Annual reports

Annual Report of the Australian Gonococcal Surveillance Programme, 2009

The Australian Gonococcal Surveillance Programme

Abstract

The Australian Gonococcal Surveillance Programme (AGSP) monitors antibiotic susceptibility testing of *Neisseria gonorrhoeae* isolated in all states and territories. In 2009 the *in vitro* susceptibility of 3,220 isolates of gonococci from public and private sector sources was determined by standardised methods. Varying antibiotic susceptibility patterns were again seen across jurisdictions and regions. Resistance to the penicillins nationally was 36% and, with the exception of the Northern Territory, ranged between 19% in Queensland and 52% in Victoria. Quinolone resistance, most at high minimal inhibitory concentration (MIC) levels, was 43% nationally (excepting the Northern Territory), and ranging from 30% in Queensland to 60% in Victoria. Decreased susceptibility to ceftriaxone (MIC 0.06 mg/L or more), was found nationally in 2% of isolates. Nationally, all isolates remained sensitive to spectinomycin. Azithromycin resistance surveillance was performed in New South Wales, Queensland, Western Australia, the Northern Territory and South Australia, and was found to be present in low numbers of gonococci with MIC values up to 16 mg/L. In larger urban centres the ratio of male to female cases was high, and rectal and pharyngeal isolates were common in men. In other centres and in rural Australia the male to female ratio of cases was lower, and most isolates were from the genital tract. *Commun Dis Intell* 2010;34(2):89–95.

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

Introduction

Gonorrhoeal infections continue to be a public health challenge globally, and effective antibiotic treatment is fundamental to disease control at the population level.[1] Around the world, the increasing prevalence of antimicrobial resistance (AMR) in *Neisseria gonorrhoeae,* and its impact on treatment outcome is a major concern.[1] Resistance to the penicillins, tetracyclines and macrolides has necessitated the widespread removal of these low cost, oral agents from standard treatment regimens. In urban Australia,[2] and in neighbouring countries, the emergence of high levels of resistance to fluoroquinolone antibiotics has compromised the efficacy of this antibiotic group at both the individual and population health level. This has resulted in widespread replacement with extended spectrum cephalosporin antibiotics as the recommended first line treatment for gonorrhoea in Australia and elsewhere.[3] Unusually, but importantly in Australia however, treatments based on the penicillins remain effective in many rural centres where extremely high disease rates persist.[2]

In large centres in urban Australia, AMR in *Neisseria gonorrhoeae* has long been influenced by the introduction of multi-resistant overseas strains.[2] There are an increasing number of reports from overseas sources[4,5] of treatment failures with orally administered extended spectrum cephalosporin. In Australia, oral, extended spectrum cephalosporin antibiotics are not available, therefore the injectable form (ceftriaxone) is recommended for use in high doses.[3] No treatment failures have yet been reported following ceftriaxone treatment of genital tract gonorrhoea; however there have been 2 instances of failure of treatment of pharyngeal gonorrhoea reported in Sydney[6] where elimination of intercurrent genital tract infection with the same organism was achieved. The gonococci involved both had raised minimal inhibitory concentrations (MICs) for ceftriaxone.

Strategies for treating and controlling gonorrhoea are based on single dose regimens effecting cure in a minimum of 95%, and the formulation of these regimens is reliant on data derived from continuous AMR monitoring of gonococcal isolates to the antibiotics in clinical use.[1,7] Recently, and following the reports of treatment failures with orally administered extended spectrum cephalosporins,[4,5] calls have been made internationally for enhanced surveillance of all forms of gonococcal AMR in order to optimise gonococcal antibiotic treatment.[8] Since 1981 the Australian Gonococcal Surveillance Programme (AGSP) has monitored the susceptibility of *N. gonorrhoeae* continuously, making it the longest, continually running national surveillance

system for gonococcal AMR.[9] The emergence and spread of penicillin and quinolone resistant gonococci in major cities in Australia has been well documented.[2]

This analysis of AMR in *N. gonorrhoeae* in Australia was derived from data collated by the AGSP during the 2009 calendar year. It provides information regarding the gonococcal isolates showing resistance to multiple antibiotics, including those with decreased susceptibility to ceftriaxone.[2,10]

Methods

Ongoing monitoring of AMR in gonococci in Australia is performed by the AGSP through a collaborative program conducted by reference laboratories in each state and territory. The AGSP is a component of the National Neisseria Network of Australia and comprises participating laboratories in each state and territory (see acknowledgements). This collaborative network of laboratories obtains isolates for examination from as wide a section of the community as possible, with both public and private sector laboratories referring isolates to regional testing centres. The increasing use of non-culture based methods of diagnosis has the potential to reduce the size of the sample of isolates available for testing. Details of the number of organisms examined are thus provided in order to indicate the AGSP sample size.

