates					
	1999		2000		2001	
	n	%	n	%	n	%
New South Wales	1,528	41.0	1,255	35	1,505	40
Northern Territory	453	12.1	445	13	460	12
Queensland	589	16.0	620	17	619	17
South Australia	93	2.5	93	3	124	4
Victoria	744	20.0	802	23	701	19
Western Australia	313	8.4	317	9	297	8
Total	3,720		3,532		3,706	

Note: data on the number and source of isolates tested are reported to provide information on the sample available for susceptibility testing, not disease incidence.

Table 2. Source and sample size of gonococcal isolates tested for antibiotic susceptibility, Australia, 2001, by sex, site and State or Territory*

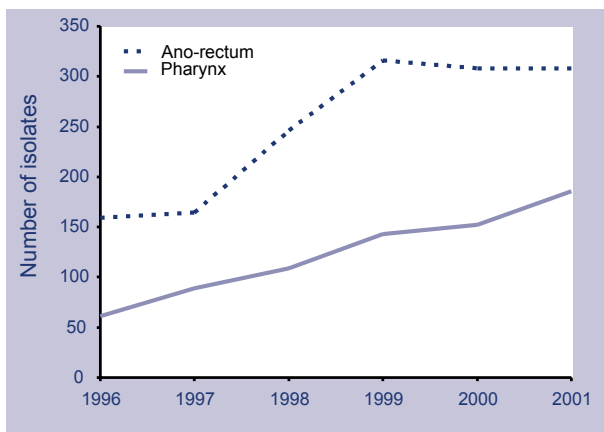
	Site	NSW	NT	Qld	SA	Vic	WA	Aust
Male	Urethra	1,040	270	408	61	539	222	2,550
	Rectal	206	1	26	13	50	9	308
	Pharynx	126	3	9	11	35	0	186
	Other/NS	34	47	16	7	22	2	130
	Sub total	1,406	321	459	92	646	233	3,174
Female	Cervix	87	129	153	30	44	62	507
	Other/NS	12	10	7	2	11	2	44
	Subtotal	99	139	160	32	55	64	551
Total		1,505	460	619	124	701	297	3,725

* The site of isolation of some infected patients was not known.

Source of isolates

There were 3,174 strains isolated from men and 551 strains isolated from women, giving a male to female (M:F) ratio of 5.7:1. This ratio changed little from the previous year. The M:F ratio remained highest in New South Wales (14.2:1) and Victoria (11.7:1) where a higher proportion of strains were obtained from urban populations. The lower ratios in Western Australia (3.6:1), Queensland (2.8:1) and the Northern Territory (2.3:1) reflected the large non-urban component of gonococcal disease in those regions. Male rectal and pharyngeal isolates were most frequently found in New South Wales (23% of isolates from men) and Victoria (13%). This pattern is similar to that noted in recent years, but may also reflect clinical sampling practices in those States (Figure 1). About 5 per cent of isolates are shown as being isolated from 'other' sites. These included 13 cases of disseminated gonococcal infection, most of these in men in New South Wales. 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, although they were not so specified. There were a small number of isolates from the eyes of both newborn and older infants and also adults.

Figure 1. Male rectal and pharyngeal isolates by year 1996 - 2001, in New South Wales and Victoria



Antibiotic susceptibility patterns

In 2001, the AGSP reference laboratories examined 3,641 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

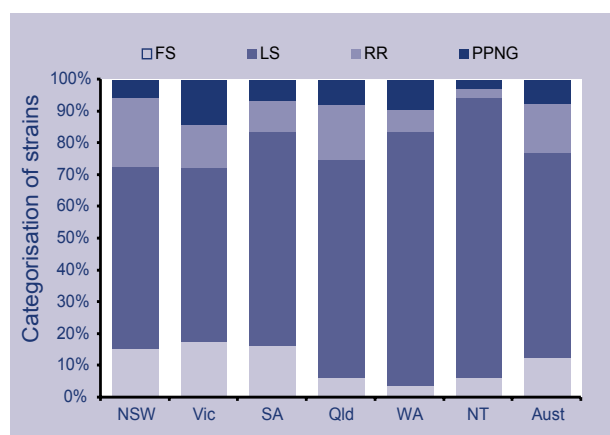
susceptibility differed between the various states and territories. For this reason data are presented by jurisdiction as well as aggregated for Australia as a whole.

