Annual report of the Australian Gonococcal Surveillance Programme, 2007

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 2007 the *in vitro* susceptibility of 3,042 isolates of gonococci from public and private sector sources was determined by standardised methods. The proportion of gonococci resistant to all antibiotics tested nationally was at historically high levels. Different antibiotic susceptibility patterns were again seen in the various jurisdictions and regions. Resistance to the penicillins nationally was at 38% and, with the exception of the Northern Territory, ranged between 24% in Western Australia and 54% in New South Wales. Quinolone resistance in gonococci also continued to increase so that nationally 49% of all isolates were ciprofloxacin-resistant, and most of this resistance was at high MIC levels. Again with the Northern Territory excepted, proportions of quinolone resistant gonococci ranged between 26% in Western Australia and 65% in New South Wales. All isolates remained sensitive to spectinomycin. Approximately 1% of isolates showed some decreased susceptibility to ceftriaxone (MIC 0.06 mg/L or more) and azithromycin resistance was present in low numbers of gonococci. 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* 2008;32:227–231.

Keywords: antimicrobial resistance, disease surveillance, gonococcal infection, *Neisseria gonorrhoeae*

Introduction

Gonorrhoea differs from the other major sexually transmitted diseases prevalent in Australia that are of bacterial origin in that treatment and disease control is compromised by antimicrobial resistance (AMR). AMR in *Neisseria gonorrhoeae* isolated in large urban centres in Australia is heavily influenced by the continuing introduction of multi-resistant gonococci. Treatment options have been severely limited by the increasing lack of efficacy of several major antibiotic groups.[1] In contrast, in remote Australia, traditional penicillin-based regimens retain their efficacy. Strategies for treating and controlling gonorrhoea are based on use of single dose treatments that cure a minimum of 95% of cases.[2] Formulation of these standard treatment regimens relies on data derived from continuous monitoring of the susceptibility of gonococci to recommended antibiotics.[2,3] The Australian Gonococcal Surveillance Programme (AGSP) has monitored the susceptibility of *N. gonorrhoeae* continuously since 1981.[4] The emergence and spread of penicillin and quinolone resistant gonococci in major cities has been well documented.[1] There are increasing concerns about the presence in Australia of gonococcal isolates showing resistance to multiple antibiotics including to the third generation cephalosporin ceftriaxone, which is used extensively in Australia.[1,5] This analysis of AMR in *N. gonorrhoeae* in Australia was derived from data generated by the AGSP during 2007.

Methods

Ongoing monitoring of AMR in gonococci in Australia is performed by the AGSP through a collaborative program conducted by reference laboratories in each state and territory. The AGSP is a component of the National Neisseria Network of Australia and comprises participating laboratories in each state and territory. 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.

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.[4,6] 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

Number of isolates

There were 3,103 gonococcal isolates referred to or else isolated in AGSP laboratories in 2007, approximately 20% fewer than the 3,937 examined in 2006. The source and site of infection of these isolates are shown in the Table. Nine hundred and seventy-three gonococci (31.4% of the Australian total) were isolated in New South Wales, 625 (20.1%) in Victoria, 455 (14.7%) in Queensland, 404 (13%) in the Northern Territory, 366 (11.8%) in Western Australia, and 240 (7.7%) in South Australia with small numbers in Tasmania (20) and the Australian Capital Territory (20). Three thousand and forty-two isolates remained viable for susceptibility testing.

