Annual report of the Australian Gonococcal Surveillance Programme, 2008

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 2008 the *in vitro* susceptibility of 3,110 isolates of gonococci from public and private sector sources was determined by standardised methods. Different antibiotic susceptibility patterns were again seen in the various jurisdictions and regions. Resistance to the penicillins nationally was at 44% and ranged between 25% in Queensland and 73% in South Australia with the exception of the Northern Territory, where the proportion of drug resistant strains was 4%. Quinolone resistance in gonococci isolates also continued to increase so that nationally 54% of all isolates were ciprofloxacin-resistant, and most of this resistance was at high minimal inhibitory concentrations (MIC) levels. The proportions of quinolone resistant gonococci detected ranged between 80% in South Australia and 31% in Western Australia. All isolates remained sensitive to spectinomycin. Approximately 1.1% of isolates showed some decreased susceptibility to ceftriaxone (MIC 0.06 mg/L or more) and azithromycin resistance was also present in low numbers of gonococci with MICs up to 16 mg/L. A high proportion of gonococci examined in larger urban centres were from male patients and rectal and pharyngeal isolates were common in men. 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* 2009;33(3):268–274.

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

Introduction

Gonorrhoea remains a major disease of public health importance in many countries including Australia. Effective antibiotic treatment is an essential component of gonococcal disease control at the population level so that the impact of antimicrobial resistance (AMR) in *Neisseria gonorrhoeae* on the outcome of treatment is a major concern, and one of long standing.[1] AMR in gonococci has emerged and spread in many parts of the world so that resistance to the penicillins, tetracyclines and macrolides has seen the widespread removal of these cheap, oral agents from standard treatment regimens. Over many years the high levels of resistance to fluoroquinolone antibiotics documented in urban centres in Australia[2] and nearby countries have also compromised the efficacy of this group of antibiotics at both an individual and population health level. This has lead to their widespread replacement with extended-spectrum cephalosporin antibiotics as the recommended treatment for gonorrhoea in Australia and elsewhere.[3] Unusually, but importantly in Australia however, treatments based on the penicillins remain effective in many rural centres where extremely high disease rates persist.[2]

AMR in *Neisseria gonorrhoeae* isolated in large urban centres in Australia is heavily influenced by the continuing introduction of multi-resistant gonococci from overseas.[2] Increasing numbers of reports of treatment failures with orally administered extended-spectrum cephalosporins have appeared from overseas sources.[4,5] In Australia, only injectable, but not oral, extended-spectrum cephalosporin antibiotics are available (ceftriaxone) and are recommended for use in high doses.[3] No treatment failures have yet been reported following ceftriaxone treatment of genital-tract gonorrhoea. Recently, 2 instances of failure of treatment of pharyngeal gonorrhoea were recorded in Sydney,[6] where elimination of intercurrent genital-tract infection with the same organism was achieved. The gonococci involved in both instances had raised minimal inhibitory concentrations (MICs) for ceftriaxone.

Strategies for treating and controlling gonorrhoea are based on the use of single dose treatments that cure a minimum of 95% of cases,[1] but formulation of these standard treatment regimens relies on data derived from continuous monitoring of the susceptibility of gonococci to recommended antibiotics.[1,7] Recently, following reports of treatment failures with orally administered extended-spectrum cephalosporins,[4,5] calls have been made for enhanced surveillance of all forms of gonococcal AMR in order to optimise gonococcal antibiotic treatment.[8]

The Australian Gonococcal Surveillance Programme (AGSP) has monitored the susceptibility of *N. gonorrhoeae* continuously since 1981[9] making it the longest continually running national surveillance system for gonococcal AMR. The emergence and spread of penicillin and quinolone resistant gonococci in major cities in Australia has

been well documented.[2] This analysis of AMR in *N. gonorrhoeae* in Australia was derived from data generated by the AGSP during the 2008 calendar year. It includes analyses and commentary arising from the increasing concerns consequent upon the presence in Australia of gonococcal isolates showing resistance to multiple antibiotics including those with decreased susceptibility to ceftriaxone.[2,10]

