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Australian Gonococcal Surveillance Programme Annual Report, 2016

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Annual Report

Australian Gonococcal Surveillance Programme Annual Report, 2016

Monica M Lahra and Rodney Enriquez

Abstract

The Australian Gonococcal Surveillance Programme (AGSP) has continuously monitored antimicrobial resistance in clinical isolates of *Neisseria gonorrhoeae* from all states and territories since 1981. In 2016, there were 6,378 clinical isolates of gonococci from public and private sector sources tested for *in vitro* antimicrobial susceptibility by standardised methods. Current treatment recommendations for the majority of Australia is a dual therapeutic strategy of ceftriaxone and azithromycin. Decreased susceptibility to ceftriaxone (Minimum Inhibitory Concentration or MIC value 0.06-0.125 mg/L) was found nationally in 1.7% of isolates, similar to that reported in the AGSP Annual Report 2015 (1.8%). The highest proportions were reported from Queensland and Tasmania (3.7% and 3.6% respectively). Resistance to azithromycin (MIC value ≥1.0 mg/L) was found nationally in 5.0% of isolates, double the proportion reported in 2015. The highest proportions were reported from South Australia (19.5%), Tasmania (14.3%) and urban Western Australia (7.6%). High level resistance to azithromycin (MIC value ≥256 mg/L) was again reported in 5 strains. Nationally in 2016, 4 from Victoria and 1 in South Australia. There was no reported azithromycin resistance in remote Northern Territory.

The proportion of strains resistant to penicillin in urban Australia ranged from 10.7% in the Australian Capital Territory to 41.8% in New South Wales. In rural and remote Northern Territory penicillin resistance rates remain low (3.0%). In remote Western Australia penicillin resistance rates have increased (5.3%) compared to the previous years, however, there were relatively low numbers of strains available for isolate based testing. To address this and to monitor resistance and inform treatment guidelines, widespread molecular testing for penicillin resistance in Western Australia is in place, and these data are included in the AGSP.

The proportion of strains resistant to ciprofloxacin in urban Australia ranged from 16.1% in the Australian Capital Territory to 41% in South Australia. Ciprofloxacin resistance rates remain comparatively low in remote areas of the Northern Territory (3.0%) and remote areas of Western Australia (4.5%).

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

Introduction

Antimicrobial resistance (AMR) in *Neisseria gonorrhoeae* was identified as an urgent level public health threat in 2013 by the United States Centers for Disease Control and Prevention.[1] The corollary of the emergence and spread of multidrug resistant gonorrhoea has been predicted to pose significant collateral health and financial costs.[1] In most settings there is continued reliance on ceftriaxone and azithromycin for treatment and the future direction of

gonococcal treatment strategies is uncertain as no new or ideal alternative therapeutic strategies identified in the event of spread of AMR.[2]

Notifications of gonococcal disease in Australia have significantly increased in recent years in both males and females in the Eastern states (Victoria, New South Wales and Queensland), and males in the Australian Capital Territory.[3] In contrast, gonococcal disease rates in the Indigenous populations in remote Northern Territory and Western Australia are markedly higher but relatively stable.[3] However, gonococcal AMR in these remote regions remains paradoxically low in infections acquired locally, and oral penicillin based therapeutic strategy remains recommended for use.[4]

From non-remote Australia AMR rates have been increasing, and in 2013 the proportion of strains with decreased susceptibility to ceftriaxone increased to 8.8%, double the rate reported in 2012 (4.4%). In 2013, the eastern states of New South Wales and Victoria reported the highest proportions nationally of both of gonococcal disease rates and gonococcal strains with elevated ceftriaxone MIC values (11.8%).[5] Also in 2013, in Australia, high level resistance to Azithromycin (MIC value >256 mg/L) was reported for the first time in two strains from Victoria and two from Queensland.[6] Further in 2013, an imported, multidrug resistant gonococcal strain was identified in Australia.[7] This strain known as the A8806 strain had important and concerning similarities to the ceftriaxone-resistant strain H041, reported once from a single case in Japan.[7] Enhanced surveillance in the Northern Territory and Queensland did not detect further evidence of the A8806 strain in 2014 or 2015 (Unpublished data from the National Neisseria Network (NNN)).