Source of isolates

There were 2,560 strains from men and 541 from women, with a male to female (M:F) ratio of 4.7:1, slightly higher than the 5.3:1 ratio for 2006. The number of strains from men increased by 27 and there was a corresponding decrease in the number of isolates from women. The M:F ratio was again high in New South Wales (8.7:1) and Victoria (9:1) where strains were more often obtained from urban populations. The lower ratios in Queensland (3.3:1) Western Australia (3.6:1), South Australia (2.8:1) and the Northern Territory (2:1) reflected the large non-urban component of gonococcal disease in those regions. Male rectal and pharyngeal isolates were most frequently found in Victoria (together 34% of isolates from men), and New South Wales (33%). One hundred and one isolates show the site as 'other' or 'not stated'. Twenty-six of these were pharyngeal and 10 were rectal isolates from women. Also included in this total were 23 cases of disseminated gonococcal infection, 13 in men (0.9% of infections) and 10 (1.8%) in women. Although not all infected sites were identified, isolates from urine samples were regarded as genital tract isolates and most of the other unidentified isolates were probably from this source, although they were not so specified. There were 10 isolates from the eyes of both newborn and older infants and also adults.

Antibiotic susceptibility patterns

In 2007 the AGSP reference laboratories examined 3,042 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 2007 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 mechanisms[1]

Table. Source and number of gonococcal isolates, Australia, by sex, site and region, 2007

Gender	Site	State or territory						
		NSW	NT	Qld	SA	Vic.	WA	Aust.*
Male	Urethra	572	262	294	148	366	259	1,922
	Rectal	178	0	38	13	117	11	364
	Pharynx	106	2	21	12	75	6	226
	Other/NS	17	3	6	4	5	11	48
	Total	873	267	359	177	563	287	2,560
Female	Cervix	82	132	89	50	57	72	488
	Other/NS	18	4	7	12	5	7	53
	Total	100	136	96	62	62	79	541
Unknown	Total	0	1	0	1	0	0	2
Total*		973	404	455	240	625	366	3,103

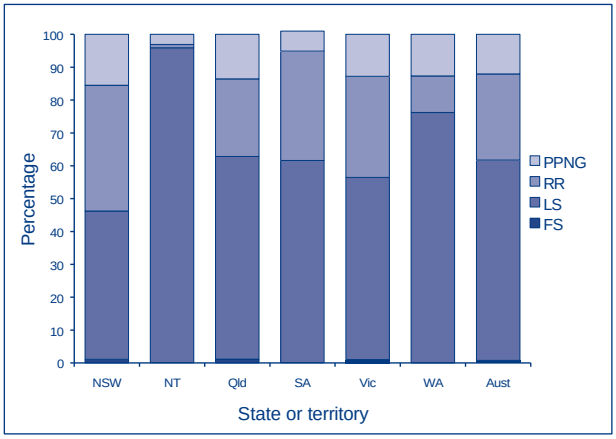
* Includes isolates from Tasmania (20) and the Australian Capital Territory (20).

NS Not stated.

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

(chromosomally mediated resistance to penicillin – CMRP). Chromosomal resistance is defined by an MIC to penicillin of 1 mg/L or more.[1,6] (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 ≤ 0.03 mg/L), less sensitive (LS, MIC 0.06–0.5 mg/L) would be expected to respond to standard penicillin treatments, although response to treatment may vary at different anatomical sites.

Figure 1. Penicillin resistance of gonococcal isolates, Australia, 2007, by state or territory



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*.

Nationally, 1,163 (38.2%) gonococci were penicillin resistant by one or more mechanisms in 2007, a further increase in the proportion of isolates resistant to this group of antibiotics recorded in 2006 (1,306 isolates, 34%), 2005 (1,148, 29.5%) and 2004 (770, 21.7%). Of these, 796 (26.2% of all isolates) were CMRP and 369 (12.1%) PPNG. The proportion of penicillin-resistant gonococci of all gonococcal isolates in New South Wales was 53.8% (PPNG 15.5%, CMRP 38.3%), Victoria 43.6% (PPNG 12.8%, CMRP 30.8%), South Australia 39.4% (PPNG 6.1%, CMRP 33.3%), Queensland 37.2% (PPNG 13.6%, CMRP 23.6%) and Western Australia 23.8% (PPNG 12.7%, CMRP11.1%). Four PPNG and 4 CMRP were identified in the Australian Capital Territory and in Tasmania there were 4 PPNG and 9 CMRP. In the Northern Territory, there were 16 penicillin resistant gonococci (13 from Darwin). Of these 12 were PPNG and 4 were CMRNG showing that 4.1% of strains were penicillin resistant (4.6% in 2006). Data on acquisition were available in 96 (23%) infections with PPNG. Half (48) of the infections with PPNG were acquired locally and half by overseas contact. These contacts were principally in Western Pacific or South East Asian countries with contacts reported from Thailand (8), the Philippines (6) and Indonesia (Bali) (5) the most numerous. Additionally, Chile, China, Ireland, Germany, Ghana, Korea, Malaysia, Singapore and Vietnam were named as countries of contact.

