

AUSTRALIAN GONOCOCCAL SURVEILLANCE PROGRAMME ANNUAL REPORT, 2012

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Abstract

The Australian Gonococcal Surveillance Programme has continuously monitored antimicrobial resistance in clinical isolates of *Neisseria gonorrhoeae* from all states and territories since 1981. In 2012, 4,718 clinical isolates of gonococci from public and private sector sources were tested for *in vitro* antimicrobial susceptibility by standardised methods. Variation in antibiotic susceptibility patterns were reported between jurisdictions and regions. Resistance to the penicillins and quinolones was high in all jurisdictions except the Northern Territory and Tasmania. Penicillin resistance ranged from 21% in Western Australia to 53% in Victoria. Quinolone resistance ranged from 17% in Queensland to 46% in Victoria, and the resistance was mostly high level. Decreased susceptibility to ceftriaxone (MIC 0.06–0.25 mg/L or greater) was found nationally in 4.4% of isolates, an increase from 3.2% in 2011, but lower than in 2010. To date, there has not been an isolate of *N. gonorrhoeae* with a ceftriaxone MIC value greater than 0.125 mg/L reported in Australia. Azithromycin susceptibility testing was performed in all jurisdictions and resistance ranged from 0.3% in the Northern Territory to 2.7% in Victoria. The highest reported azithromycin MIC value was 16 mg/L and azithromycin resistant gonococci were not detected in the Australian Capital Territory or Tasmania. Nationally, all isolates remained susceptible to spectinomycin. *Commun Dis Intell* 2013;37(3):E233–E239.

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

Introduction

The World Health Organization (WHO) estimates that 106 million new *Neisseria gonorrhoeae* infections occur amongst men and women aged 15–49 years annually worldwide,¹ and 62.7% (67.4 million) of these occur in the Asia Pacific Region. In Australia, the rate of gonorrhoea increased from 35.8 per 100,000 in 2005 to 60.0 per 100,000 in 2012.² The increased rate of infection is coupled with a global increase in the prevalence of antimicrobial resistance (AMR) in *N. gonorrhoeae*. The potential impact of this on gonococcal disease control is a growing concern, as effective antibiotic treatment is fundamental to disease control at the population level.^{3–5}

Over time, the emergence of resistance to the penicillins, tetracyclines, macrolides and fluoroquinolone antibiotics has necessitated the removal of these agents from standard treatment regimens for gonorrhoea.⁶ This was followed by replacement with extended-spectrum cephalosporin (ESCs) antibiotics as the recommended first line treatment for gonorrhoea in Australia and elsewhere.⁷ Importantly in Australia however, treatments based on the penicillins remain effective in many rural centres where high disease rates persist.⁸

In Australia, the injectable extended spectrum cephalosporin ceftriaxone is recommended for use in high doses.⁷ However, over time there has been an increasing proportion of gonococcal isolates with raised ceftriaxone minimum inhibitory concentration (MIC) values.⁸ Pharyngeal gonorrhoea treatment failures have been reported in Australia following 250 mg and 500 mg doses of ceftriaxone.^{9,10} The infecting gonococcal isolates had raised ceftriaxone MIC values (range 0.016–0.06 mg/L). In 2010, the first ceftriaxone-resistant strain (MIC value: 2.0 mg/L), the H041 strain, was reported from Japan, followed by the ceftriaxone resistant F89 strain initially reported from France (MIC value 2.0 mg/L)^{9,11} and subsequently from Spain.¹² In large centres in urban Australia, AMR in *N. gonorrhoeae* has long been influenced by the introduction of multi-resistant strains from overseas.⁶

Strategies for treating and controlling gonorrhoea are based on regimens effecting cure in a minimum of 95% of cases, and the formulation of these regimens is reliant on data derived from continuous AMR monitoring of gonococci to the antibiotics in clinical use.⁵ The increase in ceftriaxone MIC values globally, in the absence of an ideal alternate treatment for gonococcal infection, has escalated fears for gonococcal disease treatment and control.¹³ The WHO has called for enhanced surveillance as a fundamental component of the Global Action Plan to control the spread and impact of gonococcal AMR.¹⁴

The Australian Gonococcal Surveillance Programme (AGSP) has continuously monitored the susceptibility of *N. gonorrhoeae* since 1981 making it the longest, continually running national surveillance system for gonococcal AMR in the world.¹⁵

This report of the analysis of AMR in *N. gonorrhoeae* in Australia was derived from data collated by the AGSP during the 2012 calendar year.

