Annual reports

Surveillance of antibiotic resistance in *Neisseria gonorrhoeae* in the WHO Western Pacific and South East Asian Regions, 2009

The WHO Western Pacific and South East Asian Gonococcal Antimicrobial Surveillance Programmes

Abstract

Long-term surveillance of antimicrobial resistance in *Neisseria gonorrhoeae* has been conducted in the World Health Organization (WHO) Western Pacific Region (WPR) to optimise antibiotic treatment of gonococcal disease since 1992. From 2007, the Gonococcal Antimicrobial Surveillance Programme (GASP) has been enhanced by the inclusion of data from the South East Asian Region (SEAR) and recruitment of additional centres in the WPR. Approximately 8,704 isolates of *N. gonorrhoeae* were examined for their susceptibility to one or more antibiotics used for the treatment of gonorrhoea, incorporating External Quality Assurance controlled methods, from reporting centres in 21 countries and/or jurisdictions. A high proportion of penicillin and/or quinolone resistance was again detected amongst isolates tested in North Asia and the WHO SEAR. In contrast, from the Pacific Island states Fiji reported low penicillin and quinolone resistance, New Caledonia again reported no penicillin resistance and little quinolone resistance, Tonga reported no penicillin resistance and there was a continued absence of quinolone resistance reported in Papua New Guinea in 2009. The proportion of gonococci reported as 'decreased susceptibility' and 'resistant' to the third-generation cephalosporin antibiotic ceftriaxone varied widely but no major changes were evident in cephalosporin minimum inhibitory concentrations (MIC) patterns in 2009. Altered cephalosporin susceptibility has been associated with treatment failures following therapy with oral third-generation cephalosporins. There is a need for revision and clarification of some of the *in vitro* criteria that are currently used to categorise the clinical importance of gonococci with different ceftriaxone and oral cephalosporin MIC levels. The number of instances of spectinomycin resistance remained low. A high proportion of strains tested continued to exhibit high-level plasmid mediated resistance to tetracyclines. The continuing emergence and spread of antibiotic resistant gonococci in and from the WHO WPR and SEAR suggests that surveillance programs such as GASP be maintained and expanded. *Commun Dis Intell* 2011;35(1):2–7.

Introduction

Increasing antimicrobial resistance (AMR) in *Neisseria gonorrhoeae* has, over many years, compromised the treatment and public health management of gonococcal disease in the World Health Organization (WHO) Western Pacific (WPR) and South East Asian Regions (SEAR) where there continues to be a high incidence of this sexually transmitted disease.

The treatment of gonorrhoea by the public sector in the 'Asian' countries of the WHO WPR, and in the WHO SEAR is substantially based on the third-generation cephalosporin agents, most notably the injectable ceftriaxone, although there are a wide range of dosing regimens used.[1] The oral third-generation cephalosporin most commonly used is cefixime, but dosing regimens are more uniform.[1] These antibiotics are employed as single-dose treatments. Other injectable and oral cephalosporins are also used in some jurisdictions.[1]

There is also widespread resistance to penicillins, early generation cephalosporins and quinolones in the 'Asian' group of WPR and in SEAR countries.[2,3] In the 'Pacific Island' or 'Oceania' group of countries within the WHO WPR, the penicillin group of agents continues to be the recommended treatment in a number of settings.[2]

Other antibiotics such as spectinomycin and azithromycin are also recommended and used in some countries, although drug availability and cost limit their wider use. There are few reliable data on antibiotic usage and availability in the private sector in the WHO WPR and SEAR, but anecdotally, a wide variety of antibiotics are used, often in suboptimal doses.[1]

The WHO[4] and others[5,6] recommend that treatment options be refined by data from surveillance of AMR in *N. gonorrhoeae* and that routine use of an antibiotic for treatment be discontinued when therapeutic failure and/or AMR reaches a level of 5%. The WPR Gonococcal Antimicrobial Surveillance Programme (GASP) has documented the emergence and spread of AMR in *N. gonorrhoeae* in the

WHO WPR from 1992[2,7] to provide information for action and to optimise the antibiotic treatment for gonorrhoea. The WHO SEAR GASP has published similar data intermittently.[3] Considerable concerns have been expressed following the appearance and spread of gonococci 'non-susceptible' to the later-generation cephalosporins in the WHO WPR.[8–11] Their recognition followed documentation of treatment failures with several oral third-generation cephalosporins.[8,10,12] The gonococci involved were usually also resistant to other antibiotics, and would be classified as 'multi-drug resistant gonococci' by recently proposed criteria.[4]

This report provides an analysis of antimicrobial resistance in *N. gonorrhoeae* in the WHO WPR derived from the results of the WPR GASP surveillance for the calendar year 2009, and is augmented by equivalent data in a number of centres in the WHO SEAR. The difficulties currently experienced with reliable detection and reporting of gonococci with altered susceptibility to cephalosproins[4] are discussed.