Ceftriaxone

From 2001 onwards, low numbers of isolates with slightly raised ceftriaxone MICs have been found in Australia. In 2006 there were 23 (0.6%) and in 2007, 25 (0.8%) gonococci with ceftriaxone MICs in the range 0.06 to 0.25 mg/L. Twelve of these were in New South Wales (1.2% of isolates there), 4 (0.9%) in Queensland, 3 (0.5%) in Victoria, 3 (1.2%) in South Australia, 1 (0.3%) in Western Australia and 2 in the Australian Capital Territory. These isolates were generally also penicillin and quinolone resistant.

Spectinomycin

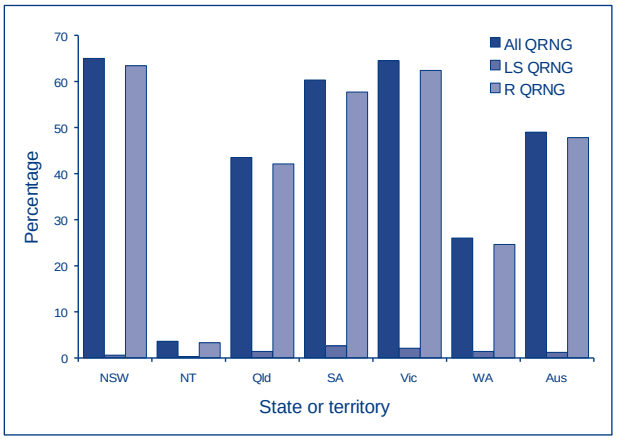
All isolates were again susceptible to this injectable antibiotic.

Quinolone antibiotics

Figure 2 shows the distribution of gonococci with altered susceptibility to quinolones nationally and by state or territory. Thus far, resistance to the quinolone antibiotics in *N. gonorrhoeae* 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 a MIC of 0.06 mg/L or more.[1,6] 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% of cases, but lower doses of the antibiotic will result in treatment failure more often. At higher levels of resistance i.e. a 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. At MIC levels of 4 mg/L or more, treatment failure approaches 100%, even with higher ciprofloxacin doses.

Nationally in 2007, 1,493, (49%) of gonococci examined had some level of resistance to quinolones (QRNG), a substantive increase over the 1,455 (37.8%) detected in 2006 and maintaining a continuing and rapid increase in the proportion of QRNG detected. In 2005 there were 1,190 (30.6%) QRNG reported and 825 (23.3%) were found in 2004. Most of the QRNG (1,456 or 98.8%) had resistance at a higher level, i.e. MICs ≥1 mg/L, and many of these had MIC levels of the order of 8–64 mg/L. High proportions of QRNG were seen in New South Wales

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, 2007, by state or territory



LS QRNG MIC 0.06–0.5 mg/L.

R QRNG MIC 1 mg/L or more.

where 630 QRNG were 65% of all isolates examined, Victoria 398 QRNG (65.5%) and South Australia 140 QRNG (60.3%). Queensland (192 QRNG, 43.5%) and Western Australia (92 QRNG, 26%) also reported large rises in the number and proportion of QRNG detected. In other jurisdictions the number of QRNG remained low – Northern Territory, 15; Tasmania, 14; Australian Capital Territory, 12: but in the latter 2 jurisdictions these represented a high proportion of all isolates.