Methods

The National Neisseria Network (NNN) of Australia comprises reference laboratories in each state and territory that collaborate to monitor clinical isolates of pathogenic *Neisseria* species nationally from as wide a section of the community as possible. The data for gonococcal isolates is collated for the AGSP, which is a product of the collaboration of the NNN laboratories. Both public and private sector laboratories refer isolates to regional testing centres. The increasing use of non-culture based methods of diagnosis has reduced the number of isolates available for testing. The number of isolates is a proportion of the number of cases of gonococcal disease notified to the National Notifiable Diseases Surveillance System (NNDSS).

Gonococci isolated in, and referred to, the NNN laboratories are examined for antibiotic susceptibility to the penicillins, quinolones, spectinomycin, third generation cephalosporins, and azithromycin and for high-level resistance to the tetracyclines. Testing is performed using previously described standardised methodology to determine the MIC values.^{15,16} The MIC value is the least amount of antibiotic that inhibits *in vitro* growth under defined conditions. The AGSP conducts a program-specific quality assurance program, to ensure that data are valid and comparable for surveillance.¹⁷

Antibiotic susceptibility data from each jurisdiction are submitted quarterly to the coordinating laboratory, which collates the results and provides individual feedback. Additionally, where available, the AGSP collects data on the gender of the patient

and site of isolation of gonococcal strains. In this report the data are further divided into urban versus rural data. Data from isolates from all jurisdictions are predominantly from urban centres, excepting the Northern Territory. Where available, data on the geographic source of acquisition of antibiotic-resistant isolates are included in analyses.

Results

Number of isolates

There were 4,784 gonococcal isolates tested in NNN laboratories in 2012, representing 35.3% of the 13,539 cases of gonococcal infection notified to the NNDSS in 2012 (Table 1).² This is proportionally the same as in 2011, but lower than the 40%–42% referred between 2008 and 2010.

Source of isolates

There were 3,860 isolates from men (81%) and 924 (19%) from women (Table 2). The proportion of gonococcal isolates from males and females tested by the AGSP has remained stable over recent years; ranging between 18% and 20% for women and 80% to 82% for men between 2009 and 2011.

The infected site reported as 'other' or 'not specified' for 47 isolates from males and 16 isolates from females (Table 2). Isolates from urine samples were regarded as genital tract isolates.

Antibiotic susceptibility patterns

In 2012, 4,718 of the 4,784 referred gonococcal isolates (99%) remained viable for antibiotic susceptibility testing. These were examined by the AGSP reference laboratories for susceptibility to penicillin (representing this group of antibiotics), ceftriaxone (representing later generation cephalosporins), ciprofloxacin (representing quinolone

Table 1: Number of clinical gonococcal isolates tested and proportion of National Notifiable Diseases Surveillance System notifications, Australia 2012, by state and territory

State or territory	Number of isolates tested	Number of cases notified*	% isolates tested AGSP/ NNDSS
ACT	56	93	60.2
NSW	1,712	4,129	41.5
Northern Territory	335	1,539	21.8
Queensland	719	2,699	26.6
South Australia	151	479	31.5
Tasmania	14	35	40.0
Victoria	1,249	2,450	50.9
Western Australia	548	2,115	25.9
Total	4,784	13,539	35.3

Table 2: Gonococcal isolates, Australia, 2012, by sex, site of isolate and jurisdiction

	Site	ACT	NSW	NT	Qld	SA	Tas.	Vic.	WA	Aust.
Male	Urethra	26	877	214	392	83	9	547	313	2,461
	Rectal	18	282	1	68	34	2	340	31	776
	Pharynx	10	279	0	37	12	2	197	25	562
	DGI	0	1	4	2	0	0	1	6	14
	Other/NS	0	10	2	3	0	0	31	1	47
	Total	54	1,449	221	502	129	13	1,116	376	3,860
Female	Cervix	2	187	108	195	19	1	112	162	786
	Rectal	0	3	0	3	0	0	2	2	10
	Pharynx	0	66	0	4	2	0	16	4	92
	DGI	0	0	6	11	0	0	0	3	20
	Other/NS	0	7	0	4	1	0	3	1	16
	Total	2	263	114	217	22	1	133	172	924
Total		56	1,712	335	719	151	14	1,249	548	4,784

DGI Disseminated gonococcal infection

NS Not specified

antibiotics), azithromycin and spectinomycin, and for high level resistance to tetracycline. As in past years the patterns of gonococcal antibiotic susceptibility differed between the states and territories, thus the data are presented by region as well as aggregated for Australia as a whole (Table 3).