Coincident with the current heightened global awareness of AMR, and increasing disease notification rates reported in Australia and elsewhere, has been the wide spread move to nucleic acid amplification testings (NAATs) for diagnosis of gonorrhoea. This has raised concerns as broad based antimicrobial susceptibility testing (AST) is not currently possible with NAATs. However, assays such as that developed to detect *Neisseria gonorrhoeae* penicillinase production[8,9] (the primary cause of penicillin resistance in remote regions in Australia) was the first documented use of routine molecular testing for gonococcal AMR detection and surveillance, and inform local treatment guidelines.[9]

The World Health Organization (WHO) estimates there are 106 million new *N. gonorrhoeae* infections reported in those aged 15-49 years annually worldwide, with almost two thirds occurring in the Asia Pacific Region.[10] In addition to the high burden of disease in the region, the WHO Gonococcal Antimicrobial Surveillance Programme data from the Asia Pacific indicates that there are high levels of gonococcal AMR in the region. Compounding this is unregulated antimicrobial use in these regions providing ideal conditions for the development of AMR.[11] The emergence of new AMR in *N. gonorrhoeae* in Australia has long been influenced by the introduction of multi-resistant strains from overseas.[12] The importation and spread of resistant gonococcal strains and/or resistance developing under selection pressure is an ongoing concern.

Strategies for treating and controlling gonorrhoea are based on regimens effecting cure in a minimum of 95% of cases. Surveillance data of antibiotics in clinical use is critical to monitor AMR, detect imported or novel resistance and to inform treatment guidelines.[13] The WHO has called for enhanced surveillance as a fundamental component of their Global Action Plan to control the spread and impact of gonococcal AMR.[14]

The NNN is a collaboration of *Neisseria* reference laboratories in each state and territory that perform phenotypic and genotypic testing of clinical isolates of pathogenic *Neisseria* species. Clinical isolates are referred to the jurisdictional NNN laboratories from both public and private sector laboratories representing as wide a section of the community as possible, for determination of phenotypic and genotypic char-

acteristics, including antimicrobial resistance, and additional investigations where required. The 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. In this 2016 AGSP Annual Report, we also report the molecular surveillance data from the penicillinase producing *Neisseria gonorrhoeae* (PPNG) assay testing in remote Western Australia as part of the AGSP.

Methods

The NNN AMR data for gonococcal isolates are collated for the AGSP quarterly and annual reports. Gonorrhoea is a nationally notifiable disease in Australia and each confirmed case is notified to the National Notifiable Diseases Surveillance System (NNDSS) at the jurisdictional level. 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. NNN tests approximately one third of the number of notified cases in Australia.

The NNN laboratories test gonococcal isolates for 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 MIC values.[18,19] The MIC value is the least concentration of an antibiotic that inhibits *in vitro* growth under defined conditions. The AGSP conducts a program-specific quality assurance program.[15]

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 data 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 is predominantly from urban centres. Data from the Northern Territory and Western Australia are further divided into urban versus rural and remote as therapeutic recommendations differ.

Statistics

Statistical analyses were performed using Prism version 5.0d. Results were compared using Fisher's exact test for differences in proportions.

Results

Numbers of isolates

There were 6,378 gonococcal isolates tested in NNN laboratories in 2016, representing 28% of the 23,044 cases of gonococcal infection notified to the NNDSS in 2016 (Table 1).[21] This is the same as the proportion tested in 2015, lower than the range of 31%-42% referred between 2008 and 2014 and coincident with widespread uptake of NAAT diagnosis in Australia.

