Annual report of the Australian Gonococcal Surveillance Programme, 1998

The Australian Gonococcal Surveillance Programme[1]

Abstract

The Australian Gonococcal Surveillance Programme examined 3,583 isolates of *Neisseria gonorrhoeae* in 1998. Again in 1998 the rates and sites of infection and antibiotic susceptibility patterns varied considerably between regions, reflecting considerable differences between rural and urban gonorrhoea in Australia. Resistance to the penicillin and quinolone groups of antibiotics was highest in urban centres, but penicillins remained suitable for use in many parts of rural Australia. Quinolone-resistant gonococci continued to be concentrated in New South Wales (NSW) where sustained domestic transmission of these strains was maintained but at a lower rate than in 1997. Endemic transmission of Quinolone-resistant gonococci in homosexually active men was found for the first time. Quinolone-resistant gonococci in other centres continued to be isolated mostly from overseas travellers and at a lower frequency. All isolates remained sensitive to spectinomycin and ceftriaxone. Strains showing high level tetracycline resistance increased by 300% in NSW and were acquired predominantly through local contact. A significant increase in the number of isolates was recorded in NSW and Victoria in 1998, this increase being mainly attributable to an increase in gonorrhoea in homosexually active males. Strains examined in South Australia (SA), NSW and Victoria were predominantly from male patients and rectal and pharyngeal isolates were common. In other centres the male to female ratio was lower, and most isolates were from the genital tract in rates similar to those occurring in 1997. *Commun Dis Intell* 1999;23:193-197.

Introduction

The Australian Gonococcal Surveillance Programme (AGSP) is a collaborative programme conducted by reference laboratories in each State and Territory. The primary aim of the programme is to monitor antibiotic susceptibility of Australian isolates of *Neisseria gonorrhoeae (N. gonorrhoeae)* to assist in the formulation of treatment regimens appropriate to proper management of gonorrhoea.

Control of gonorrhoea is a complex issue which requires a sustained and integrated approach addressing behavioural, educational and treatment issues. There is renewed interest in the means available to control the spread of gonorrhoea following converging epidemiological and biological studies [1-4] showing the significant role of this disease as an amplification factor in the spread of HIV. One essential element for any programme for the control of gonorrhoea is the availability of appropriate antibiotic treatment. Antibiotic treatment of gonorrhoea is best administered as single dose therapy to enhance compliance. The gonococcus has a well demonstrated capacity to develop antibiotic resistance by numerous chromosomal and extrachromosomal mechanisms. Continuing and long term surveillance is required to monitor and respond to changes in resistance which can occur in a short space of time.[5]

There is a close correlation between the likely outcome of treatment and the *in vitro* susceptibility of the causative organism. However, treatment is usually provided before results of susceptibility tests on individual isolates can be performed. Treatment regimens are therefore formulated using knowledge of the *in vitro* sensitivity of prevalent gonococci.[5] That is, the overall pattern of susceptibility of prevalent gonococci is the critical determinant of appropriate antibiotic therapy rather than individual strain susceptibility identified on a case by case basis.[6]

Quarterly reports have been provided to *Communicable Diseases Intelligence (CDI)* since antibiotic sensitivity data were first produced by the AGSP in 1981.[7-10] Initially only data on penicillin resistance were reported and the AGSP documented the appearance and spread of penicillinase producing gonococci (PPNG) in Australia.[8] Monitoring of resistance to other antibiotics was added as newer therapeutic agents became available. Currently the emergence and spread of gonococci resistant to the quinolone antibiotics, agents widely used in Australia, is a particular concern. This is the third annual summary of AGSP data in *CDI* and provides information on trends in disease as well as antibiotic sensitivity data.

Methods

The AGSP comprises participating laboratories in each State and Territory (see acknowledgements). It is a collaborative network of laboratories which seeks to obtain 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. For example, strains from the Northern Territory (NT) are isolated in Alice Springs, Katherine and Darwin and the laboratories of Western Diagnostic Pathology and Queensland Medical Laboratory in the NT and further tested in AGSP centres in Perth, Adelaide and Sydney.

