

# AUSTRALIAN GONOCOCCAL SURVEILLANCE PROGRAMME ANNUAL REPORT, 2013

Monica M Lahra for the Australian Gonococcal Surveillance Programme

## 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 2013, 4,897 clinical isolates of gonococci from public and private sector sources were tested for *in vitro* antimicrobial susceptibility by standardised methods. Decreased susceptibility to ceftriaxone (MIC value 0.06–0.125 mg/L) was found nationally in 8.8% of isolates, double that reported in 2012 (4.4%). The highest proportions were reported from New South Wales and Victoria (both states reporting 11.8%), with a high proportion of strains also reported from Tasmania but a low number of isolates were tested. In addition, there was a multi-drug-resistant strain of *N. gonorrhoeae* isolated from a traveller to Australia, with a ceftriaxone MIC value of 0.5 mg/L—the highest ever reported in Australia. These antimicrobial resistance data from Australia in 2013 are cause for considerable concern. With the exception of remote Northern Territory where penicillin resistance rates remain low (1.3%) the proportion of strains resistant to penicillin remained high in all jurisdictions ranging from 15.6% in the Australian Capital Territory to 44.1% in Victoria. Quinolone resistance ranged from 16% in the Australian Capital Territory to 46% in Victoria. Azithromycin susceptibility testing was performed in all jurisdictions and resistance ranged from 0.3% in the Northern Territory to 5.7% in Queensland. High level resistance to azithromycin (MIC value was >256 mg/L) was reported for the first time in Australia, in 4 strains: 2 each from Queensland and Victoria. Azithromycin resistant gonococci were not detected in the Australian Capital Territory, Tasmania or from the remote Northern Territory. Nationally, all isolates remained susceptible to spectinomycin. *Commun Dis Intell* 2015;39(1):E137–E145.

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

## Introduction

Gonococcal disease rates have markedly increased in Australia in recent years.<sup>1</sup> Whilst this may be in part due to increased use of nucleic acid amplification testing (NAAT), this situation is coupled with significant concerns regarding gonococcal

antimicrobial resistance.<sup>2</sup> The current linchpin of treatment, ceftriaxone, has no ideal replacement.<sup>3</sup> Over recent years increasing proportions of gonococcal isolates with raised ceftriaxone MIC values strains have been reported in Australia,<sup>3</sup> and this reflects the situation globally. Strategies for gonococcal disease treatment; prevention and control are placed high on the agenda of the World Health Organization (WHO)<sup>4</sup> and the Centers for Disease Control and Prevention (CDC) in the United States of America.<sup>5</sup>

Over the period 2007–2012 there was a 65% increase in gonococcal disease notifications in Australia,<sup>1</sup> with the disease rate rising from 35.4 to 58.4 per 100,000 population. The greatest increases in notifications were observed in both males and females in the eastern states (Victoria, New South Wales and Queensland), and males in the Australian Capital Territory. The highest notification rates remain in Indigenous people in the Northern Territory and Western Australia. The overall Australian age standardised gonorrhoea notification rates in 2012 for Indigenous compared with non-Indigenous Australians were 933.4 per 100,000 population and 38.5 per 100,000 population, respectively.<sup>1</sup>

Gonococcal antimicrobial surveillance programs both in Australia and internationally, have reported over time, the emergence and spread of antimicrobial resistance in gonorrhoea.<sup>3,6</sup> In recent years, ceftriaxone treatment failure has occurred in Australia and elsewhere, in strains with raised MIC values (decreased susceptibility).<sup>2</sup> In 2010, the 1st ceftriaxone-resistant strain (H041) (MIC = 2.0 mg/L), was found in Japan,<sup>7</sup> with no evidence of spread. However, in 2011, a 2nd ceftriaxone-resistant *Neisseria gonorrhoeae* strain (F89), was initially observed in France and subsequently identified in Spain, with a MIC value 2.0 mg/L.<sup>8,9</sup>

In response to increasing MIC values to the extended spectrum cephalosporin antibiotics, the United Kingdom, the United States of America, and European gonococcal treatment guidelines moved to recommend a dual therapy strategy comprising ceftriaxone plus azithromycin, in a bid to stem the development of *N. gonorrhoeae* antimicrobial resistance (AMR).<sup>10–12</sup>