Source of isolates

There were 5,078 isolates from men (80%) and 1,282 (20%) from women (Table 2). There were 7 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 (2009-14); ranging between 18 and 20% for women and 80 and 83% for men. The infected site was reported as 'other' or not specified for 56 isolates from males and 18 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. 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, 2016, by state or territory

State or territory	Number of isolates tested	Number of cases notified	Number of isolates tested/ Number of cases notified %
Australian Capital Territory	112	201	56
New South Wales	2,268	7,009	32
Northern Territory	218	1,784	12
Queensland	865	4,023	22
South Australia	349	1,114	31
Tasmania	28	82	34
Victoria	1,734	5,469	32
Western Australia	804	3,362	24
Australia	6,378	23,044	28

Table 2: Gonococcal isolates, Australia, 2016, by sex, site and jurisdiction tested.

Sex	Site	NSW	NT	Qld	SA	Vic	WA	ACT	Tas	AUSTRALIA
Male	**Genital**	**1,088**	**116**	**411**	**146**	**829**	**403**	**47**	**10**	**3,050**
	Rectal	492	3	155	61	401	82	39	7	**1,240**
	Pharynx	321	0	65	36	214	53	15	7	**711**
	DGI*	2	3	4	1	3	8	0	0	**21**
	Other/NS**	11	2	12	4	12	10	3	2	**56**
	Total	**1,914**	**124**	**647**	**248**	**1,459**	**556**	**104**	**26**	**5,078**
Female	**Genital**	**272**	**84**	**201**	**73**	**236**	**222**	**6**	**2**	**1,096**
	Rectal	7	1	5	10	3	5	0	0	**31**
	Pharynx	63	1	6	11	17	17	2	0	**117**
	DGI*	2	4	1	0	1	1	0	0	**9**
	Other/NS**	3	2	5	7	9	3	0	0	**29**
	Total	**347**	**92**	**218**	**101**	**266**	**248**	**8**	**2**	**1,282**
Unknown		**7**	**2**	**0**	**0**	**9**	**0**	**0**	**0**	**18**
Total		**2,268**	**218**	**865**	**349**	**1,734**	**804**	**112**	**28**	**6,378**

*DGI: Disseminated Gonococcal Infection; **NS: not specified

Table 3: Proportion of gonococcal isolates with resistance to azithromycin, penicillin and ciprofloxacin and decreased susceptibility to ceftriaxone reported, Australia, 2016, by state or territory

State or Territory	Number of isolates tested 2016	Decreased Susceptibility		Resistance					
		Ceftriaxone		Azithromycin		Penicillin		Ciprofloxacin	
		n	%	n	%	n	%	n	%
Australian Capital Territory	112	1	0.9	8	7.1	12	10.7	18	16.1
New South Wales	2,268	45	2.0	82	3.6	949	41.8	738	32.5
Queensland	865	32	3.7	10	1.2	243	28.1	216	25.0
South Australia	349	2	0.6	68	19.5	135	38.7	127	36.4
Tasmania	28	1	3.6	4	14.3	8	28.6	8	28.6
Victoria	1,734	19	1.1	93	5.4	598	34.5	641	37.0
Northern Territory Urban & Rural	53	0	0	1	1.9	7	13.2	15	28.3
Northern Territory Remote	165	0	0	0	0	5	3.0	5	3.0
Western Australia Urban & Rural	672	9	1.3	51	7.6	112	16.7	138	20.5
Western Australia Remote	132	0	0	1	0.8	7	5.3	6	4.5
AUSTRALIA	**6,378**	**109**	**1.7**	**318**	**5.0**	**2,076**	**32.5**	**1,912**	**30.0**

Ceftriaxone

From 2001 onwards, gonococcal isolates categorised as having decreased susceptibility to ceftriaxone by the AGSP criteria (MIC values 0.06 to 0.125 mg/L) have been reported in Australia. The proportion of gonococci with decreased susceptibility to ceftriaxone nationally increased incrementally from 0.6% in 2006, to 4.4% in 2012, then in 2013 doubled to 8.8%. In 2014, the proportion decreased to 5.4% and decreased in 2015 to 1.8%. In 2016, the proportion was 1.7%, similar to 2015. (Table 4).