The sources of isolates remained relatively unchanged in 1998. Gonococci isolated in and referred to the

1. Corresponding author, J W Tapsall, Department of Microbiology, The Prince of Wales Hospital, Randwick, New South Wales 2031

Table 1. Gonococcal isolates, Australia, by sex, site and region (excluding those from the ACT and Tasmania), 1998

	Site	Sydney	Melbourne	Brisbane	Adelaide	Perth	Northern Territory	Aust
Male	Urethra	1,023	438	336	67	320	306	2,495
	Rectal	158	63	8	7	5	4	246
	Pharynx	63	22	9	7	0	2	109
	Other/NS	6	4	19	3	3	4	36
	Total	1,250	527	372	84	328	316	2,886
Female	Cervix	121	33	133	15	118	234	654
	Other/NS	15	5	11	1	6	5	43
	Total	136	38	144	16	124	239	697
TOTAL		1,386	565	516	100	452	555	3,853

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.[8] The AGSP also conducted a programme-specific quality assurance (QA) programme.[9] Antibiotic sensitivity data were submitted quarterly to a coordinating laboratory which collated the results and also conducted the QA programme. Additionally the AGSP received data on the sex and site of isolation of gonococcal strains which allows consideration of certain trends in disease patterns. The geographic source of acquisition of resistant strains was ascertained whenever possible.

Results

Numbers of isolates from which susceptibility patterns were derived

There were 3,583 isolates examined in 1998 (Table 1). One-thousand three-hundred and eighty-six gonococci (39% of the Australian total) were isolated in NSW, 565 (16%) in Victoria, 555 (15%) in the NT, 516 (14%) in Queensland, 452 (13%) in Western Australia (WA), and 100 (3%) in South Australia (SA) with small numbers in Tasmania and the Australian Capital Territory (ACT).

Compared with data from the same sources in 1997, the greatest changes in the number and percentage of isolates were the increases in NSW (from 902) and Victoria (from 362). In both of these States the increase was of the order of 50% over the previous year. There was also an increase in the number of isolates available from the NT from 393 in 1997 to 555 in 1998, but a decrease in strains examined in Queensland. The numbers of isolates in SA and WA were only slightly different from the previous year.

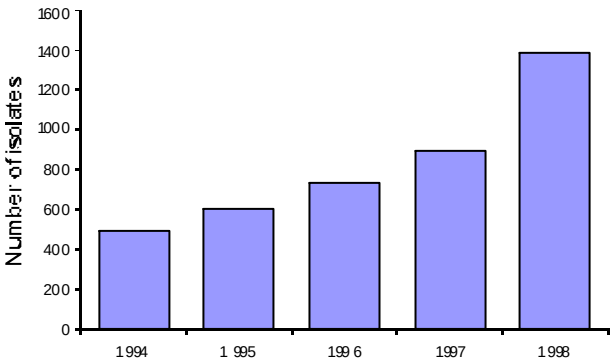
The increase in the number of isolates in NSW represents an acceleration of a trend evident since 1994 (Figure 1), but the increase in Victoria was first evident in 1998.

Source of isolates

There were 2,886 strains from men and 697 from women, with a male to female (M:F) ratio of 4.1:1. The number of strains from men increased from 2,233 in 1997, and strains from women increased from 594 in 1997, but the M:F ratio increased only slightly from the 3.7:1 figure in 1997.

The M:F ratio was higher in Victoria (13.8:1), SA (5.2:1), and NSW (9.2:1) where strains were obtained more from urban populations, but lower in WA (2.6:1), Queensland (2.6:1) and lowest in the NT(1.3:1), reflecting the large non-urban component of gonococcal disease in those regions. Male rectal and pharyngeal isolates were most frequently found in NSW (together accounting for 17.7% of male isolates there), SA (16.6%) and Victoria (16%). This pattern is similar to that noted in 1996 and 1997. Two per cent of isolates are shown as being isolated from 'other' sites. These included 9 cases of disseminated gonococcal infection, 7 in men and 2 in women. Isolates from urine samples collected were regarded as genital tract isolates. There were a small number of isolates from the eyes of new-born infants.