Of the WHO estimated 106 million new *N. gonorrhoeae* infections reported in those aged 15–49 years

annually worldwide<sup>13</sup> almost two-thirds (67.4 million, 63%) occur in the Asia–Pacific region.<sup>13</sup> The WHO gonococcal antimicrobial surveillance data from the Asia–Pacific region indicate that there are high levels of gonococcal AMR in the region, which is densely populated and has a disproportionate burden of gonococcal disease. In many countries there is uncontrolled antimicrobial use providing ideal conditions for the development of AMR.<sup>14</sup> This is of continuing concern to Australia where, in urban centres, AMR in *N. gonorrhoeae* has long been influenced by the introduction of multi-resistant strains from overseas.<sup>15</sup>

In contrast, the highest reported rate of gonococcal infection occurs amongst the Indigenous populations in some remote regions of Australia, where there are low rates of AMR. In these remote regions, gonococcal infection acquired locally or in an endemic region, can still be effectively treated with oral antibiotics (amoxicillin 3 g, probenecid 1 g and azithromycin 1 g).<sup>6</sup>

Strategies for treating and controlling gonorrhoea are based on regimens effecting cure in a minimum of 95% of cases. The formulation of these regimens is reliant on data derived from continuous monitoring of resistance to the antibiotics in clinical use.<sup>16</sup> The current global situation has raised concerns for gonococcal disease treatment, prevention and control.<sup>17</sup> 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.<sup>4</sup>

In Australia, the National Neisseria Network (NNN) is a collaboration of reference laboratories in each state and territory that monitor clinical isolates of pathogenic *Neisseria* species nationally from public and private sector laboratories, representing as wide a section of the community as possible, for phenotypic and genotypic characteristics, including antimicrobial resistance. The Australian Gonococcal Surveillance Programme (AGSP) is a key activity of the NNN and has continuously monitored the susceptibility of *N. gonorrhoeae* since 1981, making it the longest, continually running, national surveillance system for gonococcal AMR.<sup>18</sup>

## Methods

The NNN AMR data for gonococcal isolates are collated for the AGSP quarterly and annual reports. Gonococcal infection is a notifiable disease in Australia and each case is notified to the National Notifiable Diseases Surveillance System (NNDSS). The number of isolates tested by the NNN and reported by the AGSP represents a proportion of the number of cases reported to the NNDSS. The increasing use of non-culture based

methods of diagnosis has reduced the number of isolates available for AMR testing, however, the NNN still tests approximately one third of the number of notified cases in Australia.

The NNN laboratories test gonococcal isolates for antibiotic susceptibility to penicillin (representing this group of antibiotics); ceftriaxone (representing later generation cephalosporin antibiotics); ciprofloxacin (representing quinolone antibiotics); azithromycin; spectinomycin; and for high level plasmid mediated resistance to tetracycline using previously described standardised methodology to determine the minimum inhibitory concentration (MIC) values.<sup>18,19</sup> 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.<sup>20</sup>

Antibiotic susceptibility data from each jurisdiction are submitted quarterly to the coordinating laboratory (the Neisseria Reference Laboratory and WHO Collaborating Centre for Sexually Transmitted Diseases, Sydney), which collates the results for reporting. Where available, the AGSP collects data on the gender of the patient, country of acquisition, and site of isolation of gonococcal strains. Data from isolates from all jurisdictions are predominantly from urban centres, except for the Northern Territory where the data are further divided into urban versus remote.

## Statistics

Statistical analysis was performed using Prism version 5.0d. Results were compared using Fisher's exact test for proportional differences.

## Results

### Number of isolates

There were 4,897 gonococcal isolates tested in NNN laboratories in 2013, representing 33% of the 14,933 cases of gonococcal infection notified to the NNDSS in 2013 (Table 1). This was slightly lower than the proportion tested in 2012 (35%); and a further decrease from the 40%–42% referred between 2008 and 2010.