Methods

The AGSP is a component of the National Neisseria Network of Australia and conducts ongoing monitoring of AMR in gonococci through a collaborative network of reference 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.[9,11] The AGSP also conducted a program-specific quality assurance (QA) program.[12] 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 3,192 gonococcal isolates referred to or else isolated in AGSP laboratories in 2008, little changed overall from the 3,103 examined in 2007. The source and site of infection of these isolates are shown in Table 1. Eight hundred and fifty-seven gonococci (27% of the Australian total) were isolated in New South Wales, 567 (17.8%) in Victoria, 542 (17%) in Queensland, 410 (12.8%) in Western Australia, 403 (12.6%) in the Northern Territory, and 391 (12.3%) in South Australia, with small numbers in Tasmania (13) and the Australian Capital Territory (9). Numbers decreased in New South Wales (from 973), Victoria (from 625) and Queensland (from 542) from those reported in 2007, but increased from 366 in Western Australia and 240 in South Australia. The number of isolates from the Northern Territory was little changed. Three thousand one hundred and ten isolates remained viable for susceptibility testing, representing approximately 40% of the notifications made to NNDSS during 2008.

Source of isolates

There were 2,509 isolates from men and 682 from women, with a male to female (M:F) ratio of 3.7:1, lower than the 4.7:1 ratio for 2007. The number of isolates from men decreased slightly from 2,560

Table: Source and number of gonococcal isolates, Australia, 2008, by sex, site and state or territory

Gender	Site	State or territory						Aust*
		NSW	NT	Qld	SA	Vic	WA	
Male	Urethra	457	257	317	215	308	270	1,835
	Rectal	181	1	54	23	110	15	386
	Pharynx	99	0	20	31	69	9	229
	Other/NS	3	8	12	17	6	10	59
	Total	740	266	403	286	493	304	2,509
Female	Cervix	102	131	126	73	62	101	600
	Other/NS	15	6	13	31	12	5	82
	Total	117	137	139	104	74	106	682
Unknown	Total	0	0	0	1	0	0	1
Total*		857	403	542	391	567	410	3,192

NS Not stated.

* Includes isolates from Tasmania (13) and the Australian Capital Territory (9).

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

in 2007, but the number of isolates from women increased from 541. Isolates from females increased in all larger jurisdictions except for the Northern Territory. The M:F ratio remained high in New South Wales (6.3:1) and Victoria (6.6:1) where strains were more often obtained from urban populations than in Queensland (2.9:1), Western Australia (2.9:1), South Australia (2.7:1) and the Northern Territory (1.9:1) where there is a large non-urban component of gonococcal disease. Male rectal and pharyngeal isolates were most frequently found in New South Wales (together 38% of isolates obtained from men) and Victoria (36%), with about half this proportion in South Australia and Queensland. For 141 isolates in Table 1, the site is shown as 'other' or 'not stated'. Included in this total were 24 cases of disseminated gonococcal infection, 13 in men (0.5% of all infections) and 11 (1.6%) in women. Another 39 of these gonococci were pharyngeal and 18 rectal isolates from women. Other infected sites included ophthalmic infection in adults and children (6), placenta (2), peritoneal fluid in women (2) and a wound isolate (1) and several isolates from unspecified abscesses. 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.

Infections with gonococci classified as fully sensitive (FS, MIC ≤ 0.03 mg/L) or 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, 2008, 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.*

Antibiotic susceptibility patterns

In 2008 the AGSP reference laboratories examined 3,110 gonococcal isolates for sensitivity to penicillin (representing this group of antibiotics), ceftriaxone (representing later generation cephalosporins), ciprofloxacin (representing quinolone antibiotics), spectinomycin and for high level resistance to tetracycline (TRNG). As in past years the patterns of gonococcal antibiotic susceptibility differed between the 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 2008 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. In those 'relatively resistant' through the aggregation of chromosomally-controlled resistance mechanisms[1] (CMRP), chromosomal resistance is defined by an MIC to penicillin of 1 mg/L or more.[1,11] (The MIC in mg/L is the least amount of antibiotic which inhibits *in vitro* growth under defined conditions.)

