Annual report of the Australian Gonococcal Surveillance Programme, 1999

The Australian Gonococcal Surveillance Programme
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Abstract

The primary aim of the Australian Gonococcal Surveillance Programme (AGSP) is to monitor the antibiotic susceptibility of *Neisseria gonorrhoeae*. In 1999 the AGSP examined 3,740 isolates of gonococci from all States and Territories. The rates and sites of infection and antibiotic susceptibility patterns varied considerably between regions, reflecting the considerable differences between non-urban and urban gonorrhoea in Australia. Resistance to the penicillin and quinolone groups of antibiotics was highest in urban centres. Although penicillins remained suitable for use in many parts of non-urban Australia, enhanced surveillance is required as levels of resistance increase. Endemic transmission of quinolone-resistant gonococci (QRNG) in homosexually active men increased substantially in New South Wales and Victoria where more then 90% of all QRNG were found. QRNG in other centres continued to be isolated mostly from overseas travellers and at a low frequency. All isolates remained sensitive to spectinomycin and ceftriaxone. A further increase in the number of gonococcal isolates from homosexually active men was recorded in New South Wales and Victoria. Strains examined in South Australia, New South Wales and Victoria were predominantly from male patients and rectal and pharyngeal isolates were common. In other centres the male to female ratio of cases was lower, and most isolates were from the genital tract in rates similar to those occurring in previous years. The impact of non-culture based detection methods will adversely affect the ability of the AGSP to monitor trends in gonococcal disease in future years. *Commun Dis Intell* 2000;24:113-117.

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Introduction

The Australian Gonococcal Surveillance Programme (AGSP) is a collaborative programme conducted by reference laboratories in each State and Territory and its primary aim is to monitor the antibiotic susceptibility of isolates of *Neisseria gonorrhoeae.* The gonococcus has a well-recognised capacity to develop resistance to anti-microbial agents used for treatment of gonorrhoea. This ability has seen the progressive emergence and spread of antibiotic resistant gonococci in Australia with a commensurate reduction in the efficacy of cheap and/or oral treatment options. Australia's location, close to many countries where there is a high proportion of resistant isolates,[1] poses particular problems, although the appearance and spread of antibiotic resistant gonococci differs considerably throughout the country.[2] The data from this programme are used to assist in the formulation of treatment regimens appropriate to proper management of gonorrhoea.

There is a close correlation between the likely outcome of treatment and the *in vitro* susceptibility of the gonococcus. However, treatment is increasingly syndromically based and given as a single dose. Even when an aetiological agent is identified, therapy usually must be provided before results of susceptibility tests on individual isolates can be performed. Standardised treatment regimens are therefore formulated using knowledge of the *in vitro* sensitivity of prevalent gonococci.[3] 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.[3]

Treatment of gonorrhoea is essential to prevent recognised and serious complications of the disease itself. It is now also accepted that gonorrhoea, when untreated, serves to significantly amplify the transmission of HIV. Further, it has been shown that this amplification effect of gonorrhoea on HIV transmission can be greatly reduced if gonorrhoea is appropriately managed. While control of gonorrhoea requires an integrated approach addressing behavioural, educational and treatment issues, there are compelling reasons to ensure that proper antibiotic treatment of gonococcal disease is in place as part of this approach.

Continuing and long-term surveillance is required to monitor and respond to changes in antibiotic resistance that may occur in a short space of time. The AGSP has provided quarterly reports to *Communicable Diseases Intelligence (CDI)*since antibiotic sensitivity data were first produced by the AGSP in 1981.[4] Monitoring of resistance to other antibiotics was added as newer therapeutic agents became available and as penicillin treatment was replaced with other agents. Currently, the emergence and spread of gonococci resistant to the quinolone antibiotics, agents widely used in Australia, is a particular concern. This is the fourth annual summary of AGSP data in *CDI* and provides information on antibiotic sensitivity data and trends in gonococcal disease.