Penicillins

In gonococci, resistance to the penicillin group of antibiotics (penicillin, ampicillin and amoxicillin with or without clavulanic acid), is a result of penicillinase-production by the *N. gonorrhoeae* (PPNG) and/or *N. gonorrhoeae* that are chromosomally resistant to penicillin (CMRP). Resistance in the PPNG group results from the production of beta-lactamase, and in the CMRP group by

the aggregation of chromosomally-controlled resistance mechanisms.⁶ Chromosomal resistance is defined by an MIC to penicillin of 1 mg/L or more.^{6,16} Infections with gonococci classified as fully sensitive (FS: MIC \leq 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.

In 2012, in total, there were 1,513 (32%) penicillin-resistant strains, a slight increase in the proportion recorded in 2010–2011 (25%–29%) but lower than the proportion in 2008–2009 (36%–44%). In 2012, there were 815 (17%) CMRP and 698 (15%) with PPNG compared with 579 (14%) CMRP and 474 (11%) PPNG in 2011. The increase in penicillin

Table 3: Proportion of isolates with resistance to penicillin, ciprofloxacin and azithromycin and decreased susceptibility to ceftriaxone reported, Australia, 2012, by state or territory

State or territory	Number of isolates tested	Decreased susceptibility		Resistance					
		Ceftriaxone		Ciprofloxacin		Azithromycin		Penicillin	
		n	%	n	%	n	%	n	%
Australian Capital Territory	56	2	3.6	19	33.9	0	0.0	8	14.3
New South Wales	1,701	76	4.5	539	31.7	9	0.5	482	28.3
Northern Territory	324	0	0.0	9	2.8	1	0.3	10	3.1
Queensland	708	17	2.4	120	16.9	15	2.1	183	25.8
South Australia	150	1	0.7	49	32.7	1	0.7	53	35.3
Tasmania	14	0	0.0	5	35.7	0	0.0	5	35.7
Victoria	1,249	105	8.4	572	45.8	34	2.7	666	53.3
Western Australia	516	6	1.2	123	23.8	3	0.6	106	20.5
Australia	4,718	207	4.4	1,428	30.3	63	1.3	1,513	32.1

resistance nationally in 2012 was due to increased proportions of both CMRP and PPNG, but the proportion of CMRP was similar to that of 2010.

In the Northern Territory 10 of 324 (3.1%) gonococci tested were penicillin resistant: (1 CMRP and 9 PPNG) (Table 3). This was the lowest proportion of penicillin resistance reported from the Northern Territory in recent years. Data on geographic location of acquisition were available for 57 (8.2%) of the 698 infections with PPNG. Thirty-four (4.9%) of the infections with PPNG were acquired locally, and 23 (3.3%) were acquired by overseas contact. These external contacts were principally in Western Pacific or South East Asian countries with those reported from Thailand, the Philippines, Indonesia, Vietnam, Malaysia, Papua New Guinea and Taiwan.

Ceftriaxone

From 2001 onwards, a low number of gonococcal isolates with decreased susceptibility to ceftriaxone (MIC 0.06 to 0.25 mg/L) have been found in Australia. The proportion has increased incrementally from 0.6% in 2006 to 4.8% in 2010 and decreased to 3.2% (134/4,129) in 2011. In 2012, 4.4% (207/4718) of isolates tested had decreased susceptibility to ceftriaxone (Table 3). In 2011, there was a decrease from 2010 in gonococci with decreased susceptibility to ceftriaxone in all jurisdictions except the Northern Territory and Tasmania (Table 4). This was essentially unchanged in 2012 with the exception of Victoria where there was an increase in the proportion from 5.3% to 8.4%. There were no gonococci with decreased susceptibility to ceftriaxone in Tasmania. There has not been an isolate of *N. gonorrhoeae* with an MIC value greater than 0.125 mg/L reported in Australia.

Spectinomycin

In 2012, all isolates from all jurisdictions were susceptible to this injectable antibiotic.

Quinolone antibiotics

The AGSP uses ciprofloxacin as the representative quinolone and defines altered susceptibility as an MIC of 0.06 mg/L or more.¹⁶ In quinolone resistant *N. gonorrhoeae* (QRNG), resistance is defined as a MIC value of ≥ 1 mg/L and thus far has been mediated only by chromosomal mechanisms so that incremental changes in MIC values are observed.

In 2012, 1,428 of gonococci examined (30.3%) had some level of resistance to quinolones (QRNG). The proportion reported by the AGSP in 2011 was lower (27%), but there has been a trend of decreasing proportions since 2008 when 54% isolates were reported as resistant. The majority in 2012 (1,407; 98.5%) had MICs values ≥ 1 mg/L and many of these had MIC levels of 8–64 mg/L, a similar proportion to that reported in 2010 and 2011.