Methods

The methods used by the WHO WPR GASP and more recently by WHO SEAR, have been published[7] and provide full details of the source of isolates, sample populations, laboratory test methods and quality assurance programs (EQA) used to generate data. These general principles were unaltered in 2009. There continues to be expansion of the panel of *N. gonorrhoeae* control strains used in WHO WPR and SEAR EQA programs. This is to monitor the impact of emerging resistance (initially the quinolones and, latterly, the third-generation cephalosporins) and address issues related to the detection of these forms of resistance.[13,14]

Results and discussion

In 2009, there were 8,704 isolates of *N. gonorrhoeae* examined for their susceptibility to one or more antibiotics used for the treatment of gonorrhoea, by EQA controlled methods. These were reported from centres in 21 countries and jurisdictions; 17 in the WHO WPR and 4 from the WHO SEAR.

There are important limitations that apply to data generated from surveys of this kind. Inevitably only low sample numbers were available in some centres. The reasons for this include the absence or abandonment of laboratory-based diagnostic culture where syndromic management is used. More recently, there has been increasing substitution of diagnostic nucleic amplification assays in place of culture based approaches. Additionally, resource restrictions limit the capacity for susceptibility testing based on minimum inhibitory concentrations (MIC) methodology, even when gonococcal isolates are available, so that disc testing procedures remain the only practical means of *in vitro* assessment of gonococcal antibiotic susceptibility in many situations.[14] Despite these limitations, in the absence of other data sources, and when conducted over extended periods under the same conditions, the annual WHO WPR, and more recently SEAR, gonococcal surveillance provides reliable trend data for the region as a whole.

The consistent results that have been obtained over time in similar countries in the WPR reinforce the significance of the findings. Since 2007, these data now include the addition of quality controlled information from the WHO SEAR. This allows inferential extrapolation of the data obtained to those countries that are unable to participate fully in each surveillance period.

Tables 1 and 2 show the patterns of resistance to the quinolone and penicillin groups of antibiotics by jurisdiction for 2009. The WHO recommendation that an antibiotic be removed from standard treatment schedules when the proportion of resistant isolates reaches 5% or more provides guidance for interpretation of these data. The previously described patterns of resistance to these groups of antibiotics across the WHO WPR and SEAR[2,7] were again evident in 2009. A high proportion of both penicillin and/or quinolone resistance was detected amongst isolates tested in most reporting centres. From the Pacific Island states, Fiji reported low penicillin and quinolone resistance, New Caledonia again reported no penicillin resistance and little quinolone resistance, Tonga reported no penicillin resistance; and there was continued absence of quinolone resistance reported in Papua New Guinea.

In 2009, quinolone resistance (QRNG) or reduced susceptibility was in excess of 90% of all *N. gonorrhoeae* isolates examined in Brunei, China, Hong Kong SAR, Korea, the Philippines and Vietnam (WHO WPR) and in Bhutan, India, Sri Lanka and Thailand (WHO SEAR) and rates between 75% and 90% of all *N. gonorrhoeae* examined in Japan, Malaysia, Mongolia and Singapore. Lower, but still substantial, proportions of QRNG were present in Australia, Cambodia and New Zealand. Penicillin resistance rates were lower than those for the quinolone antibiotics, but followed a similar pattern to previous years. Not all jurisdictions monitored penicillin resistance because treatment of gonorrhoea with this group of antibiotics has long been discontinued, and even where this surveillance was performed, it was sometimes limited to detection of beta-lactamase production.