Methods

The AGSP comprises participating laboratories in each State and Territory (see acknowledgments). 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. The sources of isolates remained relatively unchanged in 1999. However, the introduction of a rebatable item for nucleic acid amplification assays for the detection of gonococci in the pathology services table of Medicare will see a reduction in the number of cultures available for susceptibility testing as this technology is progressively introduced. 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.[5] The AGSP also conducted a programme-specific quality assurance (QA) programme.[6] Antibiotic sensitivity data were submitted quarterly to a co-ordinating laboratory which collated the results and also conducted the QA programme. Additionally, the AGSP received data on the sex of the patient and site of isolation of gonococcal strains to analyse certain trends in disease patterns. The geographic source of acquisition of resistant strains was ascertained whenever possible.

Results

Numbers of isolates

There were 3,740 gonococcal isolates referred to or else isolated in AGSP laboratories in 1999. The distribution and site of infection of these isolates are shown in Table 1. Of these, 3,658 (97.8%) remained viable for susceptibility testing in 1999. One-thousand five-hundred and twenty-three gonococci (42% of the Australian total) were isolated and remained viable for testing in New South Wales (NSW),

Table 1. Gonococcal isolates, 1999, Australia, by sex, site and region (excluding those from the ACT and Tasmania)

	Site	New South Wales	Victoria	Queensland	South Australia	Western Australia	Northern Territory	Australia
Male	Urethra	1,133	568	369	65	226	178	2,552
	Rectal	195	83	26	5	5	0	316
	Pharynx	80	55	7	0	0	0	143
	Other/NS	6	3	23	5	1	62	100
	Total	1,414	709	425	75	232	240	3,111
Female	Cervix	103	32	148	13	75	174	548
	Other/NS	11	3	16	5	6	29	80
	Total	114	35	164	18	81	213	628
Total		1,528	744	589	93	313	453	3,740

744 (20%) in Victoria, 552 (15%) in Queensland, 428 (12%) in the Northern Territory (NT), 302 (8%) in Western Australia (WA), and 93 (2.5%) in South Australia (SA) with small numbers in Tasmania and the Australian Capital Territory (ACT).

Compared with data from the same sources in recent years, there were further increases in the number of isolates in NSW (from 902 in 1997 and 1,386 in 1998), Victoria (from 362 in 1997 and 565 in 1998) and Queensland (from 516 in 1998). There was a decrease in the number of isolates available from the NT (from 555 in 1998 to 453) and WA (from 452 in 1998 to 313). The numbers of isolates in SA were only slightly different from the previous year and those from other centres were low. The increase in the number of isolates in NSW was particularly evident in the first 6 months of 1999, but in the second half of the year numbers were comparable to those obtained in 1998.

Source of isolates

There were 3,111 strains from men and 628 from women, with a male to female (M:F) ratio of 5:1. (The sex of one patient was not specified.) The number of strains from men increased from 2,233 in 1997 and 2,886 in 1998, and strains from women numbered 594 in 1997 and 697 in 1998. The M:F ratio was 3.7:1 in 1997 and 4.1:1 in 1998. The M:F ratio was highest in Victoria (20.2:1) and NSW (12.2:1) where more strains were obtained from urban populations than from non-urban populations, but lower in SA (4.2:1). The lower ratios in WA (2.8:1), Queensland (2.6:1) and the NT (1.1:1), reflected the large non-urban component of gonococcal disease in those regions. Male rectal and pharyngeal isolates were most frequently found in NSW and Victoria (19.4% of isolates in both States). This pattern is similar to that noted in 1997 and 1998. Approximately 5% of isolates are shown as being isolated from 'other' sites. These included 13 cases of disseminated gonococcal infection, 9 in men and 4 in women. Isolates from urine samples were regarded as genital tract isolates. Not all sites were designated. There were a small number of isolates from the eyes of both new-born and older infants.

