

# Australian Gonococcal Surveillance Programme Annual Report, 2017

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## 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 2017, there were 7,835 clinical isolates of gonococci from public and private sector sources tested for *in vitro* antimicrobial susceptibility by standardised methods. Current treatment recommendations for gonorrhoea, 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 1.06% of isolates, which is lower than that reported in the AGSP Annual Report 2016 (1.7%). The highest proportions were reported from Victoria and Western Australia (urban and rural) (2.1% and 1.4% respectively). Resistance to azithromycin (MIC value  $\geq 1.0$  mg/L) was found nationally in 9.3% of isolates, which is approximately double the proportion reported in 2016 (5.0%) and more than three times the proportion reported in 2015 (2.6%). The highest proportions were reported from Victoria (13.5%), South Australia (12.8%) and New South Wales (9.3%). High level resistance to azithromycin (MIC value  $\geq 256$  mg/L) was

reported in 4 strains nationally in 2017, 2 from Victoria, one from New South Wales, and one from Queensland.

The proportion of strains resistant to penicillin in non-remote Australia ranged from 10.3% in non-remote Northern Territory to 44.1% in Tasmania. In remote Northern Territory penicillin resistance rates remain low (2.5%). In remote Western Australia penicillin resistance rates continue to increase (6.7%) compared to the previous years, however there were relatively low numbers of strains available for isolate based testing (n=12). 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 non-remote Australia ranged from 17.2% in non-remote Northern Territory to 61% in Tasmania. Ciprofloxacin resistance rates remain comparatively low in remote Northern Territory (1.3%) and remote Western Australia (5.0%).

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

## *Introduction*

Antimicrobial resistance (AMR) in *Neisseria gonorrhoeae* (NG) is a threat to global health security, and the emergence and spread of multidrug resistant (MDR) gonorrhoea is predicted to pose significant collateral health and financial costs.(1) Ceftriaxone and azithromycin dual therapy is widely recommended for treatment for gonorrhoea.

The key concerns regarding NG in Australia are increasing disease rates,(2) increasing azithromycin resistance, new reports of novel ceftriaxone resistant strains with international spread,(3) in the context of uncertainty regarding the future direction of gonococcal treatment as an ideal alternative to the current regimen has yet to be decided.

In Australia gonococcal disease notification rates have increased by 63% (62 to 101 per 100 000) in the last 5 years (2012 to 2016). Increases have been reported in both males (72%) and females (43%), and the notification rates in 2016 remains higher in males (146 per 100 000) than in females (56 per 100 000).(2) In contrast, over the same period (2012–2016), there was a 17% decrease in gonorrhoea annual notification rates in Aboriginal and Torres Strait Islander (ATSI) population; but the rate of notification of gonorrhoea in this population is markedly higher. In 2016 the notifications were 6.9 times that reported in non-Indigenous population 2016 (582 per 100 000 compared to 84 per 100 000) and highest in remote and very remote areas (1444 per 100 000) - 30 times as high as the non-Indigenous population.(2) 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)

Since 2014, when ceftriaxone and azithromycin dual therapy was introduced in Australia for the treatment of NG in an attempt to forestall resistance to ceftriaxone,(5) there has been a steady decline in the proportion of strains with raised MIC values to ceftriaxone. However there has been a coincident and marked increase in the proportion of NG strains resistant to

azithromycin following rapid emergence of azithromycin resistance in South Australia in early 2016.(6)

Coincident with the current heightened global awareness of AMR, and increasing disease notification rates reported in Australia and elsewhere,(2, 7-10) has been the wide spread adoption of nucleic acid amplification testing (NAATs) in place of bacterial culture and antimicrobial susceptibility testing (AST) is not currently possible with NAATs. However, there are NAAT assays in use in remote regions in Australia to detect penicillin resistance (11, 12) - the was the first documented use of routine molecular testing for gonococcal AMR detection and surveillance, and these continue to inform local treatment guidelines.(12)

The 2012 World Health Organization (WHO) estimates 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.(13) 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 but there are significant gaps in surveillance. Compounding this is unregulated antimicrobial use in these regions providing ideal conditions for the development of AMR.(14) The emergence of new AMR in *N. gonorrhoeae* in Australia has long been influenced by the introduction of multi-resistant strains from overseas. (15) The importation and spread of resistant gonococcal strains and/or resistance developing under selection pressure remains 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.(16) 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.(17)

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 characteristics, including antimicrobial resistance, and additional investigations where required. 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. Here follows the 2017 AGSP Annual Report.