### Source of isolates

There were 4,032 isolates from men (82%) and 863 (18%) from women (Table 2). There were 2 isolates from patients of unknown gender. The proportion of gonococcal isolates from males and females tested by the AGSP has remained stable over recent years (2009–2012); ranging between 18%–20% for women and 80%–82% for men. The infected site was reported as 'other' or not speci-

fied for 94 isolates from males and 23 isolates from females (Table 2). Isolates from urine samples were regarded as genital tract isolates.

**Antibiotic susceptibility patterns**

As in past years the patterns of gonococcal antibiotic susceptibility differed between the various states and territories, thus the data are presented by region as well as aggregated for Australia (Table 3).

**Table 1: Number of Australian Gonococcal Surveillance Programme gonococcal isolates tested as a proportion of National Notifiable Diseases Surveillance System gonorrhoea notifications, Australia, 2013, by state or territory**

State or territory	Number of isolates tested	Number of cases notified*	Number of isolates tested/ number of cases notified %
ACT	44	114	39
NSW	1,555	4,237	37
NT	344	1,985	17
Qld	670	2,734	25
SA	212	808	26
Tas.	45	71	63
Vic.	1,539	3,012	51
WA	488	1,972	25
Aust.	4,897	14,933	33

**Penicillin**

Resistance to the penicillin group of antibiotics (penicillin, ampicillin and amoxycillin with or without clavulanic acid) in gonococci is a result of the production of a specific beta-lactamase, penicillinase, and/or by the aggregation of chromosomally-controlled resistance mechanisms. These are denoted respectively, as penicillinase-producing *N. gonorrhoeae* (PPNG); and chromosomally mediated resistant to penicillin (CMRP).<sup>15</sup> Chromosomal resistance is defined by an MIC to penicillin of 1 mg/L or more.<sup>15,19</sup>

In 2013 in Australia, 1,700/4,897 (35%) isolates were penicillin resistant; a proportional increase from 2012 (32%), and higher than that reported in 2010–2011 (25%–29%), but lower than 2008–2009 (36%–44%). In 2013, there were 978 (20%) isolates with CMRP; and 722 (15%) with PPNG. In 2012, the proportion of isolates with CMRP was 17%, and 15% were PPNG. Thus the increase in penicillin resistance nationally in 2013 was due to an increase in the proportion of isolates with CMRP.

*Penicillin resistance in the Northern Territory*

In 2013 there were 344 isolates tested from the Northern Territory. There were 105 from Darwin, and 239 from the remote Northern Territory comprising 205 from Alice Springs, 19 isolates from Katherine and 15 from other areas.

Of the isolates tested from the Northern Territory, 21/105 (20%) from the city of Darwin were penicil-

**Table 2: Gonococcal isolates tested, Australia, 2013, by sex, site and state or territory**

Sex	Site	ACT	NSW	NT	Qld	SA	Tas.	Vic.	WA	Aust.
Male	Genital	23	790	208	376	120	24	695	276	2,512
	Rectal	12	292	2	67	22	12	383	48	838
	Pharynx	6	224	2	36	14	4	253	27	566
	DGI	0	4	7	5	0	0	0	6	22
	Other/NS	0	17	2	6	2	0	62	5	94
	Total		41	1,327	221	490	158	40	1,393	362
Female	Genital	3	169	115	166	42	4	129	117	745
	Rectal	0	2	0	3	5	0	1	2	13
	Pharynx	0	44	0	2	4	1	9	2	62
	DGI	0	5	7	5	0	0	0	3	20
	Other/NS	0	6	1	4	3	0	7	2	23
	Total		3	226	123	180	54	5	146	126
Unknown	Total		2							2
Total		44	1,555	344	670	212	45	1,539	488	4,897

DGI Disseminated gonococcal infection.

NS Not specified.