The right shift in the distribution of ceftriaxone MIC values over recent years 2011-2013 (Table 5), is statistically significant with a sustained increase in 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]).

The proportion of strains with a ceftriaxone MIC 0.125 mg/L also increased from 0.1% in 2010 and 2011, to 0.3% in 2012 to 0.6% in 2013 and 2014. These differences were not significant which may be attributable to the low number of strains in this MIC category. In 2015, the proportion of strains with an MIC value of 0.125 mg/L decreased to 0.1%, and further decreased to 0.05% in 2016 (Table 5). No isolates of *N. gonorrhoeae* with an MIC value greater than 0.125 mg/L were reported from Australia in 2016.

Azithromycin

Nationally, the proportion of isolates exhibiting resistance (MIC value ≥1.0 mg/L) was 5.0% (Table 3), double that reported for 2013-2015 (2.1%-2.6%), and more than four times that reported 2011-12 (1.1%-1.3%) (Table 6). The proportion of isolates exhibiting resistance was highest in South Australia (19.5% in 2016, compared with 2.8% in 2015). Large rises in the number and proportion of isolates exhibiting resistance compared with previous years were also seen in Victoria and urban Western Australia (Table 6). In 2016, there were 5 isolates that exhibited high level resistance to azithromycin (MIC value ≥ 256 mg/L), four from Victoria and one from South Australia. Of the isolates from South Australia exhibiting resistance, 64/68 (94%) demonstrated a similar antibiogram (penicillin resistant by ß-lactamase production, ceftriaxone and ciprofloxacin sensitive); 64% (41/64) were from males, and 36% (23/64) were from females.

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 ß-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). Chromosomal resistance is defined as an MIC to penicillin of 1 mg/L or more.

In 2016, in Australia, 2,076 (32.5%) of isolates were penicillin resistant, a proportional increase from 2015 (22.5%). This proportion was similar to that in 2012-2013 (32-35%), higher than in 2010-11 (25%-29%), and lower than in 2008-09 (36%-44%). In 2016, there were 989 (15.5%) isolates with CMRP; and 1,087 (17%) with PPNG.

Penicillin resistance in the Northern Territory

In 2016, there were 218 isolates tested from the Northern Territory. There were 53 from Darwin and surrounding urban areas, and 165 from remote areas of NT (Alice Springs, Katherine and other areas).

Of the isolates tested from the Northern Territory, seven (13.2%) from the city of Darwin and surrounding urban areas were penicillin resistant: (all PPNG) (Table 3: Northern Territory - Urban). None of these strains had decreased susceptibility to ceftriaxone. From the remote regions of the NT, five (3.0%) strains tested were penicillin resistant (2 CMRP and 3 PPNG). None of these strains had decreased susceptibility to ceftriaxone. Penicillin resistance

Table 4: Number (%) of gonococcal isolates with decreased susceptibility to ceftriaxone (MIC 0.06 - 0.125 mg/L), Australia, 2010 to 2016, by state or territory.