Gonococci, isolated in and referred to the participating laboratories, are examined for antibiotic susceptibility to the penicillins, quinolones, spectinomycin and third generation cephalosporins, and for high level resistance to the tetracyclines by a standardised methodology previously described.[9,11] The AGSP also conducts a program specific quality assurance (QA) program.[12]

Antibiotic sensitivity data from each jurisdiction are submitted quarterly to the coordinating laboratory, which collates the results and provides individual feedback to each participating laboratory. Additionally, the AGSP collects data on the gender of the patient and site of isolation of gonococcal strains. Where available, data on the geographic source of acquisition of antibiotic resistant isolates were included in the analyses.

Results

Number of isolates

There were 3,220 gonococcal isolates referred to, or else isolated in, AGSP laboratories in 2009, little changed overall from the 3,189 examined in 2008. The source and site of infection with these isolates are shown in the Table. Nine hundred and forty-nine gonococci (29.5% of the Australian total) were isolated in New South Wales, 786 (24.4%) in Victoria, 561 (17.4%) in Queensland, 387 (12%) in the Northern Territory and 318 (9.9%) in Western Australia, 170 (5.3%) in South Australia. There were a small number of isolates from the Australian Capital Territory (38; 1.2%) and Tasmania (11; 0.3%).

Isolate numbers increased from those reported in 2008 in New South Wales (from 857), Victoria (from 567), and the Australian Capital Territory (from 9). Conversely, there was a decrease in the number of isolates from South Australia (from 391), and Western Australia (from 410), but there was little change in Queensland (from 542), the Northern Territory (from 403) and Tasmania (from 13).

Table: Source and number of gonococcal isolates, Australia, 2009, by sex, site and region

		State or territory								
Gender	Site	ACT	NSW	NT	Qld	SA	Tas	Vic	WA	Aust
Male	Urethra	16	523	238	353	86	8	412	219	1,855
	Rectal	13	193	0	48	15	2	157	9	437
	Pharynx	7	101	2	28	19	1	105	7	270
	Other/NS	1	8	13	11	8	0	11	8	60
	Total	37	825	253	440	128	11	685	243	2,622
Female	Cervix	0	100	125	116	31	0	87	71	530
	Other/NS	1	24	9	5	9	0	14	4	66
	Total	1	124	134	121	40	0	101	75	596
Unknown*	Total	0	0	0	0	2	0	0	0	2
Total		38	949	387	561	170	11	786	318	3,220

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

NS Not serotyped

Source of isolates

There were 2,622 isolates from men and 596 from women, with the male to female (M:F) ratio of 4.4:1; higher than the 3.7:1 ratio for 2008. The number of isolates from men increased from 2,509 in 2008, but the number of isolates from women decreased from 682. Isolates from females increased from 2008 in New South Wales (from 117) and Victoria (from 74), but decreased in Queensland (from 139), and Western Australia (from 106) and with a marked decline in South Australia (from 104). The number of isolates from Northern Territory was essentially unchanged (137 in 2008). The M:F ratios in each jurisdiction were much the same as those reported in 2008, and remained high in New South Wales (6.7:1) and Victoria (6.8:1), where strains were more often obtained from urban populations, than in Queensland (3.6:1), Western Australia (3.2:1), South Australia (3.2:1) and the Northern Territory (1.9:1), where there is a large non-urban component of gonococcal disease. Male rectal and pharyngeal isolates were most frequently found in Victoria (together, 38% of isolates obtained from men), New South Wales (36%) and South Australia (27%). Further, the total number of isolates was small in the Australian Capital Territory (38), but it is notable that 54% were rectal or pharyngeal.