Nationally, 1,367 (44%) gonococci were penicillin resistant by one or more mechanisms in 2008, a further increase in the proportion of isolates resistant to this group of antibiotics recorded in 2007 (38.2%), 2006 (34%) and 2005 (29.5%). Of these, 994 (32% of all isolates) were CMRP and 373 (12%) PPNG. In 2007, 796 (26.2%) were CMRP and 369 (12.1%) PPNG, so that the increase in penicillin resistance nationally was solely due to increased chromosomally mediated resistance. The proportion of penicillin-resistant gonococci of all gonococcal isolates was highest in South Australia, 73.2% (PPNG 7.6%, CMRP 65.6%); New South Wales, 59.6% (PPNG 15.8%, CMRP 43.8%); Victoria, 56.8% (PPNG 13.9%, CMRP 43%); and Western Australia 27.1% (PPNG 11.7%, CMRP 15.4%). All these jurisdictions showed increased proportions of penicillin resistant gonococci. In Queensland the proportion of penicillin resistant gonococci decreased to 25% (PPNG 13.4%, CMRP 11.6%). One CMRP was identified in the Australian Capital Territory but no PPNG was detected. In Tasmania there were 5 PPNG and 6 CMRP. In the Northern Territory there were 15 penicillin resistant gonococci; 11 PPNG (7 from Darwin and 4 from Alice Springs) and 4 CMRP (2 each from Darwin and Alice Springs) resulting in a total of 3.9% of strains that were penicillin resistant in 2008 (4.1% in 2007; 4.6% in 2006). Data on acquisition of PPNG were available in 81 (22%) infections. Forty-three

(53%) of these infections with PPNG were acquired locally and 38 (47%) by overseas contact. These external contacts were principally in Western Pacific or South East Asian countries with those reported from Thailand (12), the Philippines (7) and Indonesia (Bali) (4) the most numerous. Additionally, China, Malaysia, Singapore and more widely Europe, the United Kingdom and the United Arab Emirates were named as countries of acquisition.

Ceftriaxone

From 2001 onwards, low numbers of isolates with slightly raised ceftriaxone MICs have been found in Australia. In 2008, 34 (1.1%) gonococci 'non-susceptible' to ceftriaxone were identified with ceftriaxone MICs in the range 0.06 to 0.25 mg/L. In 2006, there were 23 (0.6%) gonococci isolates examined of this type and 25 (0.8%) in 2007. Seventeen of these were present in New South Wales (2% of isolates there), four (0.8%) in Queensland, 11 (2.9%) in South Australia and one each in Western Australia and the Northern Territory.

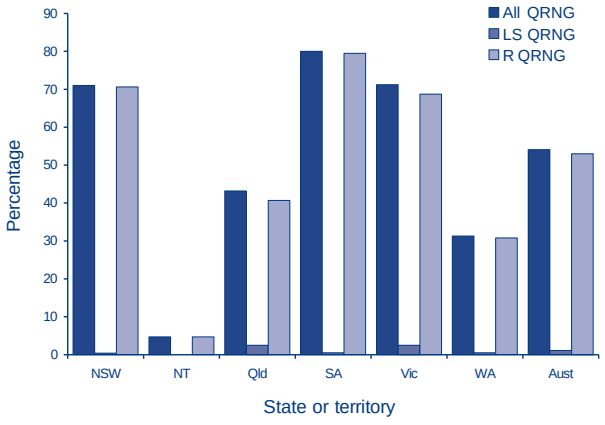
Spectinomycin

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 jurisdiction. 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 an MIC of 0.06 mg/L or more.[11] 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. an MIC of 1 mg/L or more, rates of failed treatment rise rapidly. At MIC levels of 4 mg/L or more treatment failure approaches 100%, even with higher ciprofloxacin doses.