Figure 1. The number of gonococcal isolates from similar sources in New South Wales, 1994 to 1998



Antibiotic susceptibility patterns

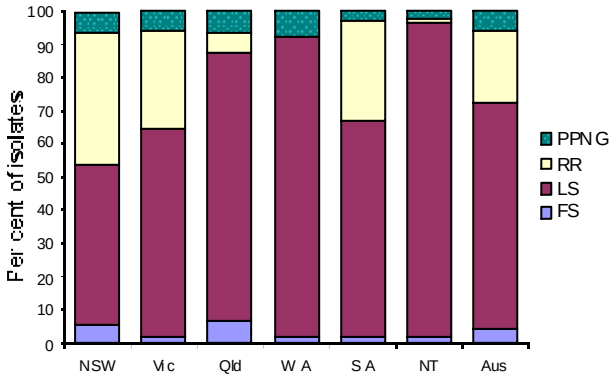
In 1998 the AGSP reference laboratories examined 3,853 gonococcal isolates for sensitivity to penicillin (representing this group of antibiotics), ceftriaxone (representing later generation cephalosporins), ciprofloxacin (representing quinolone antibiotics) and spectinomycin and for high level resistance to tetracycline (TRNG). However, the patterns of gonococcal antibiotic susceptibility differed greatly 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 1998 by penicillin MIC is shown in Figure 2. The MIC reflects the expression of multiple and different chromosomal changes present in an organism. 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 (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 with strains which are PPNG or in the relatively resistant category (CMRNG) usually fail to respond to the penicillins.

Figure 2. Penicillin resistance of gonococcal isolates, Australia, 1998, 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 782 (21.8%) isolates resistant to penicillin by chromosomal mechanisms, CMRNG, in 1998 was double the 361 (12.8%) recorded in 1997. Strains of this type were concentrated in Victoria (165 CMRNG, 30% of all isolates), NSW (545 CMRNG, 40% of all isolates) and SA (30 CMRNG, 30%). In contrast there were no CMRNG amongst WA isolates and 8 (1.4%) in NT strains. The 32 CMRNG in Queensland represented 6% of all isolates there.

The number of PPNG rose slightly in 1998 to 206, but declined as a proportion of all isolates. Again the distribution of PPNG differed by region. New South Wales had the highest number of PPNG, 92, and WA the highest proportion, 7.5%. PPNG were also prominent in Victoria and in Queensland where about 6% of strains were PPNG. Tasmania was the only State where PPNG were not isolated in 1998. Most isolates were from patients infected overseas.

Ceftriaxone and Spectinomycin

All strains from all parts of Australia were sensitive to these injectable agents.

Quinolone antibiotics

Resistance to the quinolone antibiotics is mediated only by chromosomal mechanisms and is thus incremental. The AGSP uses ciprofloxacin as the representative quinolone and defines altered resistance as an MIC≥ 0.06 mg/L. Treatment with currently recommended doses of 500 mg of ciprofloxacin is usually, but not always, effective for strains with this less developed resistance, but lower doses of the antibiotic will more often result in treatment failure. Treatment failure is also likely even with high doses in infections with strains with MICs of 1 mg/L or more. Currently gonococci with MICs up to 16 and 32 mg/L are being seen in Australia.

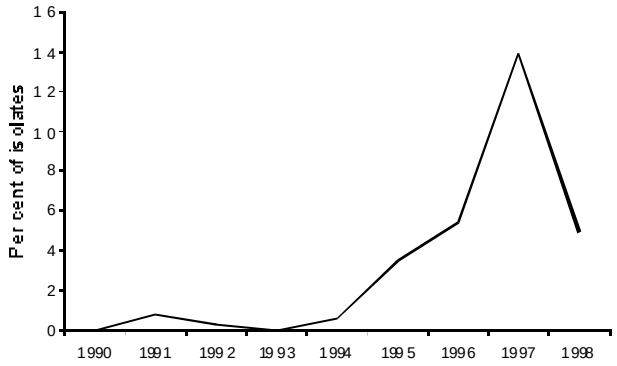
In 1998 a total of 186 (5.2%) of gonococcal isolates displayed altered sensitivity to the quinolones (QRNG). This is less than the 204 (7.2%) QRNG seen in 1997 but still a much higher number than 108 (4%) QRNG seen in 1996. QRNG were found in all States except Tasmania. Victoria had 28 (5%) QRNG, Queensland 25 (4.8%), WA 1 (3.3%) with smaller numbers in SA and the NT. Again the biggest change in QRNG numbers in 1998 occurred in NSW. The 104 (7.5%) QRNG was considerably less than the 144 QRNG (16%) detected there in 1997. An increase in the number and proportion of QRNG had been noted in NSW in the December quarter of 1996 and this rate of isolation was sustained throughout 1997 and the early part of 1998, but declined in the latter part of the year (Figure 3). The spread of QRNG in Sydney by local as opposed to overseas contact also declined throughout 1998. While most other centres showed a slight change in the number and percentage of QRNG isolated, the pattern of acquisition outside NSW is still mainly through overseas contact.