Antibiotic susceptibility patterns

In 1999 the AGSP reference laboratories examined 3,658 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 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

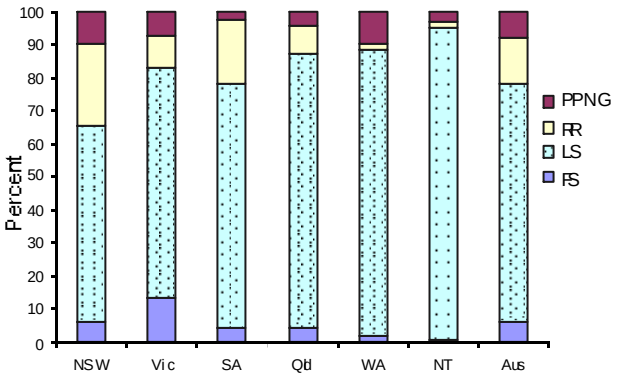
Resistance to the penicillin group (penicillin, ampicillin, amoxycillin) may be mediated by the production of beta-lactamase (penicillinase-producing *N. gonorrhoeae* – PPNG) or by chromosomally-controlled mechanisms (CMRNG).

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 1999 by penicillin MIC is shown in Figure 1. 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.

The 525 (14.3%) isolates resistant to penicillin by chromosomal mechanisms, CMRNG, in 1999 was lower than the 782 (21.8%) recorded in 1998. Strains of this type were concentrated in NSW (375 CMRNG, 24.6% of all isolates), Victoria (72 CMRNG, 9.7% of all isolates), SA (19 CMRNG, 19%) and Queensland (47 CMRNG, 8.5%). In contrast there were 6 (2%) CMRNG amongst WA isolates and 7 (1.6%) in NT strains.

PPNG increased in 1999 both numerically (to 269 from 206 in 1998), and as a proportion of all isolates (to 7.4% from 5.3% in 1998). Again the distribution of PPNG differed by region. NSW had the highest number, 148, and proportion, 9.7%, of PPNG. The 22 PPNG in WA represented 9.6% of strains in that State. PPNG were also prominent in Victoria (54, 7.2%). In Queensland about 4% of strains were PPNG and in the NT 2.8% were PPNG. One or two PPNG were found in Tasmania, the ACT and SA. Geographic acquisition details were available in about two thirds of cases of PPNG infection. Acquisition of PPNG through local contact was more common than through overseas contact in NSW but not in other centres. Indonesia, the Philippines, Thailand, Vietnam and China were the most frequently nominated countries of PPNG acquisition. PPNG acquisition was also reported from contact in Korea, Singapore, Hong Kong, Papua New Guinea, Timor, Japan, Brazil, Malaysia, Cambodia, the United States of America and the United Kingdom.

Figure 1. Penicillin resistance of gonococcal isolates, 1999, Australia, 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*.

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 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 less developed resistance in approximately 90% 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 approximately 60% 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. Newly released quinolone agents would not be expected to offer any significant advantage over ciprofloxacin for the treatment of gonorrhoea.

In 1999 a total of 628 (17.2%) of gonococcal isolates displayed altered sensitivity to the quinolones (QRNG). This is more than three times the number of QRNG seen in 1998 (186, 5.2%) and is attributable to the high rate of QRNG in homosexually active men in NSW and Victoria. Rates of QRNG have been high in NSW since an increase in the number and proportion of QRNG in heterosexuals was noted in NSW in the December quarter of 1996. This rate of isolation was sustained throughout 1997 and the early part of 1998, but declined in the latter part of that year. In NSW in 1998, QRNG appeared in homosexually active males for the first time. In 1999 QRNG increased in NSW to 26% and in Victoria to 24% of all isolates examined. More than 90% of all QRNG identified in Australia in 1999 were found in these two States. QRNG were found in all centres except the ACT. Queensland had 43 (7.8%) QRNG, WA 9 (3%), with smaller numbers in SA, Tasmania and the NT. The spread of QRNG in NSW and Victoria was mainly by local as opposed to overseas contact, but in most other centres cases were imported from overseas contact from sources similar to those described for PPNG acquisition.