**Table 3: Proportion of gonococcal isolates with resistance to penicillin, ciprofloxacin and azithromycin and decreased susceptibility to ceftriaxone reported, Australia, 2013, by state or territory**

State or territory	Number of isolates tested	Decreased susceptibility Ceftriaxone		Resistance					
		n	%	Ciprofloxacin		Azithromycin		Penicillin	
		n	%	n	%	n	%	n	%
Australian Capital Territory	44	0	0.0	9	20.0	1	2.2	7	16.0
New South Wales	1,555	183	11.8	553	35.0	14	0.9	593	38.0
Darwin, Northern Territory	105	2	1.9	24	23.0	1	1.0	21	20.0
Remote, Northern Territory	239	2	0.8	5	2.1	0	0.0	3	1.3
Queensland	670	33	4.9	194	29.0	38	5.7	209	31.0
South Australia	212	4	1.9	56	26.0	6	2.8	39	18.0
Tasmania	45	11	25.0	22	49.0	0	0.0	17	38.0
Victoria	1,539	181	12.0	683	44.0	35	2.3	678	44.0
Western Australia	488	13	2.7	123	25.0	9	1.9	133	27.0
Australia	4,897	429	8.8	1,669	34.0	104	2.1	1,700	35.0

lin resistant: (3 CMRP and 18 PPNG) (Table 3), and 2/21 also had decreased susceptibility to ceftriaxone. Of these 21 strains 19 (90%) were isolated from an urban STD clinic. In contrast, from the remote regions of the Northern Territory, 3/239 (1.3%) strains tested were penicillin resistant (1 PPNG and 2 CMRP).

### Ceftriaxone

From 2001 onwards, gonococcal isolates with ceftriaxone MIC values 0.06 to 0.125 mg/L, and categorised as having decreased susceptibility by the AGSP, have been reported in Australia. The proportion has increased incrementally from 0.6% in 2006, to 4.4% in 2012. From 2012 to 2013, the proportion of gonococci with decreased susceptibility to ceftriaxone doubled from 4.4% to 8.8%.

An increase in proportion was reported from all states and territories except the Australian Capital Territory (Table 4).

Ceftriaxone decreased susceptibility includes MIC values 0.06 and 0.125 mg/L. The right shift in the distribution of ceftriaxone MIC values over recent years (Table 5), is statistically significant with a sustained increase in the proportion of strains with an MIC value of 0.06 mg/L (2011–2012: [ $P = 0.02$ , 95% CI: 1.04–.62], and 2012–2013 [ $P < 0.0001$ , 95% CI: 1.70–2.38]). In 2010, the proportion of strains with ceftriaxone decreased susceptibility was higher than that reported in 2011. This proportion has subsequently increased as described. The proportion of strains with a ceftriaxone MIC 0.125 mg/L has also increased from 0.1% in 2010 and 2011, to 0.3% in 2012 to 0.6% in 2013 (Table 5).

**Table 4: Number and rate of gonococcal isolates with decreased susceptibility to ceftriaxone (MIC 0.06–0.125 mg/L), Australia, 2009 to 2013, by state or territory**

State or territory	Decreased susceptibility to ceftriaxone									
	2009		2010		2011		2012		2013	
	n	%	n	%	n	%	n	%	n	%
Australian Capital Territory	2	5.3	2	6.7	2	3.1	2	3.6	0	0.0
New South Wales	16	1.7	74	5.6	58	4.4	76	4.5	183	11.8
Northern Territory	1	0.2	1	0.2	2	0.4	0	0.0	4	1.5
Queensland	10	1.8	26	3.2	18	2.3	17	2.4	33	4.9
South Australia	9	5.3	19	11.6	1	0.7	1	0.7	4	1.9
Tasmania	0	0.0	0	0.0	0	0.0	0	0.0	11	24.4
Victoria	17	2.2	52	5.7	50	5.3	105	8.4	181	11.8
Western Australia	9	3.1	17	5.2	3	0.7	6	1.2	13	2.7
Australia	64	2.0	191	4.8	134	3.2	207	4.4	429	8.8

These differences were not significant, which may be attributable to the low number of strains in this MIC category. In December 2013, a gonococcal isolate (termed the A8806 strain) from a young female European traveller was found to have a ceftriaxone MIC value of 0.5 mg/L—the highest ever reported in Australia. This isolate was also resistant to penicillin and ciprofloxacin but sensitive to azithromycin. Of concern was that genetic analysis showed that the A8806 strain had a mosaic penicillin binding protein 2 (PBP2) and other key similarities to the ceftriaxone resistant H041 strain reported from Japan in 2009.<sup>21</sup>