Penicillins

Resistance to the penicillin group (penicillin, ampicillin, amoxycillin) 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 in mg/L (MIC) which is the least amount of antibiotic which inhibits *in vitro* growth under defined conditions. The categorisation of strains in Australia in 2001 by penicillin MIC is shown in Figure 2. The MIC reflects the expression of multiple and different chromosomal changes present in an organism.³ These multiple changes result in incremental increases in the MIC and strains are classified as fully sensitive (FS, MIC \leq 0.03 mg/L), less sensitive (LS, MIC 0.06 - 0.5 mg/L) or relatively resistant i.e. CMRNG (RR, MIC \geq 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.

Figure 2. Penicillin resistance of gonococcal isolates, Australia, 2001 by jurisdiction



- FS Fully sensitive to penicillin, MIC \leq 0.03 mg/L
- LS Less sensitive to penicillin, MIC 0.06 - 0.5 mg/L
- RR Relatively resistant to penicillin, MIC \geq 1 mg/L
- PPNG Penicillinase producing *N. gonorrhoeae*

The number (558) and proportion (15.3%) of isolates resistant to penicillin by CMRNG, in 2001 was higher than the 377 (10.6%) recorded in 2000 but approximated the 525 (14.3%) recorded in 1999. Strains of this type were concentrated in New South Wales (321 CMRNG, 21.5% of all isolates) Victoria (91 CMRNG, 13.4%), and Queensland (101 CMRNG, 17.3%). An increase in CMRNG was noted in Western Australia to 20 (6.9%) from 6 (2%) CMRNG in 2000. In the Northern Territory, 13 strains represented 2.9 per cent of all isolates, twice the number and proportion seen in 2000. In South Australia, nearly 10 per cent of isolates were CMRNG.

PPNG decreased slightly in 2001 both in number and as a percentage of all isolates (to 274 and 7.5% from 302 and 8.7% in 2000) but was similar to the number and proportion of PPNG in 1999. The distribution of PPNG differed significantly by jurisdiction. Victoria had the highest number (96) and proportion (14.2%) of PPNG. New South Wales had 86 PPNG (5.7%), Queensland 45, (7.7%), Western Australia 27, (9.3%) and South Australia 8, (6.5%). Twelve PPNG were found in the Northern Territory (2.7%). PPNG were acquired locally in a minority of cases and contact in countries close to Australia accounted for the source of most PPNG infections. Indonesia, the Philippines, Thailand, Vietnam and China were the most frequently nominated countries of PPNG acquisition. PPNG acquisition was also reported from contact in Dubai, Ethiopia, Korea, Malaysia, Mexico, Norway, Russia, Singapore, Hong Kong, Cambodia and Taiwan.

Ceftriaxone

Ceftriaxone resistance leading to treatment failure has yet to be encountered. A small but increasing number of strains in a number of jurisdictions showed a small increase in ceftriaxone MICs. The mechanisms by which these alterations occurred have not been determined but are presumed to be the result of changes in penicillin binding sites.

Spectinomycin

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

Quinolone antibiotics

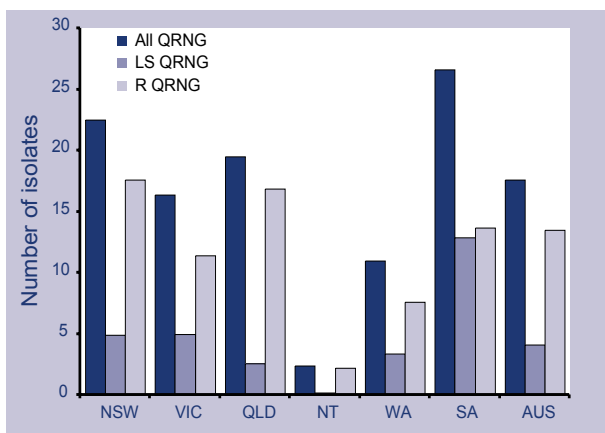
Resistance to the quinolone antibiotics is mediated only by chromosomal mechanisms so that incremental increases in MICs are observed. The AGSP uses ciprofloxacin as the representative quinolone and defines altered resistance as an MIC of 0.06 mg/L or more. Treatment with currently recommended doses of 500 mg of ciprofloxacin is effective for strains with this level of developed resistance in about 90 per cent of cases, but lower doses of the antibiotic will more often result in treatment failure. The proportion of treatment failures increases exponentially as MICs rise. Treatment failure occurs in about 60 per cent of infections with strains with MICs of 1 mg/L or more, even when higher doses are used. Currently, gonococci with MICs up to 16 and 32 mg/L are being seen in Australia.