For 126 of the isolates in the Table, the site is shown as 'other' or 'not stated'. Included in this total were 27 cases of disseminated gonococcal infection; 23 in men (0.9% of all infections), and 4 (0.7%) in women. From women, 23 gonococci were pharyngeal, and there were 9 rectal isolates. Although not all infected sites were identified, isolates from urine samples were regarded as genital tract isolates and most of the other unidentified isolates were probably from this source, although they were not specified.

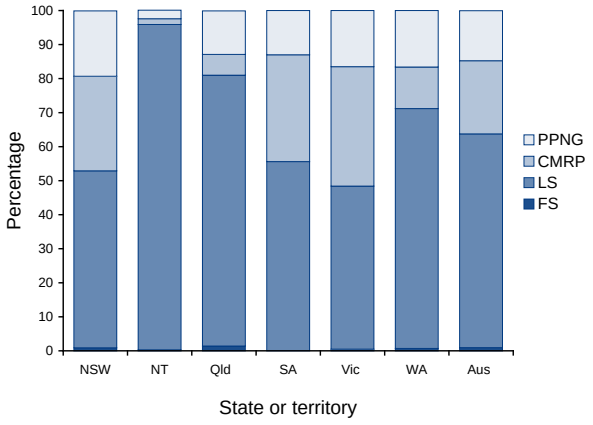
Antibiotic susceptibility patterns

Three thousand one hundred and fifty-seven (98%) gonococcal isolates in 2009 remained viable for susceptibility testing. These were examined by the AGSP reference laboratories for sensitivity to penicillin (representing this group of antibiotics), ceftriaxone (representing later generation cephalosporins), ciprofloxacin (representing quinolone antibiotics), spectinomycin; and for high level resistance to tetracycline (TRNG). As in past years, the patterns of gonococcal antibiotic susceptibility differed between the various states and territories. For this reason data are presented by region as well as aggregated for Australia as a whole.

Penicillins

The categorisation of gonococci isolated in Australia in 2009 by penicillin MIC is shown in Figure 1. Infections unlikely to respond to the penicillin group of antibiotics (penicillin, ampicillin, amoxycillin, with or without clavulanic acid) are those caused by gonococci shown as 'penicillinase producing' *N. gonorrhoeae* (PPNG) and 'relatively resistant'. Resistance in the PPNG group results from the production of beta-lactamase, and in those termed 'relatively resistant' by the aggregation of chromosomally controlled resistance mechanisms[1] – so called CMRP. Chromosomal resistance is defined by an MIC to penicillin of 1 mg/L or more.[1,11] (The MIC in mg/L is the least amount of antibiotic which inhibits *in vitro* growth under defined conditions). Infections with gonococci classified as fully sensitive (FS: MIC ≤ 0.03 mg/L) or less sensitive (LS: MIC 0.06–0.5 mg/L) would be expected to respond to standard penicillin treatments, although response to treatment may vary at different anatomical sites.

Figure 1: Penicillin resistance of gonococcal isolates, Australia, 2009, by region



FS	Fully sensitive to penicillin, MIC ≤ 0.03 mg/L
LS	Less sensitive to penicillin, MIC 0.06–0.5 mg/L
CMRP	Chromosomally mediated resistant to penicillin, MIC ≥ 1 mg/L
PPNG	Penicillinase producing *Neisseria gonorrhoeae*

Nationally, 1,145 (36%) gonococci were penicillin resistant by one or more mechanisms in 2009, a decrease in the proportion of isolates resistant to this group of antibiotics recorded in 2008 (44%) but similar to that of 2007 (38%). Of these 680 (22% of all isolates) were CMRP and 465 (15%) were PPNG, compared with 994 (32%) CMRP and 373 (12%) PPNG in 2008. The decrease in penicillin resistance nationally was predominantly due to decreased numbers of gonococci with chromosomally mediated resistance.

The proportion of penicillin resistance of all gonococcal isolates was highest in Victoria with 51.6%

(PPNG 16.5%, CMRP 35.1%), New South Wales 47.0% (PPNG 19.2%, CMRP 27.8%) and South Australia 44.4% (PPNG 13.0% and CMRP 31.4%), and although all proportions were lower than those reported in 2008, the most marked was from South Australia (from 73.2% in 2008). In Western Australia, the proportion at 28.8% (PPNG 16.6%, CMRP 12.2%) was essentially unchanged from 2008. In Queensland, the proportion of penicillin resistant gonococci again decreased, from 25% (PPNG 13.4%, CMRP 11.6%) in 2008 to 19.0% (PPNG 12.8%, CMRP 6.1%) in 2009, with the reduction being related to the proportion of CMRP isolates. Ten CMRP and 1 PPNG were identified in the Australian Capital Territory, while in Tasmania there were 3 CMRP and 2 PPNG. In the Northern Territory, there were 15 penicillin resistant gonococci, unchanged from 2008; 9 PPNG and 6 CMRP (2 from Darwin and 4 from Alice Springs) so representing a total of 4.2% of strains that were penicillin resistant in 2009 (3.9% in 2008, 4.1% in 2007, 4.6% in 2006).