N. gonorrhoeae in the WPR and SEAR has also been shown to have decreased susceptibility to third-generation cephalosporins for a number of

Table 1: Quinolone resistance in 8,704 strains of *Neisseria gonorrhoeae* in the World Health Organization Western Pacific Region and the South East Asia Region, 2009

Country	n	Less susceptible		Resistant		All QRNG	
		n	%	n	%	n	%
Western Pacific Region							
Australia	3,220	23	0.7	1,346	41.8	1,370	42.5
Brunei	387	134	34.6	226	58.4	360	93.0
Cambodia	6	0	0.0	4	66.7	4	66.7
China	1,026	27	2.6	999	97.4	1,026	100.0
Fiji	541	0	0.0	1	0.2	1	0.2
Hong Kong SAR	1,366	20	1.5	1,333	97.6	1,353	99.0
Japan	263	3	1.1	207	78.7	210	79.8
Korea	61	6	9.8	50	82.0	56	91.8
Malaysia	10	1	10.0	7	70.0	8	80.0
Mongolia	150	84	56.0	28	18.7	112	74.7
New Caledonia	79	0	0.0	1	1.3	1	1.3
New Zealand	234	0	0.0	82	35.0	82	35.0
Papua New Guinea	54	0	0.0	0	0.0	0	0.0
Philippines	40	0	0.0	39	97.5	39	97.5
Singapore	160	4	2.5	134	83.8	138	86.3
Vietnam	80	1	1.3	79	96.0	80	100.0
South East Asia Region							
Bhutan	181	4	2.2	172	95.0	176	97.2
India	51	2	3.9	49	96.1	51	100.0
Sri Lanka	75	0	0.0	69	92.0	69	92.0
Thailand	720	143	19.9	549	76.3	692	96.1
Total	8,704	452	5.2	5,375	61.8	5,828	67.0

QRNG Quinolone resistant *Neisseria gonorrhoeae*

Tonga Quinolones not tested.

years.[4,7–12] This altered susceptibility was accompanied by treatment failures following therapy with oral third-generation cephalosporins in a significant number of cases,[6,8,10,12] No major changes were evident in these patterns over the 12 months of surveillance reported for 2009. There are however, concerns regarding assessment of the proportion of *N. gonorrhoeae* that display altered susceptibility to the third-generation cephalosporin antibiotics in the WHO WPR and SEAR.

Surveillance of gonococcal susceptibility to 'third-generation' cephalosporins has focused on assessment of ceftriaxone susceptibility (the injectable agent) because of its wide use throughout both regions.[1] The MIC data reported here were based mostly on assessment of the *in vitro* susceptibility of gonococcal isolates to ceftriaxone. However, recent investigations have shown that the mechanisms of resistance to the third-generation cephalosporins are multiple and complex, and involve the aggregation and expression of a number of different genes within *N. gonorrhoeae*.[15–17] The effects of this polygenic involvement on *in vitro* susceptibility of the injectable agents such as ceftriaxone and on the oral cephalosporins such as cefixime and ceftibuten differ considerably, meaning that susceptibility data for ceftriaxone cannot be used to reliably predict the outcomes of treatment with the oral drugs.[4,12] Further, it would also appear that there is a need for revision and clarification of some of the *in vitro* criteria that are currently used to categorise and report on the different MIC levels that arise with both the injectable and oral cephalosporins as the various resistance mechanisms appear in *N. gonorrhoeae*.[4] This process is currently in train through WHO working groups.[4] It is also now known that other important mechanisms of gonococcal cephalosporin resistance also exist, but are yet to be fully elucidated.[16] In 2009, these limitations were again evident in reporting and in EQA data.[14]

In 2009, the revised panel of *N. gonorrhoeae* WHO control strains was further developed and distributed in the WPR and SEAR. It is anticipated that more widespread use of these controls from 2010 onwards

Table 2: Penicillin resistance in 8,703 strains of *Neisseria gonorrhoeae* in the World Health Organisation Western Pacific Region and the South East Asia Region, 2009