**Table 5: Proportion of gonococcal isolates tested with MIC values at 0.06 mg/L and 0.125 mg/L, Australia, 2010 to 2013**

Ceftriaxone MIC mg/L	2010	2011	2012	2013
0.06	4.8%	3.2%	4.1%	8.2%
0.125	0.1%	0.1%	0.3%	0.6%

### Azithromycin

Nationally, the proportion of isolates exhibiting any resistance (2.1%) was higher than that reported in 2011–2012 (1.1%–1.3%) (Table 3). There were marked increases in the proportion of strains with resistance to azithromycin in 2012 from Queensland (from 2.7% to 5.7%), South Australia (from 0.7% to 2.8%) and Western Australia (from 0.6% to 1.9%).<sup>2</sup> In 2013, there were 4 isolates, 2 from Queensland and 2 from Victoria, that exhibited high level resistance to azithromycin (MIC value > 256 mg/L).

### Quinolone antibiotics

The AGSP uses ciprofloxacin as the representative quinolone. Quinolone resistant *N. gonorrhoeae* is defined as MICs  $\geq$  1 mg/L. The resistance mechanism in *N. gonorrhoea* has thus far been mediated only by chromosomal mechanisms so that incremental changes in MIC values are observed.

In 2013, 1,669 of the 4,897 gonococci examined (34%) were resistant to ciprofloxacin (Table 3). The proportion reported by the AGSP in 2012 (30%) was lower; however overall, there has been a trend of decreasing proportions since 2008 when 54% isolates were reported as ciprofloxacin resistant.

### 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 gonococcal infection in Australia. The proportion of TRNG detected nationally increased between 2006 and 2011 from 12% to 21% and decreased to 14% in 2012, and was again reported as 14% in 2013.

TRNG were present in all jurisdictions in 2013, with the highest proportions in Western Australia (21%), Queensland (19%), South Australia (17%), New South Wales (14%) and the Northern Territory (14%).

### Spectinomycin

In 2013, all isolates from all jurisdictions were susceptible to spectinomycin.

### Discussion

High quality, representative AMR data are critical for public health security and effective antibiotic treatments for infections, including gonococcal infection, are essential for disease control. The WHO recommends that treatment regimens for gonococcal infection are based on epidemiological surveillance of the distribution and extent of AMR.<sup>22</sup> An AMR rate of 5% or more is the nominal threshold for change of treatment recommendations.<sup>22</sup> 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.<sup>19,22,23</sup> For quality assurance and quality control of gonococcal AMR data, the AGSP provides the NNN laboratories with the AGSP External Quality Assurance Program, and WHO *N. gonorrhoeae* reference strains.<sup>20,24</sup>

The overall number of gonococcal strains examined by the AGSP in 2013 was higher in number but proportionally lower than previous years. These clinical isolates were from both the public and private health sectors, constituting a comprehensive sample of 33% of all notifications nationally. Of concern for gonococcal AMR surveillance programs worldwide, is the increasing use of NAAT for diagnosis, both in urban and remote settings. Whilst NAAT has an advantage over culture in terms of sensitivity and is more robust and reliable for remote settings where cultures may not survive, they have the distinct disadvantage in that they cannot test broadly for AMR. However, currently molecular AMR testing strategies can give targeted and specific information.<sup>6,25,26</sup> At this stage however, NAAT is unable to provide definitive data for predicting AMR, thus the continued commitment to the support of surveillance programs such as the

AGSP is vital. Culture based AMR surveillance is a foundation component for disease control strategies, essential in the current context of emerging gonococcal AMR globally.<sup>4</sup>

In the AGSP, decreased susceptibility to ceftriaxone is reported as an MIC value in the range 0.06–0.125 mg/L.<sup>27</sup> In 2013, in Australia, the proportion of strains in this MIC range doubled from 4.4% in 2012 to 8.8%, with the highest rates (11.8%) reported from the eastern states of Victoria, New South Wales and Queensland, where the largest increases in notifications were observed. Twenty-four per cent of the isolates from Tasmania were in this category, but the number of isolates tested was low (n=45). The data showed that the proportion of strains tested with an MIC value of 0.06 mg/L was 8.2% in 2013, significantly higher than that reported at that MIC value in 2012. The proportion of strains tested that had a ceftriaxone MIC value of 0.125 mg/L also doubled from 0.3% in 2012 to 0.6% in 2013. The multi-drug-resistant A8806 strain reported in late 2013, with a ceftriaxone MIC of 0.5 mg/L is cause for considerable public health concern, particularly if spread occurs into remote Indigenous communities where disease rates are high, and extreme remoteness limits access to medical and diagnostic services. Enhanced surveillance strategies have been put in place by the NNN and to date no evidence of spread has been detected.

