Annual report of the Australian Gonococcal Surveillance Programme, 2002

The Australian Gonococcal Surveillance Programme

Abstract

The Australian Gonococcal Surveillance Programme (AGSP) monitors the antibiotic susceptibility of *Neisseria gonorrhoeae* isolated in all states and territories. In 2002 the *in vitro* susceptibility of 3,861 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 at 18 per cent but ranged up to 22 per cent in larger urban centres. Quinolone resistance in gonococci (QRNG) remained widespread. Nationally 10 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 demonstrated some decreased susceptibility to ceftriaxone (MIC 0.06 mg/L or more) and were concentrated in New South Wales. Patterns of infection were unaltered from previous years. 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* 2003;27:189–195.

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

Introduction

Laboratory analyses can materially assist the control and treatment of gonorrhoea by confirmation of the diagnosis and in provision of antibiotic susceptibility data. The latter activity is crucial as antimicrobial resistance in *Neisseria gonorrhoeae* continues to spread to the detriment of treatment of the individual patient and public health management of gonococcal disease. The public health management of gonorrhoea is based on the use of standardised single dose treatment regimens, the efficacy of which is determined by in vitro resistance monitoring.[1] 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 and 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 2002 calendar year.

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Methods

The AGSP is a component of the National Neisseria Network (NNN) 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. Although the sources of gonococci remained unchanged in 2002, continuing efforts are needed to obtain cultures as the increasing use of non-culture-based methods of diagnosis reduces the number 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.

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.[2] The AGSP also conducted a program-specific quality assurance (QA) program.[3] 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.

Results

Numbers of isolates

There were 3,951 gonococcal isolates referred to or else isolated in AGSP laboratories in 2002. The source and site of infection with these isolates are shown in the Table. One-thousand six-hundred and twenty-five gonococci (41% of the Australian total) were isolated in New South Wales, 694 (17.5%) in Victoria, 588 (14.9%) in Queensland, 565 (14.3%) in the Northern Territory, 347 (8.8%) in Western Australia, and 132 (3.3%) in South Australia with small numbers in Tasmania and the Australian Capital Territory. Of these, 3,861 remained viable for susceptibility testing.

Nationally 226 (6%) more isolates were received in 2002 than in 2001. The number of isolates rose by 120 in New South Wales, 105 in the Northern Territory and 50 in Western Australia. In Victoria and South Australia, numbers were stable in 2002. Queensland was the only state with more than a small decrease in numbers tested (5%). Numbers in other centres were low.

Table. Source and number of gonococcal isolates, Australia, 2002, by sex, anatomical site and state or territory*

	Site	NSW	Vic.	Qld	SA	WA	NT	Aust.
Male	Urethra	1,061	477	416	62	245	344	**2,605**
	Rectal	270	96	14	24	8	1	**413**
	Pharynx	145	50	11	17	2	1	**226**
	Other/NS	39	11	17	12	6	6	**91**
	Total	**1,515**	**634**	**458**	**115**	**261**	**352**	**3,335**
Female	Cervix	84	48	121	17	82	191	**543**
	Other/NS	15	12	9	0	4	10	**50**
	Total	**99**	**60**	**130**	**17**	**86**	**201**	**593**
Unknown	**Total**	**11**	**0**	**0**	**0**	**0**	**12**	**23**
Total		**1,625**	**694**	**588**	**132**	**347**	**565**	**3,951**

* Excluding those from the Australian Capital Territory and Tasmania.

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

Source of isolates

There were 3,335 strains from men and 593 from women, with a male to female (M:F) ratio of 5.6:1, similar to that for 2001. The number of strains from men increased by 161 and from women by 86 strains. The M:F ratio was again high in New South Wales (15.3:1) and Victoria (10.5:1) where strains were more often obtained from urban populations. The lower ratios in Queensland (3.5:1), Western Australia (3:1), and the Northern Territory (1.7:1), reflected the large non-urban component of gonococcal disease in those regions. Male rectal and pharyngeal isolates were most frequently found in South Australia (35% of isolates from men), New South Wales (27%) and Victoria (23%). These percentages are higher than in 2001 but also may reflect clinical sampling practices in those states. About four per cent of isolates are shown as being isolated from 'other' or unknown sites. These included nine cases of disseminated gonococcal infection in men in New South Wales, also noted in 2001. 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, 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.

Antibiotic susceptibility patterns

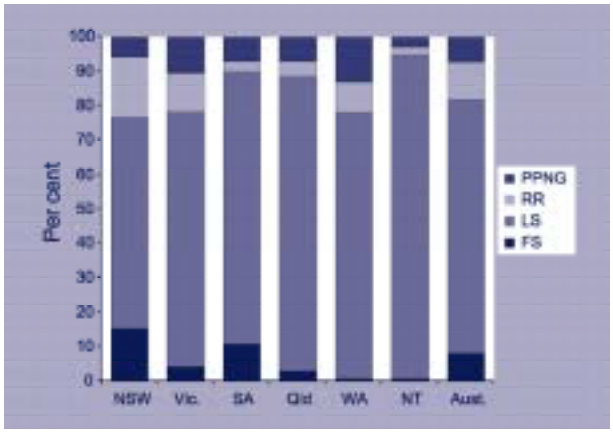
In 2002 the AGSP reference laboratories examined 3,861 gonococcal isolates for sensitivity to penicillin (representing this group of antibiotics), ceftriaxone (representing later generation cephalosporins), ciprofloxacin (representing quinolone antibiotics) and spectinomycin and for high level resistance to tetracycline. 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, 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 2002 by penicillin MIC is shown in Figure 1. The MIC reflects the expression of multiple and different chromosomal changes present in an organism.[4] 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.