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, 2008, by state or territory



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

Nationally in 2008, 1,685 (54%) of gonococci examined had some level of resistance to quinolones (QRNG), again showing an increase over the 1,493, (49%) detected in 2007 and the 1,455 (37.8%) in 2006. In 2005, there were 1,190 (30.6%) QRNG reported compared with 825 (23.3%) in 2004. Most of the QRNG in 2008 (1,651 or 98.9%) had resistance at a higher level i.e. MICs ≥ 1mg/L and many of these had MIC levels of the order of 8–64 mg/L. High proportions of QRNG were seen in South Australia, where 304 QRNG represented 80% of all isolates examined. Victoria had 401 (71.2%) QRNG and New South Wales had 606 (71%). In Queensland (228 QRNG, 43.2%) and Western Australia (118 QRNG, 31.3%), lower proportions of QRNG were maintained than in the other mainland states. In other jurisdictions, the number of QRNG remained low with 18 in the Northern Territory, 8 in Tasmania, and 2 in the Australian Capital Territory.

Information on the acquisition of QRNG was available in 408 of the 1,685 (24%) cases. Three hundred and thirty-eight of these (83%) were acquired locally and 70 (17%) were acquired overseas. The most prominent overseas sources of QRNG acquisition were Thailand (17 cases), the Philippines (8) and Indonesia (Bali) (7). Others were from sources referred to under PPNG acquisition with contacts additionally reported in Egypt, Hong Kong, Germany, Poland and South Africa.

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 and are rarely, if ever, used for treatment of gonorrhoea in Australia. Despite this lack of use of this antibiotic group, the proportion of TRNG detected continues to increase. In 2006, 12% of isolates were TRNG. In 2007, 505 (16.6%) of gonococci examined were TRNG, the highest proportion of TRNG detected in this series at that time. In 2008, 553 (18%) of isolates tested were TRNG.

TRNG were present in all jurisdictions except the Australian Capital Territory, with the highest proportion in Western Australia (111 TRNG, 27%). Lower proportions of TRNG were present in New South Wales (172, 20.2%), Queensland (98, 18.6%), Victoria (95, 16.9%) and South Australia (32, 8.4%). There were 39 (10.1%) TRNG found in the Northern Territory and five in Tasmania.

Discussion

The World Health Organization has long-established strategies designed to optimise standardised treatment regimens for gonorrhoea on the basis of epidemiological surveys of the distribution and extent of gonococcal AMR[1] and these have been recently revised.[13] For public health purposes, AMR at a rate of 5% or more in gonococci sampled in a general population is the 'threshold for action' for removal of an antibiotic from treatment schedules and for substitution of another effective agent.[1,13] Programs such as the AGSP therefore seek to determine the proportion of strains in a defined patient population that are resistant to antibiotics relevant to the treatment of gonorrhoea and relate these findings to likely efficacy of current treatment schedules.[1,2,7,11,13] These strategies require quality AMR data, and the special requirements for *in vitro* growth and AMR testing of the fastidious *N. gonorrhoeae* complicate this requirement. One aspect that requires attention is the ability to obtain and examine a sufficient and representative sample of isolates.[1,11,13] The 3,110 strains examined by the AGSP and their source from public and private health sectors constitutes a comprehensive sample that meets these requirements despite the increasing use of nucleic acid amplification assays for diagnosis of gonorrhoea in Australia. The AGSP also distributes reference panels of gonococci for use in internal quality control and external quality assurance schemes[14] necessary for the validation of gonococcal AMR data.