In 2001, a total of 638 gonococci (17.5%) displayed altered sensitivity to the quinolones (QRNG) (Figure 3). This is about the same number and proportion of QRNG seen in 2000 (619, 17.8%) and 1999 (628, 17.2%) but more than the three times the number of QRNG seen in 1998 (186, 5.2%). Up to 1999, QRNG were particularly concentrated in homosexually active men (HAM) in New South Wales and Victoria. In 2001, the distribution of QRNG became more widespread, with larger numbers found in more jurisdictions while a slight decline in QRNG numbers occurred in the two larger States. The QRNG seen previously in HAM were predominantly in the lower MIC range, namely, 0.06 - 0.5 mg/L. In 2001 in all centres, the predominant QRNG were those with MICs of 1 mg/L or more.

In South Australia the 33 QRNG represented 26 per cent of all gonococci and 114 QRNG represented 20 per cent of all isolates in Queensland. The 337 QRNG in New South Wales comprised 22.5 per cent of all isolates. In Victoria 111 QRNG accounted for 16.4 per cent of all isolates and 32 QRNG represented 11 per cent of gonococci in Western Australia. The Northern Territory recorded 11 QRNG (2.4%).

In most centres endemic transmission of QRNG was prominent. Importation of QRNG continued from many countries, and as for PPNG was most often from acquisition in nearby countries.

Figure 3. Percentage of gonococcal isolates which were less sensitive to ciprofloxacin* or with higher level ciprofloxacin resistance* and all strains with altered quinolone susceptibility, by jurisdiction, Australia, 2001



* LS QRNG, MIC 0.06 – 0.5 mg/L
R QRNG, MIC 1 mg/L or more

High level tetracycline resistance

The spread of TRNG is examined as an epidemiological marker of drug resistance and tetracyclines are not a recommended treatment for gonorrhoea. Three hundred and forty-three high level tetracycline resistant *N. gonorrhoeae* (TRNG, 9.4 % of isolates) were detected throughout Australia in 2001, similar to that observed in 2000. Most TRNG were found in New South Wales where local spread was more evident. Victoria had the highest proportion of TRNG (98 TRNG, 14.4%) with Queensland 78 TRNG (13.3 %). Lower numbers and proportions were found in Western and South Australia, the Australian Capital Territory and the Northern Territory. Overall the number of TRNG detected altered little in 2001.

Discussion

Patterns of gonococcal disease in Australia show considerable regional differences. A considerable proportion of the gonorrhoea contracted in larger urban centres is in HAM and antibiotic resistant gonococci are often encountered. In contrast, gonorrhoea in rural settings is more often heterosexually transmitted and antibiotic resistance is a lesser concern.⁴ The considerable regional variation in susceptibility of gonococci to antibiotics noted in AGSP reports over many years was again present in 2001. Standard treatment regimens are thus best derived from a consideration of local patterns of susceptibility rather than aggregated national data.

The World Health Organization guidelines suggest that a rate of gonococcal resistance to an antibiotic of 5 per cent or more is an indication to change treatment schedules, although this 'acceptable' resistance rate is much lower in groups with a high rate of disease transmission. A high proportion of the gonococci isolated in urban centres has been resistant to the penicillins for many years. This situation was unaltered in 2001, and these agents should not be used in these settings. Rates of penicillin resistance in New South Wales, Victoria, South Australia, Queensland and Western Australia ranged between 16 and 27 per cent. Most of this resistance was chromosomally mediated, but in Western Australia and Victoria PPNG were prominent. The proportion of CMRNG in the Northern Territory remains low, but there has been a continuing shift upwards in MICs so that close surveillance needs to be maintained if penicillins are to remain the preferred treatment option.