### *Methods*

The NNN AMR data for gonococcal isolates are collated for the AGSP quarterly and annual reports. All confirmed cases of gonorrhoea in Australia are notifiable 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 total number of cases reported to the NNDSS.

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) 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.(19)

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 sex of the patient, country of acquisition, and site of isolation of gonococcal strains. Data from isolates from all jurisdictions are 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 7,835 gonococcal isolates tested in NNN laboratories in 2017, representing 28% of the 28,399 cases of gonococcal infection notified to the NNDSS in 2017 (Table 1).(20) This is the same as the proportion tested in 2015 and 2016 and lower than the range of 31%-42% referred between 2008 and 2014, and coincident with widespread uptake of NAAT diagnosis in Australia.

**Table 1: Number of Australian Gonococcal Surveillance Programme gonococcal isolates tested as a proportion of National Notifiable Diseases Surveillance System gonorrhoea notifications, Australia, 2017, by state or territory**

| <b>State or territory</b>    | <b>Number of isolates tested</b> | <b>Number of cases notified</b> | <b>Number of isolates tested/Number of cases notified %</b> |
|------------------------------|----------------------------------|---------------------------------|---|
| Australian Capital Territory | 145                              | 251                             | 58  |
| New South Wales              | 2806                             | 9219                            | 30  |
| Northern Territory           | 216                              | 1788                            | 12  |
| Queensland                   | 1249                             | 5058                            | 25  |
| South Australia              | 359                              | 1272                            | 28  |
| Tasmania                     | 59                               | 117                             | 50  |
| Victoria                     | 2258                             | 7355                            | 31  |

|                   |       |        |    |
|-------------------|-------|--------|----|
| Western Australia | 743   | 3339   | 22 |
| Australia         | 7,835 | 28,399 | 28 |

### Source of isolates

There were 6,404 isolates from males (81.7%) and 1,395 (17.8%) from females (Table 2). 36 isolates were from patients where gender was not recorded. The proportion of gonococcal isolates from males and females tested by the AGSP has remained stable over recent years (2009-14); ranging between 17 and 20% for women and 80 and 83% for men. The infected site was reported as 'other' or not specified for 86 isolates from males and 32 isolates from females (Table 2). Isolates from urine samples were regarded as genital tract isolates.

**Table 2: Gonococcal isolates, Australia, 2017, by sex, site and jurisdiction tested.**

| Sex            | Site         | NSW         | NT          | QLD         | SA         | VIC         | WA          | ACT        | TAS        | AUSTRALIA   |
|----------------|--------------|-------------|-------------|-------------|------------|-------------|-------------|------------|------------|-------------|
| <b>Male</b>    | Genital      | 1226        | 115         | 555         | 141        | 923         | 390         | 43         | 29         | <b>3422</b> |
|                | Rectal       | 727         | 5           | 251         | 66         | 599         | 67          | 38         | 7          | <b>1760</b> |
|                | Pharynx      | 439         | 4           | 112         | 43         | 413         | 41          | 40         | 9          | <b>1101</b> |
|                | DGI          | 9           | 3           | 7           | 1          | 5           | 9           | 1          | 0          | <b>35</b>   |
|                | Other/NS     | 23          | 1           | 19          | 10         | 20          | 6           | 0          | 7          | <b>86</b>   |
|                | <b>Total</b> |             | <b>2424</b> | <b>128</b>  | <b>944</b> | <b>261</b>  | <b>1960</b> | <b>513</b> | <b>122</b> | <b>52</b>   |
| <b>Female</b>  | Genital      | 287         | 83          | 273         | 79         | 228         | 212         | 19         | 7          | <b>1188</b> |
|                | Rectal       | 16          | 0           | 9           | 6          | 4           | 4           | 0          | 0          | <b>39</b>   |
|                | Pharynx      | 51          | 0           | 14          | 6          | 46          | 9           | 1          | 0          | <b>127</b>  |
|                | DGI          | 3           | 1           | 1           | 0          | 1           | 3           | 0          | 0          | <b>9</b>    |
|                | Other/NS     | 8           | 3           | 8           | 5          | 6           | 2           | 0          | 0          | <b>32</b>   |
|                | <b>Total</b> |             | <b>365</b>  | <b>87</b>   | <b>305</b> | <b>96</b>   | <b>285</b>  | <b>230</b> | <b>20</b>  | <b>7</b>    |
| <b>Unknown</b> | Total        | 17          | 1           | 0           | 2          | 13          | 0           | 3          | 0          | <b>36</b>   |
| <b>TOTAL</b>   |              | <b>2806</b> | <b>216</b>  | <b>1249</b> | <b>359</b> | <b>2258</b> | <b>743</b>  | <b>145</b> | <b>59</b>  | <b>7835</b> |