During 2012 information on country of acquisition of QRNG was available for 91 (6.4%) of the 1,428 cases reported. Of these, 64 (4.5%) were acquired locally and 27 (3.7%) overseas from the same countries reported for PPNG acquisition and with contacts additionally reported from the United States of America.

Azithromycin

In 2012, data on azithromycin susceptibility was available from all states and territories. Nationally, the proportion of isolates exhibiting any resistance

Table 4: Number and percentage of gonococcal isolates with decreased susceptibility to ceftriaxone,* Australia, 2009 to 2012, by state or territory and year

State or territory	Decreased susceptibility to ceftriaxone							
	2009		2010		2011		2012	
	n	%	n	%	n	%	n	%
Australian Capital Territory	2	5.3	2	6.7	2	3.1	2	3.6
New South Wales	16	1.7	74	5.6	58	4.4	76	4.5
Northern Territory	1	0.2	1	0.2	2	0.4	0	0.0
Queensland	10	1.8	26	3.2	18	2.3	17	2.4
South Australia	9	5.3	19	11.6	1	0.7	1	0.7
Tasmania	0	0.0	0	0.0	0	0.0	0	0.0
Victoria	17	2.2	52	5.7	50	5.3	105	8.4
Western Australia	9	3.1	17	5.2	3	0.7	6	1.2
Australia	64	2.0	191	4.8	134	3.2	207	4.4

* MIC value 0.06–0.125 mg/L

was low (1.3%) similar to that reported in 2011 (1.1%) (Table 3). No isolates exhibiting high level resistance were reported.

High-level tetracycline resistance

High-level tetracycline resistant *N. gonorrhoeae* (TRNG) is used 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. The proportion of TRNG detected increased between 2006 and 2010 from 12% to 21% and decreased to 18% in 2011. In 2012, there was a further decrease in TRNG nationally to 13.6% (641/4,718) of isolates reported.

TRNG were present in all jurisdictions in 2012, with the highest proportions in Western Australia (133 TRNG, 25.8%), Queensland (151, 21.3%), South Australia (25, 16.7%) and the Northern Territory (44 TRNG, 13.6%).

Discussion

Gonococcal disease control is contingent on the availability of effective treatment strategies that are informed by surveillance data. The WHO recommendations for standardised treatment regimens for gonorrhoea are based on data from epidemiological surveillance of the distribution and extent of AMR in gonococci.⁵ An antimicrobial resistance rate of 5% or more in gonococci isolated from a general population is the 'threshold' for removal of an antibiotic from treatment schedules and substitution with another.⁵ Programs such as the AGSP are conducted to determine the proportion of antimicrobial resistance in gonococcal strains isolated in a defined patient population and relate these findings to the likely efficacy of current treatment schedules.^{5,7,16} The quality of the AMR data and the size and representativeness of the sample is imperative. For quality assurance and quality control of gonococcal AMR data, the AGSP distributes the 2008 WHO *N. gonorrhoeae* reference strain panel for use in internal quality control practices and provides the AGSP External Quality Assurance Programme.^{17,18} In 2012, the AGSP examined clinical isolates from both the public and private health sectors, constituting a comprehensive sample comprising 35% of all notifications nationally. Of concern for gonococcal AMR surveillance programs is the increasing use of nucleic acid amplification testing for diagnosis of gonorrhoea in Australia and elsewhere. Currently, molecular testing strategies are unable to provide definitive data for predicting AMR, thus the continued support of surveillance programs such as

the AGSP is a critical component of disease control strategies in the current context of emerging ESC resistance globally.¹⁴

The overall number of gonococcal strains examined by the AGSP in 2012 (4,784) was higher than the number examined in previous years. However, the proportion of isolates received from notified cases in Australia was the same as 2011 (35%) but lower than the 40%–41% examined in the years 2008 to 2010.

In 2012, 32% of gonococci nationally were resistant to penicillin, and 30% were resistant to quinolone antibiotics. These proportions were higher than those reported in 2011, where there was 25% resistance to penicillin, and 27% to the quinolone antibiotics. Over the period 2008 to 2011 there was a reduction in penicillin and quinolone resistance whereas prior to 2008 resistance to both classes of antibiotics had been increasing annually since 2003.⁶ Fluctuations in the proportions of penicillin and quinolone resistance have been reported over time by the AGSP. Since 2003, aggregated data have shown a predominant clone of CMRP coupled with high-level quinolone resistance circulating with increasing frequency annually.^{6,8} In 2012, the increase in the proportion of isolates with penicillin and quinolone resistance is likely to be a further reflection of the clonal shift in gonococcal isolates nationally.