State or territory	Decreased susceptibility to ceftriaxone													
	2010		2011		2012		2013		2014		2015		2016	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Australian Capital Territory	3	**6.7**	2	**3.1**	2	**3.6**	0	**0**	2	**2.7**	0	**0.0**	1	**0.9**
New South Wales	74	**5.6**	58	**4.4**	76	**4.5**	183	**11.8**	119	**7.1**	52	**2.7**	45	**2.0**
Northern Territory	1	**0.2**	2	**0.4**	0	**0**	4	**1.5**	4	**1.7**	0	**0.0**	1	**0.1**
Queensland	17	**3.2**	18	**2.3**	17	**2.4**	33	**4.9**	21	**3.2**	7	**1.0**	32	**3.7**
South Australia	12	**11.6**	1	**0.7**	1	**0.7**	4	**1.9**	2	**1.0**	9	**3.6**	2	**0.6**
Tasmania	0	**0**	0	**0**	0	**0**	11	**24.4**	0	**0**	0	**0.0**	1	**3.6**
Victoria	52	**5.7**	50	**5.3**	105	**8.4**	181	**11.8**	95	**6.6**	25	**1.5**	19	**1.1**
Western Australia	17	**5.2**	3	**0.7**	6	**1.2**	13	**2.7**	15	**3.0**	5	**1.0**	9	**1.1**
Australia	**191**	**4.8**	**134**	**3.2**	**207**	**4.4**	**429**	**8.8**	**258**	**5.4**	**98**	**1.8**	**109**	**1.7**

in Western Australia. In 2016, there were 804 isolates tested from Western Australia (WA), with 132 of these from remote regions and 672 from rural and urban regions. Of the isolates tested from rural and urban regions, 16.7% were reported as resistant, whereas of the 132 isolates tested from remote regions, there were 7 isolates (5.3%) that were penicillin resistant (all PPNG). The proportion of isolates resistant to penicillin from remote regions was higher than that compared with 2015 (2.3%). In addition to the isolate based surveillance for penicillin, specimens from Western Australia that were NAAT *Neisseria gonorrhoeae* (NG) positive were tested using a PPNG assay now routinely in use. In 2016, there were 59,843 specimens tested and 1,679 gonococcal detections were reported from 1,357 patients. Of these 1,282/1,357 were able to be tested for PPNG by the assay and 99/1,282 were positive (7.7%). Perth continues to have high rates of PPNG, detected in 58/418 (11%) of extracts tested. Much lower numbers of specimens were tested from other populated regions: Wheatbelt 0/5; Great Southern 0/5 and SouthWest 1/14 (7%); and therefore results should be interpreted with caution. The remote regions continue to have lower rates of PPNG positive NG: there were 6/446 (1.3%) from the Kimberley region; from the Goldfields there was 1/34 (2.9%); and 9/180 (5.0%) from the Pilbara; and from the Midwest there were 28/121 (23%) that were PPNG positive by this assay. These

Table 5: Proportion (%) of gonococcal isolates tested in Australia with MIC values at 0.06 mg/L and 0.125 mg/L 2010 - 2016.

Ceftriaxone MIC mg/L	2010	2011	2012	2013	2014	2015	2016
0.06	4.80%	3.20%	4.10%	8.20%	4.80%	1.70%	1.65%
0.125	0.10%	0.10%	0.30%	0.60%	0.60%	0.10%	0.05%

Table 6: Number (%) of gonococcal isolates with resistance to azithromycin (MIC ≥1.0mg/L), Australia, 2012 to 2016, by state or territory.

State or territory	Azithromycin Resistance									
	2012		2013		2014		2015		2016	
	n	%	n	%	n	%	n	%	n	%
Australian Capital Territory	0	**0**	1	**2.2**	7	**9.3**	0	**0**	8	**7.1**
New South Wales	9	**0.5**	14	**0.9**	33	**2.0**	43	**2.3**	82	**3.6**
Northern Territory Urban & Rural	0	**0**	1	**1.0**	0	**0**	0	**0**	1	**1.9**
Northern Territory Remote	0	**0**	0	**0**	0	**0**	0	**0**	0	**0**
Queensland	15	**2.1**	38	**5.7**	23	**3.5**	42	**5.8**	10	**1.2**
South Australia	1	**0.7**	6	**2.8**	1	**0.5**	7	**2.8**	68	**19.5**
Tasmania	0	**0**	0	**0**	1	**3.3**	1	**4.3**	4	**14.3**
Victoria	34	**2.7**	35	**2.3**	33	**2.3**	30	**1.8**	93	**5.4**
Western Australia Urban and Rural	3	**0.6**	9	**1.9**	21	**5.3**	15	**3.8**	51	**7.6**
Western Australia Remote	0	**0**	0	**0**	0	**0**	0	**0**	1	**0.8**
Australia	**62**	**1.3**	**104**	**2.1**	**119**	**2.5**	**138**	**2.6**	**318**	**5.0**