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

## 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 3:** Proportion of gonococcal isolates with resistance to azithromycin, penicillin and ciprofloxacin and decreased susceptibility to ceftriaxone reported, Australia, 2017, by state or territory

| State or Territory              | Number of isolates tested<br>2017 | Decreased Susceptibility |             | Resistance   |            |             |             |               |             |
|---------------------------------|-----------------------------------|--------------------------|-------------|--------------|------------|-------------|-------------|---------------|-------------|
|                                 |                                   | Ceftriaxone              |             | Azithromycin |            | Penicillin  |             | Ciprofloxacin |             |
|                                 |                                   | n                        | %           | n            | %          | n           | %           | n             | %           |
| Australian Capital Territory    | 145                               | 0                        | 0           | 3            | 2.1        | 25          | 17.2        | 36            | 24.8        |
| New South Wales                 | 2806                              | 13                       | 0.5         | 261          | 9.3        | 709         | 25.3        | 857           | 30.5        |
| Queensland                      | 1249                              | 11                       | 0.9         | 61           | 4.9        | 325         | 26.0        | 265           | 21.2        |
| South Australia                 | 359                               | 2                        | 0.6         | 46           | 12.8       | 149         | 41.5        | 136           | 37.9        |
| Tasmania                        | 59                                | 0                        | 0           | 5            | 8.5        | 26          | 44.1        | 36            | 61.0        |
| Victoria                        | 2258                              | 48                       | 2.1         | 304          | 13.5       | 668         | 29.6        | 691           | 30.6        |
| Northern Territory (non-remote) | 58                                | 0                        | 0           | 1            | 1.7        | 6           | 10.3        | 10            | 17.2        |
| Northern Territory (remote)     | 158                               | 0                        | 0           | 1            | 0.6        | 4           | 2.5         | 2             | 1.3         |
| Western Australia (non-remote)  | 624                               | 9                        | 1.4         | 40           | 6.4        | 125         | 20.0        | 115           | 18.4        |
| Western Australia (remote)      | 119                               | 0                        | 0           | 4            | 3.4        | 8           | 6.7         | 6             | 5.0         |
| <b>AUSTRALIA</b>                | <b>7835</b>                       | <b>83</b>                | <b>1.06</b> | <b>726</b>   | <b>9.3</b> | <b>2045</b> | <b>26.1</b> | <b>2154</b>   | <b>27.5</b> |

## Ceftriaxone

From 2001 onwards, gonococcal isolates categorised as having decreased susceptibility to ceftriaxone by the AGSP criteria (MIC values  $\geq 0.06$  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 1.8% in 2015 and 1.7% in 2016. In 2017, the proportion has again decreased to 1.06%. (Table 4).

**Table 4: Number (%) of gonococcal isolates with decreased susceptibility to ceftriaxone (MIC  $\geq$ 0.06mg/L), Australia, 2010 to 2017, by state or territory. Remote Western Australian data is de-aggregated from 2014.**