The proportion of gonococci with high-level tetracycline resistance in Australia increased over the period 2006 to 2008 then stabilised at 21% in 2009 to 2010. In 2011, the proportion of TRNG decreased to 18%, with a further decrease to 13.6% in 2012.

Low rates of penicillin and ciprofloxacin resistance in the Northern Territory underscore the continued need for disaggregated surveillance data, as these are used 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 inexpensive and acceptable treatment is contingent on continued, timely and vigilant monitoring of resistance patterns.

Decreased susceptibility to ceftriaxone is quantified by the determination of the MIC value, and encompasses the range 0.06–0.25 mg/L. The emergence and spread of gonococci with decreased susceptibility to ceftriaxone has been documented in AGSP reports.¹⁸ These gonococci have also been found in rapidly increasing numbers in the WHO Western Pacific Region.¹⁹ Ceftriaxone is now the standard treatment for gonorrhoea in the majority of public sector clinics. Decreased susceptibility

to the ESCs has been accompanied by increasing numbers of reports of treatment failures,^{9,10,20–22} and concerns are escalating locally and globally as increasing proportions of strains with decreased susceptibility are reported.²³ To date, there have been no strains of *N. gonorrhoeae* reported in Australia with a ceftriaxone MIC value greater than 0.125 mg/L.

In Australia in 2012, the proportion of gonococcal isolates with decreased susceptibility to the ESCs (4.4%) was higher than 2011 (3.1%) but lower than the 4.8% reported in 2010. The trend has been that of incremental increases annually from the proportion reported in 2009 (2%). Surveillance to monitor *N. gonorrhoeae* with elevated MIC values coupled with sentinel site surveillance in high risk populations is critically important to inform therapeutic strategies and to detect instances of treatment failure. Sentinel site surveillance programs involve patient follow up and test of cure cultures after treatment of *N. gonorrhoeae* infections, in particular those in oropharyngeal sites. This is currently conducted in a very limited number of settings in Australia, and needs to be expanded throughout all jurisdictions as a matter of priority.

All gonococcal isolates tested in Australia in 2012 were susceptible to spectinomycin, including those with altered cephalosporin susceptibility. A low proportion of gonococci were found to be resistant to azithromycin in 2012. Recently, the United States Centers for Disease Control and Prevention, and United Kingdom gonococcal treatment guidelines have moved to recommend a dual therapy strategy of ceftriaxone with oral azithromycin for uncomplicated gonococcal infection.^{24,25} Resistance to azithromycin, (which is widely used as an anti-chlamydial agent in conjunction with gonococcal treatment), has been frequently reported with very high MIC levels overseas,^{26,27} but these strains have not been detected in Australia.

The continued emergence and spread of AMR in *N. gonorrhoeae* cannot be ignored. The evolution of gonococcal AMR is complex, and widely recognised as a global public health threat that requires attention to broad based disease control strategies including the rational use of antibiotics.^{4,5,24,28} It is critical that disease control strategies and the understanding of the global scope of AMR continue to be informed by surveillance programs of AMR nationally and internationally.¹⁴ Continuing maintenance of culture-based systems and commitment to surveillance of AMR in *N. gonorrhoeae* is fundamental to gonococcal disease control.

Acknowledgements

The AGSP thanks the Australian Government Department of Health for continued financial support and the many laboratories, private and public, throughout Australia for submission of isolates for testing.

The members of the Australian Gonococcal Surveillance Programme in 2012 (and to whom isolates should be referred) were: John Bates and Vicki Hicks (Queensland Health Scientific Services, Coopers Plains, Queensland); Athena Limnios, Tiffany Hogan, Ratan Kundu, Rodney Enriquez and Monica Lahra (Department of Microbiology, The Prince of Wales Hospital, Randwick, New South Wales); Kerrie Stevens, Janet Strachan, Mark Veitch, and Geoff Hogg (The Microbiological Diagnostic Unit, Department of Microbiology and Immunology, University of Melbourne, Parkville, Victoria); Andrew Lawrence (SA Pathology at Women's and Children's Hospital, Adelaide, South Australia); Julie Pearson and Hui Ileen Tan (Department of Microbiology and Infectious Diseases, PathWest Laboratory Medicine, Royal Perth Hospital, Western Australia); Mark Gardam and Belinda Chamley (Department of Microbiology and Infectious Diseases, Royal Hobart Hospital, Hobart, Tasmania) Paul Southwell and Microbiology Staff, (Microbiology Laboratory, Royal Darwin Hospital, Casuarina, Northern Territory); and Susan Bradbury, Angelique Clyde-Smith and Peter Collignon (Microbiology Department, Canberra Hospital, Garran, Australian Capital Territory).

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