Figure 1. Penicillin resistance of gonococcal isolates, Australia, 2002, 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 *N. gonorrhoeae*.

The number (421) and proportion (10.9%) of isolates resistant to penicillin by chromosomal mechanisms in 2002 was lower than the 558 (15.3%) recorded in 2001 but were similar to numbers and proportions seen in 2000.

Strains of this type were concentrated in New South Wales (275 CMRNG, 17 per cent of all isolates) and Victoria (76 CMRNG, 11%). A further increase in CMRNG was noted in Western Australia to 28 (8.5%) from 20 (6.9%) in 2001 and 6 (2%) in 2000. In contrast, the number and proportion of CMRNG in

Queensland (26, 4.6%) decreased markedly from 101 (17.3%) in 2001. In the Northern Territory, 12 strains represented 2.2 per cent of all isolates, similar to the number and proportion seen in 2001. In South Australia, about 3 per cent of isolates were CMRNG.

The number of PPNG isolated in 2002 (274) was identical to that seen in 2001, although as a proportion of all isolates, the 7.1 per cent was a little less than the 7.5 per cent in the previous year. Again the distribution of PPNG differed significantly by region. Western Australia had the highest proportion of PPNG; the 44 isolates representing 13.3 per cent of all gonococci. New South Wales had 94 PPNG (5.8%), Victoria 72 (10.5%), Queensland 39 (6.9%), and South Australia 9 (7.4%). Sixteen PPNG were found in the Northern Territory (3%). Information on the geographic location of the acquisition of PPNG was available in only 98 of the 274 infections and most data were from New South Wales and Western Australia. In both centres local acquisition was prominent. Indonesia, the Philippines, Thailand, Vietnam and China were the most frequently identified countries of probable overseas gonococcal infection. PPNG was also reported from infections acquired in Greece, Hong Kong and Papua New Guinea.

Ceftriaxone

Resistance leading to the third generation injectable agent ceftriaxone that is associated with treatment failure with the 250 mg dose recommended in Australia has yet to be described. In 2001, a small but increasing number of strains in a number of states showed a small increase in ceftriaxone MICs. In 2002, there were 21 gonococci with ceftriaxone MICs > 0.03 mg/L isolated in Australia. Nineteen of these were in New South Wales and there was one each in Victoria and Queensland. Isolates were sporadic of multiple phenotypes and usually resistant to quinolones and penicillins, but spectinomycin sensitive. Isolates with MICs of 0.06 mg/L and above, as determined by the AGSP methodology, are included in this category.

Spectinomycin

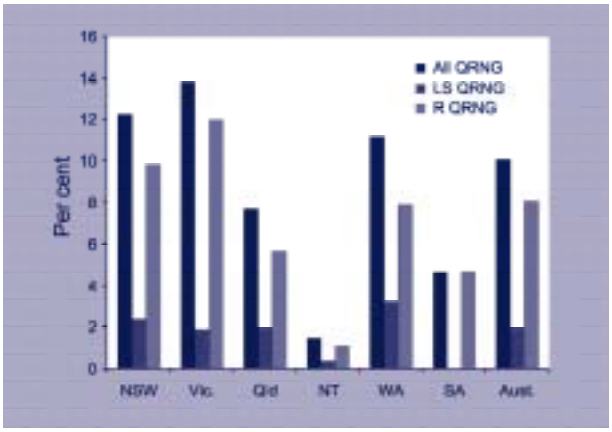
All isolates were susceptible. Resistance most often occurs as a result a single step ribosomal change.

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 lower level of resistance 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, treatment failure occurs in about 60 per cent of cases. The proportion of treatment failures 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 2002 a total of 389 (10%) gonococci had some level of resistance to quinolones (Figure 2). This is substantially less than the 638 (17.5%) gonococci QRNG seen in 2001. There has been considerable volatility in QRNG numbers in different patient populations in Australia over recent years. Until 1999, QRNG was particularly concentrated in homosexually active men (HAM) in New South Wales and Victoria. These QRNG seen in HAM were predominantly in the lower MIC range, namely, 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 pattern 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) The highest proportion of QRNG was seen in Victoria where 96 QRNG were 14 per cent of the total number of isolates examined. In New South Wales there were 199 QRNG (12.3%), in Western Australia 37 (11%) and in Queensland 43 (7.7%). In other jurisdictions less than five per cent of isolates were QRNG.