| State or territory              | Decreased susceptibility to ceftriaxone |            |            |            |            |            |            |            |            |            |           |            |            |            |           |            |
|---------------------------------|---|------------|------------|------------|------------|------------|------------|------------|------------|------------|-----------|------------|------------|------------|-----------|------------|
|                                 | 2010                                    |            | 2011       |            | 2012       |            | 2013       |            | 2014       |            | 2015      |            | 2016       |            | 2017      |            |
|                                 | n                                       | %          | 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        | 0         | 0          |
| New South Wales                 | 74                                      | 5.6        | 58         | 4.4        | 76         | 4.5        | 183        | 11.8       | 119        | 7.1        | 52        | 2.7        | 45         | 2.0        | 13        | 0.5        |
| Northern Territory (non-remote) | 1                                       | 0.2        | 2          | 0.4        | 0          | 0          | 2          | 1.9        | 3          | 3.0        | 0         | 0          | 0          | 0          | 0         | 0          |
| Northern Territory (remote)     | 0                                       | 0          | 0          | 0          | 0          | 0          | 2          | 0.8        | 1          | 0.8        | 0         | 0          | 0          | 0          | 0         | 0          |
| Queensland                      | 17                                      | 3.2        | 18         | 2.3        | 17         | 2.4        | 33         | 4.9        | 21         | 3.2        | 7         | 1.0        | 32         | 3.7        | 11        | 0.9        |
| South Australia                 | 12                                      | 11.6       | 1          | 0.7        | 1          | 0.7        | 4          | 1.9        | 2          | 1.0        | 9         | 3.6        | 2          | 0.6        | 2         | 0.6        |
| Tasmania                        | 0                                       | 0          | 0          | 0          | 0          | 0          | 11         | 24.4       | 0          | 0          | 0         | 0          | 1          | 3.6        | 0         | 0          |
| Victoria                        | 52                                      | 5.7        | 50         | 5.3        | 105        | 8.4        | 181        | 11.8       | 95         | 6.6        | 25        | 1.5        | 19         | 1.1        | 48        | 2.1        |
| Western Australia               | 17                                      | 5.2        | 3          | 0.7        | 6          | 1.2        | 13         | 2.7        |            |            |           |            |            |            |           |            |
| Western Australia (non-remote)  |   |            |            |            |            |            |            |            | 14         | 3.6        | 5         | 1.3        | 9          | 1.3        | 9         | 1.4        |
| Western Australia (remote)      |   |            |            |            |            |            |            |            | 1          | 0.9        | 0         | 0          | 0          | 0          | 0         | 0          |
| <b>Australia</b>                | <b>191</b>                              | <b>4.8</b> | <b>134</b> | <b>3.2</b> | <b>207</b> | <b>4.4</b> | <b>429</b> | <b>8.8</b> | <b>258</b> | <b>5.4</b> | <b>98</b> | <b>1.8</b> | <b>109</b> | <b>1.7</b> | <b>83</b> | <b>1.1</b> |

The significant right shift in the distribution of ceftriaxone MIC values over 2011- 2013 (Table 5), with the 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]) declining steadily in the following years. In 2015 the proportion of strains with an MIC value of  $\geq$ 0.125 mg/L decreased to 0.1%, and further decreased to 0.04% in 2017 (Table 5). However, in 2017, there were two NG isolates with a ceftriaxone MIC value of 0.5 mg/L reported, the highest MIC value obtained in Australia since the A8806 isolate reported in 2013.(21) These ceftriaxone resistant isolates were resistant to ciprofloxacin (MIC >32 mg/L); susceptible to spectinomycin (MIC 8 mg/L) and azithromycin (MIC 0.25 mg/L); and, unlike all previously

described ceftriaxone-resistant strains, were penicillinase-producing *NG* (PPNG; MIC  $\geq$ 32 mg/L).

**Table 5: Proportion (%) of gonococcal isolates tested in Australia with MIC values at 0.06 mg/L and  $\geq$ 0.125 mg/L 2010 - 2017.**

| Ceftriaxone MIC mg/L | 2010  | 2011  | 2012  | 2013  | 2014  | 2015  | 2016  | 2017  |
|----------------------|-------|-------|-------|-------|-------|-------|-------|-------|
| 0.06                 | 4.80% | 3.20% | 4.10% | 8.20% | 4.80% | 1.70% | 1.65% | 1.02% |
| $\geq$ 0.125         | 0.10% | 0.10% | 0.30% | 0.60% | 0.60% | 0.10% | 0.05% | 0.04% |

### Azithromycin

Nationally, the proportion of isolates exhibiting resistance (MIC value  $\geq$ 1.0 mg/L) was 9.3% (Table 3), greater than an eight-fold increase from that reported in 2012 (1.3%) (Table 6). The proportion of isolates exhibiting resistance was highest in Victoria (13.5% in 2017, compared with 5.4% in 2016) (Table 6). Increases in the number and proportion of isolates exhibiting resistance compared with previous years were also seen in NSW, Queensland and remote Western Australia (Table 6). In 2017, there were 4 isolates that exhibited high level resistance to azithromycin (MIC value  $\geq$  256 mg/L), two from Victoria and one from Queensland and one from NSW.