International and national surveillance programs define decreased susceptibility to ceftriaxone differently. For example, Public Health England's Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP), which reports AMR data from England and Wales; and the CDC gonococcal AMR surveillance programs define decreased susceptibility to ceftriaxone as MIC  $\geq$  0.125 mg/L. In recent years, both these programs have reported low proportions of strains with ceftriaxone decreased susceptibility by their criteria. In 2012, the GRASP reported 0.2% of isolates; and the CDC reported 0.3% with decreased susceptibility to ceftriaxone. In contrast, the European Centre for Disease Prevention and Control Gonococcal (ECDC), defines decreased susceptibility to ceftriaxone as MIC > 0.125 mg/L.<sup>28,29</sup> The most recent (2011) ECDC gonococcal antimicrobial susceptibility surveillance reported 10 of 1,902 isolates with decreased susceptibility to ceftriaxone (MIC > 0.125 mg/L) and all 10 isolates were from a total of 214 strains tested in Austria and Germany.<sup>29</sup> The absence of an international standard definition of decreased susceptibility to ceftriaxone, and non-uniform methods of AMR testing confound comparison of surveillance data. However, in 2012 the WHO Global Action Plan nominated the criteria for decreased susceptibility to ceftriaxone as an MIC value  $\geq$  0.125 mg/L.<sup>4</sup> The 2013 surveillance

data from the GRASP; the CDC and the ECDC are yet to be published. Interestingly, comparison of 2011 and 2012 data between these international surveillance programs shows that the rates of gonococci with reduced susceptibility to ceftriaxone were very similar to that reported in Australia (Table 6). It remains to be seen if the substantial increase in the proportion of strains with decreased susceptibility seen in Australian gonococci in 2013 is also reported in the United States of America, the United Kingdom and Europe.

**Table 6: Proportion of gonococcal isolates with decreased susceptibility to ceftriaxone reported in the gonococcal antimicrobial resistance programs of the United States Centres for Disease Control, the European Centres for Disease Control and Public Health England's Gonococcal Resistance to Antimicrobials Surveillance Programme, 2011 to 2012**

Surveillance program criteria for decreased susceptibility MIC mg/L	2011 % Decreased susceptibility	2012 % Decreased susceptibility
ECDC MIC >0.125 mg/L	0.5	NA
CDC MIC > 0.125 mg/L	0.4	NA
AGSP MIC 0.125 mg/L	0.1	0.3
PHE GRASP MIC $\geq$ 0.125 mg/L	0.0	0.2

Gonococci with decreased susceptibility to ceftriaxone have also been reported in increasing numbers in the WHO Western Pacific Region;<sup>14</sup> however, the scope of this is not known as wide scale MIC based data from this region are not available.<sup>14</sup> Decreased susceptibility to the cephalosporin antibiotics has been accompanied by increasing numbers of reports of treatment failures.<sup>8,30–33</sup>

The primary concern is that molecular studies have shown that many circulating gonococcal strains harbour a mosaic penicillin binding protein 2 (PBP2). This mosaic PBP2 sequence has been shown to be a stepping stone for ceftriaxone resistance: the 2010 Japan H041 strain had only 3 important additional amino acid substitutions, the A8806 strain had 2 of the 3 amino acid substitutions found in the H041 strain, and the F89 strain, found in France, then Spain, had only 1 additional amino acid substitution to the mosaic PBP2.<sup>6</sup>

In essence therefore, there are a significant proportion of circulating strains that likely harbour the key foundation elements for ceftriaxone resistance (mosaic PBP2). Moreover, the difference between decreased susceptibility and resistance is now known to be only a few point mutations, and further, these strains are under constant selection pressure.<sup>3,6</sup> Given this, the level of concern about the development of ceftriaxone resistance is growing globally.