A new feature of QRNG spread in NSW in 1998 was the isolation of these strains from homosexually active men. Prior to 1998 QRNG had been transmitted only by heterosexual contact.

High level tetracycline resistance

Two-hundred and forty-one high level tetracycline resistant *N. gonorrhoeae* (TRNG, 6.7% of isolates) were detected throughout Australia in 1998, a slight increase over the 1997 numbers. Most TRNG were found in NSW (147), representing 10.6% of all isolates. There were 34 TRNG in

Figure 3. **High level quinolone resistance (MIC ≥ 1 mg/L) in gonococci in New South Wales, 1990 - 1998**



WA, 32 in Queensland, 16 in Victoria, and 10 in the NT. Infections with TRNG were mainly acquired overseas in Indonesia, Thailand and Singapore. However an increasing number of isolates were acquired through local contact, especially in NSW.

Discussion

Major regional differences in the antibiotic susceptibility of *N. gonorrhoeae* have been evident for many years and continued in 1998. There was also considerable volatility in the patterns of susceptibility. As a point of reference, the World Health Organization recommends that an antibiotic should no longer be used for treatment when 5% of isolates are resistant to its action.

A high proportion of the gonococci isolated in urban centres have been resistant to the penicillins for many years and this trend was increased in 1998. Between 30% and 50% of isolates in NSW, Victoria and SA were resistant to this group of antibiotics. Most of this resistance was chromosomally mediated (CMRNG) and in locally acquired strains. PPNG have declined in most centres to relatively low proportions, and most PPNG were from imported infections. The proportion of CMRNG in Queensland, the NT and WA remains low so that penicillins remain a suitable treatment strategy in these settings. However, fully sensitive isolates have also declined considerably in numbers indicating an almost inexorable increase in MICs to the point where it seems inevitable that resistance to the penicillins will also emerge in these regions, posing significant problems for management of gonococcal disease.

Patterns of resistance to the quinolone antibiotics also showed a degree of volatility in 1998, especially in NSW. The high levels of resistance to the quinolones evident in 1997 decreased so that QRNG represented 7.5% of isolates. However, endemic transmission of QRNG continued in NSW in 1998 and for the first time was evident in homosexually active males. The proportion and patterns of QRNG in other centres altered little from 1997 and were nearly all imported infections. The quinolone group of antibiotics, with the penicillins, represented the only oral treatments for gonorrhoea available in Australia.

The continuing presence of QRNG in numbers shown in these data remains a cause for concern, especially as Australia is located in a region where the prevalence of QRNG is high. The AGSP used ciprofloxacin as the representative quinolone for assessing resistance to this antibiotic group. Recently, later generation quinolones with increased activity have become available in Australia. Whether this increased activity translates into an ability to treat those QRNG at present found in Australia will require assessment.

All gonococcal isolates were susceptible to the third generation cephalosporin ceftriaxone. Oral third generation cephalosporins are not available in Australia. Earlier generation cephalosporins are less active in gonococcal disease than ceftriaxone. They should be used with caution as overseas studies have indicated that where CMRNG are present in high numbers, (as is the case in Australia), these agents represent suboptimal therapy.

In 1998 the number of TRNG was about 50% more than the 1997 figure. Most of this increase was in NSW where the number of TRNG isolated increased from 47 to 147 and resulted from sustained domestic transmission. Although tetracyclines are not a recommended treatment for gonorrhoea, the appearance and spread of these strains is yet another indication of failure to control this disease.