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, Australia, 2002, by region



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

Information on acquisition of QRNG was available in 125 of the 389 cases. In New South Wales 44 infections were acquired locally and 34 were acquired overseas, but in Western Australia only a quarter of cases were acquired locally. Overseas acquisition was from many sources. In addition to those listed above for PPNG acquisition, QRNG were acquired from Bangladesh, Malaysia, Fiji, New Zealand, the United Kingdom 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 increase in TRNG isolation in 2002 when 442 (11.4%) strains of this type were detected. In 2001, 343 (9.4 %) TRNG were detected throughout Australia and a similar number and proportion were detected in 2000. Most TRNG were found in New South Wales (209, 12.9% of isolates) where local spread was noted. Western Australia (46, 13.8%) had the highest proportion of TRNG, closely followed by Queensland (77 isolates, 13.6%) and Victoria (91 isolates, 13.2%). Lower numbers and proportions were found in South Australia and the Northern Territory.

Discussion

Treatments for gonorrhoea are based on patterns of susceptibility of prevalent gonococci to recommended antibiotics. The World Health Organization states that once resistance to an antibiotic has reached a level of five per cent, then use of that agent should be discontinued. It is important to ensure that a sufficient number of samples are examined to reliably detect this level of resistance. Although the non-random distribution of antibiotic resistant gonococci makes it more difficult to estimate of the size of the sample required for surveillance purposes, the number of isolates available in Australia in 2002 remained sufficient for the purpose of detecting resistance at the five per cent level. However the sample size needed to detect low numbers of resistant gonococci distributed in a non-random fashion in a gonococcal population is extremely large. The limitations of culture-based diagnosis, especially in remote settings, decreases the number of gonococci available for testing. The AGSP examines all isolates available to its members. The use of non-culture-based methods for the diagnosis of gonorrhoea decreases this sample of gonococcal isolates for testing. A continuing commitment to maintenance of culture-based systems is required, while molecular methods for determining gonococcal antibiotic susceptibility remain problematic.[5]

The wider introduction of non-culture-based diagnostic methods 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 2002, as in previous years, considerable regional variation in susceptibility of gonococci to antibiotics was observed in Australia. The AGSP has been able to show that a considerable proportion of the gonorrhoea contracted in larger urban centres remains in homosexually active men where antibiotic resistant gonococci are also most often encountered. In contrast, gonorrhoea in rural settings is more often heterosexually transmitted and antibiotic resistance is a lesser current concern[6] while still requiring close attention as resistance patterns

shift. These differences in patterns of gonorrhoea in Australia mean that programmatic and standard treatment regimens are best derived from a consideration of local patterns of susceptibility rather than aggregated national data.

Penicillin resistance continues at a high rate in urban centres in 2002 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 11 and 23 per cent. CMRNG predominated in New South Wales. In Victoria, CMRNG and PPNG were in similar proportions whereas in Western Australia, Queensland and South Australia PPNG was prominant. The proportion of CMRNG in the Northern Territory remains low, but there has been a continuing shift upwards in MICs so that close surveillance was continued to ensure the efficacy of penicillin-based regimens.

Quinolone resistance also continued at higher than acceptable rates in 2002. Despite a continuing decrease in the number and proportion of QRNG in Australia, the percentage remains high at 10 per cent nationally. QRNG are widely dispersed and the majority of QRNG (8% of all gonococci) have MICs in the range 1–32 mg/L. Sustained domestic transmission continued together with the continued importation of QRNG from many sources. The widespread distribution of QRNG in neighbouring countries and noted in WHO based surveillance,[7] is relevant to treatment of individuals who acquire gonorrhoea overseas but present for treatment locally. 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.[8]

Of increasing concern in recent AGSP reports, and reinforced by findings in 2002, has been the appearance of gonococci with decreased susceptibility to third generation cephalosporin antibiotics. While most gonococcal isolates remained fully susceptible to ceftriaxone, the injectable third generation cephalosporin recommended for treatment in Australia, reports from Japan confirmed treatment failures with other oral third generation agents including cefixime.[9] This treatment failure with oral third generation cephalosporins in Japan coincided with the appearance of an increasing number of strains with increased MICs to these agents.[10] The increased cephalosporin MIC was subsequently shown to be associated with an altered *penA* gene in the gonococci.[11] The AGSP obtained examples of the Japanese isolates for comparative purposes and for use in the AGSP QA program. The gonococci encountered in Australia have characteristics similar to those obtained from Japan. It is emphasised in the Japanese reports that, although ceftriaxone is not used for gonococcal treatment in that country, it was believed that if used in appropriate doses, ceftriaxone would effect a cure with infections caused by these strains. 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 NNN has reviewed its methodology for the detection of gonococci with altered susceptibility to third generation cephalosporins and will continue to monitor the situation in Australia closely. Currently, these isolates are concentrated in New South Wales, but experience would suggest that spread to other regions will inevitably follow. 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 an NNN laboratory. All gonococci tested in Australia, including those with altered cephalosporin susceptibility, were susceptible to spectinomycin.

It is now well established that both the rates of gonorrhoea and the incidence of antibiotic resistance in *N. gonorrhoeae* continue to increase. One important element of control of gonorrhoea is the programmatic use of optimal antibiotic treatment and these regimens are best determined by use of data from surveillance of resistance patterns such as those derived by the AGSP.

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