Data on the country of acquisition were available for 72 (15.5%) of the infections with PPNG. Thirty-five (49%) of these were acquired locally and 37 (51%) were associated with overseas contact. These overseas contacts were principally in Western Pacific or South East Asian countries with those reported from Thailand (8), the Philippines (7) and Indonesia (5) the most numerous. Additionally, China, Vietnam, Cambodia and more widely The Netherlands and the United Kingdom were reported as countries of acquisition.

Ceftriaxone

From 2001 onwards, low numbers of isolates with raised ceftriaxone MICs have been found in Australia. This proportion has increased incrementally with data from recent years showing a rise from 0.6% in 2006; 0.8% in 2007 to 1.1% in 2008. In 2009, 64 (2.0%) gonococci were 'non-susceptible' to ceftriaxone with MICs in the range of 0.06–0.25 mg/L. Seventeen of these were present in Victoria (2.2% of isolates there); 16 in New South Wales (1.7%); 10 (1.8%) in Queensland; 9 (5.3%) in South Australia; nine in Western Australia (3.1%); 2 (5.3%) in the Australian Capital Territory; and 1 (0.3%) from the Northern Territory.

In Victoria in 2008, there were no gonococci with raised ceftriaxone MICs compared with 17 non-susceptible isolates in 2009. Sixteen of the 17 isolates were from the latter 2 quarters of the year.

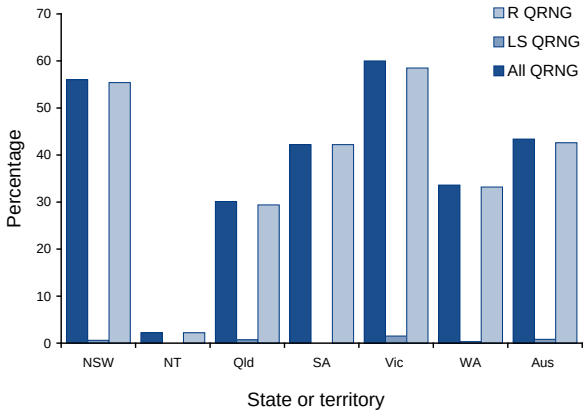
Spectinomycin

All isolates from all jurisdictions were again susceptible to this injectable antibiotic.

Quinolone antibiotics

Figure 2 shows the distribution of gonococci with altered susceptibility to quinolones nationally and by jurisdiction. Thus far, resistance to the quinolone antibiotics in *N. gonorrhoeae* is mediated only by chromosomal mechanisms so that incremental increases in MICs are observed. The AGSP uses ciprofloxacin as the representative quinolone and defines altered susceptibility as an MIC of 0.06 mg/L or more.[11] Treatment with currently recommended doses of 500 mg of ciprofloxacin is effective for strains with a lower level of resistance, viz. 0.06–0.5 mg/L, in about 90% of cases, but lower doses of the antibiotic will result in treatment failure more often. At higher levels of resistance i.e. an MIC of 1 mg/L or more, rates of treatment failure rise rapidly. At MIC levels of 4 mg/L or more, treatment failure, even with higher ciprofloxacin doses, approaches 100%.