High level tetracycline resistance

Two-hundred and eighty-eight high level tetracycline resistant *N. gonorrhoeae* (TRNG, 7.9 % of isolates) were detected throughout Australia in 1999, a slight increase over the 1998 numbers. Most TRNG were found in NSW (168), representing 11% of all isolates. There were 33 (11%) TRNG in WA, 32 (6%) in Queensland, 47 (6%) in Victoria, and 6 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

Two typical features of the antibiotic susceptibility patterns of gonococci isolated in Australia were again evident in 1999; major regional differences continued and there was considerable volatility in resistance especially to quinolone antibiotics. As a point of reference, the World Health Organization recommends that an antibiotic should no longer be used for treatment of gonorrhoea when 5% or more of isolates are resistant to its action.

A high proportion of the gonococci isolated in urban centres has been resistant to the penicillins for many years and this trend was maintained in 1999. Between one eighth and one third of isolates in NSW, Victoria, Queensland and SA were resistant to this group of antibiotics. Most of this resistance was chromosomally mediated (CMRNG) and in locally acquired strains. CMRNG increased in Queensland to 8.5% of all isolates. The decline in the rate of PPNG noted over the past few years was arrested, and local transmission of PPNG was evident in NSW and Victoria. Although the proportion of CMRNG in the NT and WA remains low, there has been a continuing shift upwards in MICs to the point where close surveillance needs to be maintained if penicillins are to remain the preferred treatment option.

Patterns of resistance to the quinolone antibiotics also showed further volatility in 1999, especially in NSW and Victoria. The high levels of endemic transmission of QRNG observed in these two centres indicate that use of this group of therapeutic agents should be discontinued there. The proportion and patterns of QRNG in other centres has altered little in recent years and the QRNG isolated were nearly all from imported infections.

The quinolone group of antibiotics, with the penicillins, are 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.

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 and this figure and proportion increased again in 1999. Sustained domestic transmission of TRNG was evident especially in NSW. The spread of TRNG is examined as an epidemiological marker and tetracyclines are not a recommended treatment for gonorrhoea.

The AGSP has until now been able to confirm other findings on rates of gonococcal disease in Australia 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. This situation has altered as the use of non-culture based methods (such as nucleic-acid-based amplification assays - NAA) has increased and the availability of cultures and accompanying clinical data has decreased. It is not possible to estimate the effect of NAA testing on the data set available to the AGSP. NAA testing became available as a Medicare rebatable item late in 1999, but was widely used across Northern Australia prior to this. Any decline in AGSP numbers to date has been, ironically, in those areas where enhanced susceptibility surveillance is required as penicillin resistance emerges. In other parts of

Australia the impact of NAA testing on isolate availability is yet to be felt.

There was a further increase in the number of isolates in NSW in 1999, although this was not maintained in the second half of the year. There has been a continuing and, until 1998, accelerating increase in the number of gonococcal isolates in NSW since 1994.[2,7] A significant increase in rates of isolation of gonococci was again noted in Victoria in 1999. Numbers had increased by about 50% in 1998 and a further substantial rise was noted in 1999. 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 to 275 in 1999. In Victoria the corresponding figures were 68 to 85 to 138. An increasing incidence of gonorrhoea in homosexually active men has been reported from London.[8] The M:F ratio of disease increased in Victoria from 14:1 in 1998 to almost 20:1 in 1999. In NSW this ratio increased from 9:1 in 1998 to 12:1 in 1999. The M:F ratio of disease altered less in WA and Queensland in 1999 and was lowest (1.1:1) in the NT.

In previous reports 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 and Victoria. The different pattern of gonococcal disease in Northern Australia is shown in the lower male to female ratio and the high rate of genital tract isolates in data from Queensland, WA and the NT. This pattern continued in 1999.

Gonococcal disease is again increasing in some developed countries and this has also been evident in parts of Australia for some time. The increased number of cases is becoming more difficult to treat as the choice of suitable therapy is becoming more restricted by antibiotic resistance. Continued monitoring of resistance patterns is required to optimise treatment regimens. Although non-culture based diagnostic techniques decreases the number of isolates for susceptibility surveillance in gonococci, the sample base currently available is sufficient for this purpose. However, assessment of trends in gonococcal disease by the AGSP will be compromised by these changes.

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