**Table 6: Number (%) of gonococcal isolates with resistance to azithromycin (MIC  $\geq$ 1.0mg/L), Australia, 2012 to 2017, by state or territory.**

| State or territory              | Azithromycin Resistance |     |      |     |      |     |      |     |      |     |      |     |
|---------------------------------|-------------------------|-----|------|-----|------|-----|------|-----|------|-----|------|-----|
|                                 | 2012                    |     | 2013 |     | 2014 |     | 2015 |     | 2016 |     | 2017 |     |
|                                 | n                       | %   | n    | %   | n    | %   | n    | %   | n    | %   | n    | %   |
| Australian Capital Territory    | 0                       | 0   | 1    | 2.2 | 7    | 9.3 | 0    | 0   | 8    | 7.1 | 3    | 2.1 |
| New South Wales                 | 9                       | 0.5 | 14   | 0.9 | 33   | 2.0 | 43   | 2.3 | 82   | 3.6 | 261  | 9.3 |
| Northern Territory (non-remote) | 0                       | 0   | 1    | 1.0 | 0    | 0   | 0    | 0   | 1    | 1.9 | 1    | 1.7 |
| Northern Territory (remote)     | 0                       | 0   | 0    | 0   | 0    | 0   | 0    | 0   | 0    | 0   | 1    | 0.6 |

|                                   |           |            |            |            |            |            |            |            |            |            |            |            |
|-----------------------------------|-----------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Queensland                        | 15        | 2.1        | 38         | 5.7        | 23         | 3.5        | 42         | 5.8        | 10         | 1.2        | 61         | 4.9        |
| South Australia                   | 1         | 0.7        | 6          | 2.8        | 1          | 0.5        | 7          | 2.8        | 68         | 19.5       | 46         | 12.8       |
| Tasmania                          | 0         | 0          | 0          | 0          | 1          | 3.3        | 1          | 4.3        | 4          | 14.3       | 5          | 8.5        |
| Victoria                          | 34        | 2.7        | 35         | 2.3        | 33         | 2.3        | 30         | 1.8        | 93         | 5.4        | 304        | 13.5       |
| Western Australia<br>(non-remote) | 3         | 0.6        | 9          | 1.9        | 21         | 5.3        | 15         | 3.8        | 51         | 7.6        | 40         | 6.4        |
| Western Australia<br>(remote)     | 0         | 0          | 0          | 0          | 0          | 0          | 0          | 0          | 1          | 0.8        | 4          | 3.4        |
| <b>Australia</b>                  | <b>62</b> | <b>1.3</b> | <b>104</b> | <b>2.1</b> | <b>119</b> | <b>2.5</b> | <b>138</b> | <b>2.6</b> | <b>318</b> | <b>5.0</b> | <b>726</b> | <b>9.3</b> |

## Penicillin

Resistance to the penicillin group of antibiotics (penicillin, ampicillin and amoxicillin 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). Chromosomal resistance is defined as an MIC to penicillin of 1 mg/L or more.

In 2017, in Australia, 2,045 (26.1%) of isolates were penicillin resistant, a proportional decrease from 2016 (32.5%). The proportion of penicillin resistant strains has continued to fluctuate in the range 22.5-44% over the period 2008 – 2017. In 2017, there were 1052 (13.4%) isolates with CMRP; and 993 (12.7%) with PPNG.

### *Penicillin resistance in the Northern Territory*

In 2017 there were 216 isolates tested from the Northern Territory. There were 58 from Darwin (non-remote), and 158 from remote areas of NT (including Alice Springs, Katherine, Tennant Creek, and Arnhem Land region).

Of the isolates tested from the Northern Territory, 6 (10.3%) from the city of Darwin and surrounding urban areas were penicillin resistant: (4/6 PPNG) (Table 3: Northern Territory

non-remote). From the remote regions of the NT, 4 (2.5%) strains tested were penicillin resistant (2 PPNG). No strains from the NT had decreased susceptibility to ceftriaxone. In 2017 there were 743 isolates tested from Western Australia (WA), with 119 of these from remote regions, and 624 from non-remote regions. Of the isolates tested from non-remote regions, 20% were reported as resistant, whereas of the 119 isolates tested from remote regions, there were 8 isolates (6.7%) that were penicillin resistant (all PPNG).