Information on acquisition of QRNG was available in 495 of the 1,493 (33%) cases. Four hundred and twenty-two of these (84%) were acquired locally and 73 (16%) were acquired overseas from sources referred to under PPNG acquisition with contacts also reported in Brazil, Greece, Spain, the United Kingdom and the United States of America.

High-level tetracycline resistance

The spread of high-level tetracycline resistance in *N. gonorrhoeae* 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% of strains of this type were detected nationally with little further change in 2003. A further increase in TRNG numbers to 490 in 2004 saw them represent 13.8% of all gonococci. This proportion was unchanged in 2005 when 534 TRNG were detected. In 2006 there were slightly fewer TRNG (12%). In 2007, the highest proportion of TRNG detected in this series was recorded when 505 (16.6%) of gonococci examined were TRNG.

TRNG were present in all jurisdictions except Tasmania, with the highest proportion in Western Australia (110 TRNG, 31.1%). Lower proportions of TRNG were present in New South Wales (181, 18.7%), Queensland (76, 17%), Victoria (100, 16.2%) and South Australia (21, 9%). There were 13 (3.4%) TRNG found in the Northern Territory and 4 in the Australian Capital Territory.

Discussion

Urban Australia has seen continuing upward trends in the proportion of *N. gonorrhoeae* resistant to multiple antibiotics. In 2007 this trend continued with resistance to the penicillins and quinolones approximating 40% and 50% respectively of all isolates examined. There was also a historical high rate of gonococci with high-level tetracycline resistance. The 'rural–urban divide',[1] in gonococcal resistance rates was maintained, (Figures 1 and 2) illustrating the need for disaggregated information rather than pooled national data to define treatment regimens appropriate for the various jurisdictions. Remote areas in some jurisdictions with high disease rates continue to be able to use penicillin-based treatments, but effective use of this cheap and acceptable treatment requires close monitoring of resistance patterns.

Specific comment has been made in recent reports regarding gonococci with decreased susceptibility to ceftriaxone.[5] In 2007, the number of these isolates remained low at about 1% of all isolates tested, but they are almost always also resistant to quinolones and penicillins. Recent regional surveys and local studies have confirmed the wider distribution of these ceftriaxone-less sensitive gonococci[8,9] in countries in close proximity to Australia. The mechanism of resistance to ceftriaxone in these isolates is not fully elucidated, although alterations in the *penA* gene, including the presence of mosaic PBP2, are important.[9,10] The presence of mosaic PBP2 in gonococci can be detected by recently described molecular methods.[11] These changes appear to affect the efficacy of oral third generation agents such as cefixime and ceftibuten, disproportionately, but these antibiotics are not available for use in Australia. AGSP reports have also consistently emphasised that the local recommendation for a minimum dose of 250 mg of ceftriaxone is prudent given the presence of these isolates and the propensity for resistance to develop in *N. gonorrhoeae*.

All gonococci tested in Australia in 2007, including those with altered cephalosporin susceptibility, were susceptible to spectinomycin. A low proportion of gonococci was also found to be resistant to azithromycin in 2007. Resistance to azithromycin, widely used as an anti-chlamydial agent in conjunction with gonococcal treatment, has been reported with increasing frequency overseas.[12]

These data showing increasing and multiple problems with anti-microbial resistance in *N. gonorrhoeae* indicate a continuing need for surveillance of antimicrobial resistance in this organism. The declining number of gonococcal isolates available for testing in 2007, almost certainly in part as a consequence of the increasing use of non-culture based methods for the diagnosis of gonorrhoea, will be an important issue for surveillance in future years. While the number of gonococcal isolates available for testing in Australia under the AGSP remains satisfactory for surveillance purposes, a continuing commitment to maintenance of culture-based systems will be required while this surveillance is still based on testing of gonococcal isolates.[13]

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