data show that the PPNG rate is rising in remote regions, especially in the MidWest. Of those that were PPNG positive from remote regions, 29/43 were from Indigenous patients whereas previously all PPNG positive NG NAATs from remote regions were determined to be in non-Indigenous residents or residents in the major regional centres. Jurisdictional investigations and monitoring continue. These data support and enhance the isolate based surveillance findings of the AGSP.

Quinolone antibiotics

The AGSP uses ciprofloxacin as the representative quinolone. Ciprofloxacin resistance is defined as MIC ≥ 1 mg/L.

In 2016, there were 1,912 isolates (30%) that were resistant to ciprofloxacin (Table 3). This was slightly higher than the proportion of isolates resistant in 2015 (27%), 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) (MIC value ≥ 256 mg/L) 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 nationally between 2006 and 2015 has ranged from 12% to 21%. In 2016, the proportion of TRNG was 12%.

TRNG were present in all jurisdictions, except for Tasmania, in 2016, with the highest proportions in remote Northern Territory (26%), urban and rural Northern Territory (17%) and urban and rural Western Australia, Queensland and South Australia (16%).

Spectinomycin

In 2016, all isolates tested were susceptible to spectinomycin.

Discussion

The WHO recommends that treatment regimens for gonorrhoea are based on epidemiological surveillance of the distribution and extent of AMR, and that a resistance rate of 5% or more is the nominal threshold for change of treatment recommendations.[13] The AGSP has continuously monitored antimicrobial resistance in Australia since 1981, and has established quality assurance and quality control for gonococcal AMR testing with the AGSP External Quality Assurance Program, and WHO *N.gonorrhoeae* reference strains, thus ensuring the quality of the AGSP data.[15,16]

The overall number of gonococcal strains examined by the AGSP in 2016, was higher in number when compared with 2015. The clinical isolates were referred from both the public and private health sectors, constituting a comprehensive sample of nearly one-third of all notifications nationally. However, the increasing use of molecular diagnostic assays in place of culture and susceptibility testing threatens the scope and scale of gonococcal AMR surveillance programs worldwide. Whilst the advantages of molecular diagnostic assays over culture, in terms of sensitivity, and robustness and reliability for remote settings where cultures may not survive transportation, their primary disadvantage is that they cannot test broadly for AMR. However, molecular AMR testing strategies can give targeted and specific information which is clinically and epidemiologically important,[2] and can contribute to surveillance programmes; and be used to inform treatment guidelines.[9] This report includes PPNG NAAT data from Western Australia, providing additional situational AMR surveillance data for the AGSP in a region where penicillin based treatment strategies are in place. In 2016, these data indicate that the PPNG rate is rising in remote regions, especially in the MidWest. Further, in 2016, PPNG positive strains were reported from Indigenous patients whereas previously all PPNG positive NG NAATs from remote regions were determined to be in non-Indigenous residents or residents in the major regional centres.