Figure 2: Percentage of gonococcal isolates which were less sensitive to ciprofloxacin and all strains with altered quinolone susceptibility, Australia, 2009, by region



LS QRNG MIC 0.06–0.5 mg/L or with higher level ciprofloxacin resistance

R QRNG MIC 1 mg/L or more

Nationally in 2009, 1,370 (43.4%) gonococci examined had some level of resistance to quinolones (QRNG). A decrease from 1,685 (54%) detected in 2008; and 1,493, (49%) detected in 2007. Most of the QRNG found in 2009 (1,346 or 98.3%) had resistance at a higher level i.e. MICs ≥ 1 mg/L and many of these had MIC levels of the order of 8–64 mg/L. High proportions of QRNG were seen in Victoria where 469 (60.1%) of all isolates examined in this jurisdictions, were QRNG. The next highest rates were in New South Wales, 531 (56.0%); South Australia, 70 (41.4%); Western Australia, 99 (33.6%); and Queensland 167 (30.1%). In the Australian Capital Territory there were 21 (55.3%) QRNG

isolated, representing an increase from 2008 when 2 QRNG were identified. In other jurisdictions the number of QRNG remained low: Northern Territory 8; Tasmania 5.

Information on the country of acquisition of QRNG was available for 200 (14.6%) of the 1,370 cases. One hundred and thirty-six of these (68%) were acquired locally and 64 (32%) were acquired overseas from sources referred to under PPNG acquisition and with contacts additionally reported in Germany, Switzerland, Italy, South Africa, Sri Lanka, Hong Kong, the United States of America and Iran.

High level tetracycline resistance

The spread of high level tetracycline resistance in *N. gonorrhoeae* (TRNG) is examined as an epidemiological marker even though tetracyclines are not a recommended treatment for gonorrhoea and are rarely, if ever, used for treatment of gonorrhoea in Australia. Despite the lack of use of this antibiotic group, the proportion of TRNG detected continues to increase. In 2006, 12% of isolates were TRNG; increasing in 2007 (505 TRNG 16.6%) and again in 2008 (553 TRNG, 18%). In 2009, this increase continued with 650 (21%) TRNG detected.

TRNG were present in all jurisdictions, with the highest proportion in Western Australia (94 TRNG, 31%) and New South Wales (241 TRNG 25.4%). Lower proportions of TRNG were present in Victoria (148, 19.0%), Queensland (92, 16.6%) and South Australia (26, 15.4%). There were 47 (13.0% TRNG found in the Northern Territory, one in Tasmania and one in the Australian Capital Territory.

Discussion

The World Health Organization recommendations for standardised treatment regimens for gonorrhoea are based on data from epidemiological surveys of both the distribution and extent of AMR in gonococci.[1] AMR at a rate of 5% or more in gonococci sampled in a general population is the 'threshold' for removal of an antibiotic from treatment schedules and substitution with another, effective, agent.[1,13] Programs such as the AGSP seek to determine the proportion of AMR in gonococcal strains isolated in a defined patient population and relate these findings to the likely efficacy of current treatment schedules.[1,2,7,11,13] These strategies are dependant on quality AMR data, and the requirements for *in vitro* growth and AMR testing of the fastidious *N. gonorrhoeae* complicate this process. An important aspect of surveillance is to obtain and examine a sufficient and representative sample of isolates.[1,11,13] In 2009, the strains examined by the AGSP were sourced from both the public and private health sectors, constituting a comprehensive sample that meets these requirements, in spite of the increasing use of nucleic acid amplification testing for diagnosis of gonorrhoea in Australia. The AGSP distributes reference panels for use in internal quality control practice and for External Quality Assurance Schemes,[12,14] which are necessary for validation of gonococcal AMR data.

The overall number of gonococcal strains examined by the AGSP in 2009 (3,220) was essentially unchanged from 2008 (3,192), however there was a shift in proportions of the whole reported by jurisdiction with increased numbers from New South Wales, Victoria and the Australian Capital Territory and decreases from South Australia (391 in 2008 to 170 in 2009) and Western Australia (410 in 2008 to 318 in 2009).

In 2009, 36% of gonococci nationally were resistant to the penicillins, and 43% to the quinolone antibiotics. These proportions were reduced from those reported nationally in 2008 (penicillin resistance, 44%; quinolone resistance, 54%), where previously they have been increasing each year since 2003.[2] The decrease in penicillin resistance in 2009 is primarily accounted for by a reduction in CMRP rates, from 32% in 2008 to 22% in 2009. Aggregated data have shown that there is a predominant clone of CMRP coupled with high level quinolone resistance circulating with increasing frequency annually since 2003.[2,10] It is possible that the reduction in resistance to both penicillin and the quinolones in 2009 reflects a 'clonal shift' in gonococcal isolates.