Quinolone resistance remained a major problem in 2001. More QRNG were found in more centres and the MICs were higher. High levels of endemic transmission of QRNG continue together with continuing importation of QRNG from other countries. This suggests that the spread of QRNG in the regions close to Australia, noted in WHO based surveillance,⁵ continues to be relevant to treatment of individuals who acquire gonorrhoea overseas but present locally. The increasing numbers of locally and overseas acquired QRNG severely diminishes the effectiveness of quinolone based treatments for gonorrhoea in Australia. Newer quinolone agents, while marginally more effective for some types of QRNG, are unlikely to be sufficiently efficacious for satisfactory treatment of gonorrhoea in Australia.⁶

Most gonococcal isolates were fully susceptible to the third generation cephalosporin, ceftriaxone, although an increasing number of strains had slightly increased MICs. This too is a trend noted in other reports,^{5,7} and warrants close monitoring. It is emphasised that there have been no treatment failures with later generation cephalosporins attributable to antibiotic resistance. However, because of decreasing efficacy of quinolones, this group of antibiotics is now the first line treatment for gonorrhoea in a number of Australian centres.

The sample of available isolates in 2001 was maintained, and was sufficient for the purpose of susceptibility surveillance. However, the increasing use of non-culture based methods for the diagnosis of gonorrhoea may well pose significant problems in the future unless there is a continuing

commitment to maintaining culture-based systems. Use of non-culture based diagnostic methods has meant that commentary by the AGSP on comparative rates and trends in gonorrhoea is now difficult. It is now established however, that rates of gonorrhoea are again increasing in developed countries, and this coupled with emergence and spread of antibiotic resistance in *Neisseria gonorrhoeae* suggests that efforts for control of this disease must be vigorously maintained. An important element in control is the use of optimal antibiotic treatment and this is best determined by use of data from programs of antibiotic susceptibility surveillance.

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Participating laboratories in the AGSP (to whom isolates should be referred):

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Paul Southwell, Susan Bradbury and Peter Collignon. Microbiology Department, Canberra Hospital, Woden, Australian Capital Territory.

References

1. Australian Gonococcal Surveillance Programme. Penicillin sensitivity of gonococci in Australia: the development of an Australian Gonococcal Surveillance Programme. *Br J Vener Dis* 1984;60: 226-230.
2. Australian Gonococcal Surveillance Programme. Use of a quality assurance scheme in a long-term multicentric study of antibiotic susceptibility of *Neisseria gonorrhoeae*. *Genitourin Med* 1990;66: 437-444.
3. Ropp PA, Hu M, Olesky M, Nicholas RA. Mutations in *ponA*, the gene encoding penicillin-binding protein1, and a novel locus, *penC*, are required for high-level chromosomally mediated penicillin resistance in *Neisseria gonorrhoeae*. *Antimicrob Agent Chemother* 2002; 46:769-777.
4. Tapsall JW. Perspectives on gonococcal disease in Australia, 1999. In: Asche V, ed. Recent advances in microbiology 1999;Volume 7. The Australian Society for Microbiology Inc, Melbourne 1999;7:171-196.
5. The WHO Western Pacific Gonococcal Antimicrobial Surveillance Programme. Surveillance of antibiotic resistance in *Neisseria gonorrhoeae* in the WHO Western Pacific Region, 2000. *Commun Dis Intell* 2001;25:274-276.
6. Shultz TR, Tapsall JW, White PA. Correlation of in vitro susceptibilities to newer quinolones of naturally occurring quinolone-resistant *Neisseria gonorrhoeae* strains with changes in *GyrA* and *ParC*. *Antimicrob Agent Chemother* 2001;45:734-738.
7. CDC. Sexually transmitted disease surveillance 2000 supplement: Gonococcal Isolate Surveillance Project (GISP) annual report - 2000. Atlanta, Georgia: U.S. Department of Health and Human Services, October 2001.