The primary focus for gonococcal AMR surveillance for the majority of Australia, and in most countries, is the monitoring of ceftriaxone and azithromycin MIC values. With regard to ceftriaxone, MIC values in the range 0.06-0.125 mg/L are reported to have decreased susceptibility. The proportion of strains with decreased susceptibility to ceftriaxone been recently reported in increasing proportions in Australia, with the rate doubling over the period 2012 to 2013 from 4.4% to 8.8%.[5,17] In 2014, there was a decrease in the proportion of isolates with decreased susceptibility to ceftriaxone reported nationally to 5.4% and this decreased further in 2015 to 1.8%, and was similar in 2016. However, little reassurance should be taken from this, as fluctuation of circulating clones of *N. gonorrhoeae* within a population is to be expected. In recent years, increasing proportions of strains with decreased susceptibility to the cephalosporin antibiotics has been accompanied by reports of treatment failures. Multidrug resistant strains with high level resistance to ceftriaxone have been reported from Japan, France, Spain and Australia.[7,18-20] All of these strains were reported to have a mosaic penicillin binding protein 2 (PBP2), encoded by a mosaic *PenA* gene, with as few as one additional amino acid substitution.[21] However, a significant proportion of circulating NG strains globally have a mosaic PBP2 but without an elevated ceftriaxone MIC value, but are potentially only one point mutation from high level ceftriaxone resistance. These strains are under constant selection pressure. Given these considerations, the level of concern about the development of ceftriaxone resistance has heightened globally.[21]

In 2012, the WHO Global Action Plan nominated the criteria for decreased susceptibility to ceftriaxone as an MIC value ≥0.125 mg/L.[14] The proportion of strains tested by the AGSP with a ceftriaxone MIC value of 0.125 mg/L also doubled from 0.3% in 2012 to 0.6% in 2013 and 2014, then decreased in 2015 to 0.1% and further decreased in 2016 to 0.05%.

A dual therapy strategy of ceftriaxone with oral azithromycin for uncomplicated gonococcal infection continues to be recommended in Australia.[4] In 2013, high level resistance to azithromycin in gonococci was reported for the first time in Australia in four strains; two from Victoria and two from Queensland, and of these, two were likely acquired from China.[6] Since then, there have been sporadic reports of HLR (MIC value ≥ 256 mg/L) to azithromycin with 2 strains reported nationally in 2014 and 2015 and five strains in 2016. Continued close observation is ongoing as evidence of coevolving cephalosporin and azithromycin resistance is being observed outside Australia and is of significant concern.[21]

The most important and concerning findings by the AGSP in 2016 were related to the increase in isolates reported with low level resistance to azithromycin in most jurisdictions in Australia, particularly in South Australia, New South Wales and Victoria and excepting Queensland and the remote regions in the Northern Territory (Table 6). Until recently azithromycin resistance in Australia in *N. gonorrhoeae* has remained relatively low but increasing from 1.3-2.6% over the years 2012-1015 then increasing to 5% nationally in 2016 (Table 6). Notably in South Australia in 2016, azithromycin resistance in *N. gonorrhoeae* significantly increased ($p<0.0001$) from less than 5% in the latter half of 2015 to 26% in the first half of 2016 before decreasing to 8% in the third quarter of 2016.[22] These strains had azithromycin MIC values in the range 1.0 mg/L to 8.0 mg/L.[23] Enhanced surveillance was conducted in South Australia, and one treatment failure was reported in a patient treated with azithromycin single agent therapy.[23] A review and change of the South Australian gonococcal treatment guidelines followed.[23] Globally, there have been increasing reports of azithromycin resistance.[24]

The recent fluctuations in proportions of NG with decreased susceptibility to ceftriaxone and the emergence of azithromycin resistance offer little reassurance in the context of gonococcal AMR, which is a global public health threat. The rapid emergence of azithromycin resistance escalates concerns for future treatment strategies for gonorrhoea and underscores the

importance of bacterial culture and antimicrobial susceptibility testing of *N. gonorrhoeae* for clinical management, test of cure and surveillance programmes such as the AGSP. 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.[14] The ongoing need for close and enhanced monitoring of gonococcal AMR can be supported to a limited extent by molecular based assays, however, isolate based surveillance programmes, and sentinel site surveillance in high risk populations are critically important to inform therapeutic strategies and to detect instances of treatment failure.

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