Although the regional sensitivity patterns provide a more precise guide to suitable treatment in different localities than aggregated Australian data, trends towards resistance noted in the larger urban centres have in the past been indicative of subsequent directions in resistance in other regions. For this reason it is essential to maintain an integrated approach to susceptibility surveillance in Australia.

It has also been known for some time from other epidemiological evidence that rates of gonococcal disease differ greatly in the various jurisdictions in Australia. Rates of disease in rural and Northern Australia may be 100 times those in urban centres. The AGSP has until now been able to confirm these findings with its sample of isolates obtained from relatively unchanging sources. Additionally AGSP data record site of isolation which is not always available in other data sets. This has allowed the AGSP to comment on trends in gonococcal disease in Australia as a by-product of its prime role in antibiotic susceptibility surveillance.[11]

This situation may change as the use of non-culture based methods (such as nucleic-acid-based amplification assays - NAA) increases and the availability of cultures and accompanying clinical data is altered. However, for 1998 the impact of NAA on AGSP data has not been significant, so trend data analysis from traditional sources was still possible.

From these data it seemed that the increase in the number of cases of gonorrhoea noted in NSW in 1997 had accelerated and that a similar situation had arisen in Victoria. In both States the number of gonococcal isolates increased by more than 50% in 1998. In the case of NSW compounding increases in gonococcal isolation rates of 20% had been noted since 1994. The increase in 1998 was on top of these previous increases in isolation rates whereas in Victoria it was the first increase for some years. In both NSW and Victoria the increase in disease

appeared to be in homosexually active males. In NSW the number of rectal and pharyngeal isolates in males increased from 124 in 1997 to 221 in 1998. In Victoria the corresponding figures were 68 to 85. An increasing incidence of gonorrhoea in homosexually active men has been reported from the United States of America.[12]

In NSW there also appeared to be an increase in heterosexually transmitted gonorrhoea with the number of isolates from women doubling from 1997 to 1998 (68 to 136). In Victoria the number of isolates from females in 1998 was essentially unchanged from the 1997 figure. The M:F ratio of disease increased in Victoria from 9:1 in 1997 to almost 14:1 in 1998. In NSW the additional numbers of isolates from females saw this ratio decrease from 12:1 to 9:1 in 1998. In the NT the number of isolates available for testing increased from just under 400 to 555. This may have been the result of initiatives designed to detect gonorrhoea and other STDs in that jurisdiction. The M:F ratio of disease altered less in the NT, SA, WA and Queensland in 1998.

In 1997 it was noted that although all participating centres have an urban and non-urban component in their mix of isolates, the relative contributions of each differs. The greater urban impact is reflected in the high male to female ratio and rate of extra-genital infection in NSW, Victoria and SA. The different pattern of gonococcal disease in Northern Australia is shown in the lower male to female ratio and high rate of genital tract isolates in data from Queensland, WA and the NT. This pattern continued in 1998.

The global decline in incidence of gonococcal disease in some more developed countries has now been arrested and, in parts of Australia at least, the number of cases is again increasing. The choice of suitable treatment for gonorrhoea in Australia is becoming increasingly restricted, especially in the larger cities, so that the unenviable situation of having more disease that is more difficult to treat is now arising. Continued monitoring of resistance patterns is required to optimise treatment regimens. Use of non-culture based diagnostic techniques decreases the opportunity for susceptibility surveillance in gonococci, and the development of strategies for maintenance of this surveillance requires urgent attention.

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Athena Limnios, Tiffany Shultz and John Tapsall. Department of Microbiology, The Prince of Wales Hospital, Randwick, New South Wales

Julia Griffith and Geoff Hogg. The Microbiological Diagnostic Unit, Department of Microbiology and Immunology, University of Melbourne, Parkville, Victoria

Ingrid Lusers and Rosemary Perrie. Infectious Diseases Laboratories, Institute of Medical and Veterinary Science, Adelaide, South Australia

Cheryll McCullough. Microbiology Department, Royal Perth Hospital, Perth, Western Australia

Mark Gardam and Keith Ott. Department of Microbiology and Infectious Diseases, Royal Hobart Hospital, Hobart, Tasmania

Gary Lum and Microbiology Staff. Microbiology Department, Royal Darwin Hospital, Casuarina, Northern Territory

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

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