A dual therapy strategy of ceftriaxone with oral azithromycin for uncomplicated gonococcal infection is now in use in many states and territories of Australia. Resistance to azithromycin has been reported with very high MIC levels overseas.<sup>34,35</sup> In 2013, for the first time in Australia, there were 4 strains with high level resistance to azithromycin reported, two from Victoria and two from Queensland, and of these, two were likely acquired from China.<sup>36</sup>

In 2013, in the majority of Australia, with the exception of remote Northern Territory, 35% of gonococci were resistant to penicillin and 34% were resistant to quinolone antibiotics. These proportions were higher than those reported in 2012, where there was 32% resistance to penicillin and 30% to the quinolone antibiotics. Prior to 2012, there was a reduction in penicillin and quinolone resistance nationally from 2008 to 2011, whereas previously, resistance to both classes of antibiotics had been increasing annually since 2003.<sup>15</sup> Fluctuations in penicillin and quinolone resistance have been reported over time by the AGSP. Since 2003, aggregated data has shown a predominant clone of CMRP coupled with high-level quinolone resistance circulating with increasing frequency annually.<sup>2,15</sup> 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 from 2006 to 2008 and stabilised at 21% in 2009 to 2010. The proportion of TRNG decreased to 18% in 2011, then to 14% in 2012 and remained unchanged (14%) in 2013.

In the remote areas of the Northern Territory, low rates of penicillin and ciprofloxacin resistance continue to be reported. This underscores the continued need for disaggregated surveillance data, as these data 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. However, effective use of this treatment is contingent on continued, timely and vigilant

monitoring of resistance patterns. In some regions culture and AMR testing are logistically difficult. A PPNG assay developed in Australia by members of the NNN<sup>26</sup> is currently being utilised in Western Australia to enhance surveillance for penicillin resistance and to inform local gonorrhoea treatment guidelines.<sup>6</sup>

The continued emergence and spread of AMR in *N. gonorrhoeae* is widely recognised as a global public health threat, and in 2013 this threat was rated as urgent by the CDC.<sup>5</sup> Broad based disease control strategies including the rational use of antibiotics have been called for.<sup>3,22,37,38</sup> The WHO Global Action Plan states that disease control strategies and the understanding of the global scope of AMR need to continue to be informed by surveillance programs of AMR, nationally and internationally.<sup>4</sup>

Enhanced surveillance to monitor *N. gonorrhoeae* with elevated MIC values coupled with sentinel site surveillance in high risk populations remains critically important to inform our 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.

In summary, gonococcal infection rates and AMR rates are increasing in Australia. In 2013 the proportion of strains with elevated ceftriaxone MIC values doubled from 2012. A multi-drug-resistant strain with high level ceftriaxone MIC has now been reported and, in addition, in another first for Australia, in 2013, high level resistance to azithromycin was reported.<sup>36</sup> The next direction for treatment is uncertain, but what is clear is that additional and renewed efforts for disease prevention and disease control are urgently called for, and that continued monitoring of AMR to inform treatment and monitor interventions is paramount.

## Acknowledgements

The National Neisseria Network is supported by the Australian Department of Health. We thank the many laboratories, private and public, throughout Australia for submission of isolates for testing.

Members of the Australian Gonococcal Surveillance Programme in 2013 (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 (PHL), 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 leen 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); Kevin Freeman and Microbiology Staff, (Microbiology Laboratory, Royal Darwin Hospital, Casuarina, Northern Territory); Susan Bradbury, Angelique Clyde-Smith and Peter Collignon (Microbiology Department, Canberra Hospital, Garran, Australian Capital Territory).

## Author details

Corresponding author: Associate Professor Monica M Lahra, World Health Organization Collaborating Centre for STD, Sydney and, Neisseria Reference Laboratory, Microbiology Department, SEALS, The Prince of Wales Hospital, RANDWICK NSW 2031. Telephone: +61 2 9382 9054. Facsimile: +61 2 9382 9210. Email: monica.lahra@sesiahs.health.nsw.gov.au

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