### **Quinolone antibiotics**

The AGSP uses ciprofloxacin as the representative quinolone. Ciprofloxacin resistance is defined as MIC  $\geq$  1 mg/L. In 2017, there were 2,154 isolates (27.5%) that were resistant to ciprofloxacin (Table 3). 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 NG (TRNG) (MIC value  $\geq$  16mg/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 2016 has ranged from 12% to 21%. In 2017 the proportion of TRNG was 10.2% TRNG were present in all jurisdictions

### **Spectinomycin**

In 2017, 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.(16) The AGSP has continuously monitored AMR 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 NGreference strains, thus ensuring the quality of the AGSP data.(19, 22)

In 2017 the NNN examined 7835 clinical isolates for susceptibility testing to ceftriaxone, azithromycin, ciprofloxacin, penicillin and high level resistance to tetracycline. These isolates were referred from both the public and private health sectors, constituting a comprehensive sample of nearly one-third of all notifications nationally.

For the majority of Australia, and in most countries, the monitoring of ceftriaxone and azithromycin MIC values is the primary focus of surveillance for gonococcal AMR. 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 has steadily and substantially declined since 2013 from 8.8% to 1.1% in 2017 (Table 4). However little reassurance should be taken from this, as fluctuation of circulating clones of NG within a population is to be expected and multidrug resistant strains with high level resistance to ceftriaxone have been reported from Asia, Europe and Australia in recent years.(23-26).

In 2017 we identified two new multidrug resistant NG strains isolated in Australia from heterosexual males visiting from Asia. These strains were phenotypically similar to ceftriaxone resistant strain first reported in Japan in 2015 (FC428), and similar strains in Denmark (GK124) and Canada (47707). As part of a WHO collaboration we investigated the possible spread of the FC428 using bioinformatic analyses including core single-nucleotide variation phylogeny and *in silico* molecular typing. Phylogenetic analyses showed genetic relatedness amongst these five isolates providing further evidence of international transmission of ceftriaxone-resistant *N. gonorrhoeae*.(3)

In contrast the remote populations of Australia, which are predominantly Aboriginal and Torres Strait Islander, have low rates of AMR despite very high rates of disease, but require continued vigilance with monitoring of AMR in NG using molecular and culture based surveillance strategies.

In 2013, high level resistance (HLR; MIC value  $\geq$  256 mg/L) to azithromycin in gonococci was reported for the first time in Australia in four strains, two with suspected contact in China. (27) Since then there have been only sporadic reports of HLR to azithromycin and there were four such strains in 2017. Continued close observation is ongoing as evidence of coevolving cephalosporin and azithromycin resistance is being observed outside Australia and is of significant concern.(28)

Another important and concerning finding by the AGSP in 2017 is the increase in isolates with low level resistance to azithromycin in all jurisdictions of Australia, excepting the ACT and Northern Territory (Table 6). In remote WA there were four azithromycin resistant strains reported. Until recently azithromycin resistance in Australia in NG has remained relatively low at 1.3-2.6% over the years 2012-2015 but has then increase from 5% in 2016 to 9.3% in 2017 (Table 6). In South Australia in 2016, azithromycin resistance in NG significantly increased ( $p < 0.0001$ ) from less than 5% in the latter half of 2015 to 26% in the first half of 2016.(29) Overall in 2016, there were 68/349 (19.5%) strains in South Australia that were azithromycin resistant with MIC values in the range 1.0 mg/L to 8.0 mg/L. Enhanced surveillance was conducted, and one treatment failure was reported in a patient treated with azithromycin single agent therapy. (30) A review and change of the South Australian gonococcal treatment guidelines followed.(30) In 2017 azithromycin resistance was highest in Victoria (13.5%); South Australia (12.8%) and NSW (9.3%) and Tasmania (8.5%). Globally there have been increasing reports of azithromycin resistance.(31)

The recent reports of international spread of NG with resistance to ceftriaxone, and the emergence of azithromycin resistance heighten concerns about the future treatment strategies for NG AMR. Public health strategies promoting primary prevention of gonorrhoea and other sexually transmissible infections are urgently required and NG vaccine development is a research priority to control this disease.

This report underscores the importance of bacterial culture and antimicrobial susceptibility testing of NG for clinical management, detection of resistance and novel resistant strains, AMR surveillance, and test of cure. Clinicians should note and consider travel history given the association with NG AMR.

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.(17) The ongoing need for close and enhanced monitoring of gonococcal AMR can be supported, but not replaced, by molecular based assays and strain specific assays can be used for routine and sentinel site surveillance in high risk populations. The data are critically important to inform therapeutic strategies, monitor for the presence and spread of resistance and to detect instances of treatment failure.

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