The proportion of *N. gonorrhoeae* resistant to multiple antibiotics continued to increase in urban Australia in 2008, and nationally, approximately 44% of gonococci were resistant to the penicillins and 54% to the quinolone antibiotics, together with an historical high in Australia of the presence of gonococci with high-level tetracycline resistance. This increase in quinolone and tetracycline resistance occurred despite low exposure to these antibiotics in Australia.[2] The 'rural–urban divide'[2] in gonococcal resistance rates was maintained (Figures 1 and 2) insofar as remote areas in some jurisdictions with high disease rates continue to be able to use penicillin-based treatments. Effective use of this cheap and acceptable treatment requires continuing close monitoring of resistance patterns. This dichotomy also illustrates the need for disaggregated information rather than pooled national data to define treatment regimens appropriate for the various jurisdictions.

Specific comment has been made in recent reports regarding gonococci with decreased susceptibility to ceftriaxone.[2,10] In 2008, the number of these isolates remained low at about 1% of all isolates tested, but in most cases they were also resistant to quinolones and penicillins. However, the parameters for laboratory recognition of altered susceptibility to the cephalosporins are poorly defined and differ for the oral and injectable extended-spectrum cephalosporins. Proper comparisons of the frequency of their isolation in Australia and other countries are thus difficult to obtain at present. However, regional surveys and local studies have confirmed the wider distribution of these gonococci in countries in close proximity to Australia and also locally.[2,4,5]

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 regarded as pivotal.[15,16] The presence of a mosaic PBP2 can be detected by molecular methods[17] and *N. gonorrhoeae* with this mosaic PBP2 are present in local isolates. Additionally, molecular typing methods have shown that multiple gonococcal sequence types (STs) may harbour these mosaic PBP2.[18] Gonococci of STs associated with treatment failures following cephalosporin therapy in Hong Kong have now been found in Australia, as have gonococci of other STs that also harbour mosaic PBP2. The presence of a mosaic PBP2-containing lesion does not however of itself equate with clinical resistance, and other gene polymorphisms are required to increase MIC levels to those that may impact on treatment efficacy.[16] Other non-mosaic allele changes in *penA* are also associated with ceftriaxone non-susceptibility, but have no impact on the equivalent oral agents. Additionally, ceftriaxone treatment failures have now been documented in pharyngeal gonorrhoea in Australia where the infection was due to gonococci with *penA* alterations other than those associated with a mosaic gene.[6]

Thus considerable further clarification is required regarding the laboratory detection of these gonococci and the interpretation of their likely clinical impact. AGSP reports have also consistently emphasised that the previous local recommendation for a minimum dose of 250 mg of ceftriaxone was prudent given the presence of these isolates and the propensity for resistance to develop in *N. gonorrhoeae*. It is thus reassuring to note that current treatment recommendations are for an increased 500 mg dose of ceftriaxone.

All gonococci tested in Australia in 2008, including those with altered cephalosporin susceptibility, were

susceptible to spectinomycin. A low proportion of gonococci was also found to be resistant to azithromycin in 2008. Azithromycin has been suggested as a possible component of treatment for gonorrhoea that uses dual antibiotic treatment.[19] Resistance to azithromycin, widely used as an anti-chlamydial agent in conjunction with gonococcal treatment, has been reported with increasing frequency overseas. MIC levels in azithromycin-resistant gonococci have reached very high levels in Europe, but these strains have not been detected in Australia.

These recent data showing emergence and spread of anti-microbial resistance in *N. gonorrhoeae* indicate a continuing need for surveillance of antimicrobial resistance in this organism both at a national and international level. The problems of emergence and spread of resistance are complex and require attention to both disease control as well as rational use of antibiotics.[8,15,20] A continuing commitment to surveillance of AMR in *N. gonorrhoeae,* which is an essential component of these control measures,[1,13] means that maintenance of culture-based systems will be required while this surveillance is still based on testing of gonococcal isolates.

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