In 2009, the level in Australia of gonococci isolates with high level tetracycline resistance was low but continues to rise annually despite low exposure to these antibiotics in Australia.[2] Evidence of the 'rural–urban divide',[2] in gonococcal resistance was maintained, (Figures 1 and 2) underscoring the necessity for disaggregated information rather than pooled national data to define treatment regimens appropriate for the various jurisdictions. Remote areas in some jurisdictions with high disease rates continue to be able to use penicillin based treatments, but effective use of this cheap and acceptable treatment is contingent on vigilant monitoring of resistance patterns.

Recent AGSP reports have drawn attention to the emergence and spread of gonococci in Australia that exhibit decreased susceptibility to the later generation cephalosporin antibiotics, also referred to as the extended spectrum cephalosporins (ESC). These gonococci have also been found in increasing numbers in the WHO Western Pacific Region.[15] In 'urban' Australia, the injectable agent ceftriaxone is now the standard treatment for gonorrhoea in public sector clinics, and is currently

given by intramuscular injection in a dose of 500 mg. This dose is higher than the 250 mg dose that is more commonly used throughout the Western Pacific Region,[3] however 500 mg is the smallest volume vial available in Australia. This decreased susceptibility to the ESC has been accompanied by an increasing number of reports of treatment failures with the orally administered members of this group.[3,4,16] This decreased susceptibility is quantified by the determination MIC. To date, there have been no substantiated reports of treatment failure in genital tract gonorrhoea following ceftriaxone therapy. In 2009, the number of strains with decreased susceptibility to the ESC in Australia was higher than 2008, reflecting the view that has been expressed that it is a matter of when, not if, the number of these strains will increase and that this will be accompanied by further MIC increases.

During 2009 there has been clarification of the mechanisms of resistance that are responsible for the MIC increases to ceftriaxone in gonococci. Attention has been paid particularly to the presence of 'mosaic' *penA* genes in gonococci with raised ESC MICs. *PenA* encodes penicillin binding protein 2 (PBP2), the major site of action of ceftriaxone and mosaic PBP2 are altered to reduce this activity. Additional gene polymorphisms that affect antibiotic access to the organism complement these PBP2 changes and further increase ESC MICs. Of recent interest has been an extension of a study from 2001 to 2005 on the dynamics of spread of mosaic PBP2-containing gonococci (mPBP2-GC) in Australia. This initial investigation suggested that mPBP2-GC found locally were also present in Hong Kong (where they were associated with treatment failure with an oral ESC, ceftibuten),[16] and also in Japan.[4] Continuing studies in 2007 and 2008 showed that the subtypes of the mPBP2-GC present in Australia had altered markedly and that these strains had increased as a proportion of all gonococci tested.[17]

Also of relevance have been local studies that showed other non-mosaic lesions in *penA* were also responsible for increases in ceftriaxone MICs similar to those found in mosaic PBP2 containing gonococci.[18] These lesions were single nucleotide polymorphisms that represented mutations occurring in the *penA* of *N. gonorrhoeae*. This contrasted with the mosaic *penA* alteration that results from acquisition of 'foreign' DNA by the gonococcus.[19] Despite these advances, not all the increases detected in ESC MIC levels can be explained by the molecular mechanisms described so far, and poses difficulties in developing reliable laboratory methods for the detection of ESC 'resistant' gonococci.

All gonococcal isolates tested in Australia in 2009, including those with altered cephalosporin susceptibility, were susceptible to spectinomycin. A low proportion of gonococci was also found to be resistant to azithromycin in 2009. Azithromycin has been suggested as a possible component of treatment for gonorrhoea that uses dual antibiotic treatment.[20] Resistance to azithromycin, widely used as an anti-chlamydial agent in conjunction with gonococcal treatment, has been reported with increasing frequency overseas. MIC levels in azithromycin resistant gonococci have reached very high levels in Europe, but these strains have not been detected in Australia.

The emergence and spread of antimicrobial resistance in *N. gonorrhoeae* is a global public health issue, and evolving problems of emergence and spread of resistance are complex and require attention to both disease control strategies and rational use of antibiotics.[8,21,22] Critically, both disease control strategies and the understanding of the global scope of AMR are informed by surveillance programs of AMR nationally and internationally. Continuing commitment and vigilance to surveillance of AMR in *N. gonorrhoeae* means that maintenance of culture-based systems will be required while this surveillance is still based on testing of gonococcal isolates.

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