Country	n	PPNG		CMRP		All penicillin resistance	
		n	%	n	%	n	%
Western Pacific Region							
Australia	3,220	465	14.4	680	21.1	1,145	35.6
Brunei	384	249	64.8	27	7.0	276	71.9
Cambodia	6					6	100.0
China	1,026	431	42.0	NS	ND	NS	ND
Fiji	541	21	3.9	24	4.4	45	8.3
Hong Kong SAR	1,366	442	32.4	253	18.5	695	50.9
Japan	263	0	0.0	65	24.7	65	24.7
Korea	61	11	18.0	23	37.7	34	55.7
Malaysia	10	3	30.0	2	20.0	5	50.0
Mongolia	105	0	0.0	56	53.3	56	53.3
New Caledonia	133	0	0.0	0	0.0	0	0.0
New Zealand	234	5	2.1	56	23.9	61	26.1
Papua New Guinea	54	33	61.1	1	1.9	34	63.0
Philippines	40	33	82.5	0	0.0	33	82.5
Singapore	160	89	55.6	19	11.9	108	67.5
Tonga	4	0	0.0	0	0.0	0	0.0
Vietnam	80	26	32.5	5	6.3	31	38.8
South East Asia Region							
Bhutan	181					180	99.4
India	51	23	45.1	3	5.9	26	51.0
Sri Lanka	75	51	68.0	9	12.0	60	80.0
Thailand	709	619	87.3	67	9.4	686	96.8
Totals	8,703	2,501	28.7	1,290	14.8	3,546	40.7

PPNG Penicillinase producing Neisseria gonorrhoeae (β-lactamase positive).
CMRP Chromosomally mediated resistance to penicillin.
ND Gonococci in China were examined for penicillinase production only.
NS Not specified.

will better define 'decreased susceptibility' and 'resistance' to the different third-generation cephalosporin antibiotics.[13,14,18] This is not an easy task because of the need to define 'clinical' as opposed to *in vitro* resistance through better and more complete examination of gonococci isolated from documented treatment failures, and also by use in various circumstances of the different treatment doses, especially for ceftriaxone.[1] It is also established that elimination of *N. gonorrhoeae* from some infected sites is also more difficult, e.g. extra-genital tract infections are harder to eradicate.[19] The following data are therefore indicative of a well documented increase in the MIC values of cephalosporins in gonococci found in both regions.

Twenty-one centres examined *N. gonorrhoeae* for cephalosporin susceptibility in 2009. The proportions of gonococci with 'decreased susceptibility' or that were 'resistant' varied widely A large number of centres including Australia, Bhutan, Brunei, Fiji, Hong Kong, India, Japan, New Caledonia, New Zealand, Papua New Guinea, the Philippines, Sri Lanka, Singapore, Thailand and Vietnam reported no or very low proportions of strains with altered ceftriaxone susceptibility when tested in large numbers. Most of these centres tested isolates for susceptibility to ceftriaxone only, and it is not surprising that very few strains exhibited altered susceptibility to this antibiotic. Brunei, China, Korea and Mongolia reported gonococci with 'decreased susceptibility' or that were 'resistant' to ceftriaxone in much larger proportions. The number of strains tested in the countries and jurisdictions mentioned above are as shown in Tables 1 and 2.

Very few isolates were tested separately for their susceptibility to the oral cephalosporin agents. It is

thus not possible at present to interpret the *in vitro* data in terms of likely clinical outcome other than in general terms.

Spectinomycin resistance has been only infrequently found in earlier reports in this series. A form of high-level resistance due to a single-step ribosomal mutation has been described,[20] and there are other reports of unexplained low-level resistance or decreased susceptibility.

As in previous years, only a few sporadic cases of resistance to spectinomycin in a limited number of settings were reported from the 17 centres testing this antibiotic in 2009. Low numbers of isolates (10 or less) with *in vitro* resistance or decreased susceptibility to spectinomycin were found in Bhutan, Brunei, China and Mongolia. The number of strains tested in the countries and jurisdictions mentioned above are shown in Tables 1 and 2. The availability of spectinomycin as a treatment option has been significantly reduced following a lack of reliable supplies of the drug. However, spectinomycin is still used as a first line and second line treatment in a number of WPR jurisdictions. Korea is one such country, and an outbreak of spectinomycin resistant *N. gonorrhoeae* was reported there many years ago. Notably, no spectinomycin resistance has been detected there for many years and overall resistance has remained low to this antibiotic in both regions.

Tetracyclines are not a recommended treatment for gonorrhoea in the WHO WPR or SEAR, but historical data on the spread of high-level plasmid mediated tetracycline resistant *N. gonorrhoeae* (TRNG), continue to be monitored in some countries. Eighteen centres tested gonococci for TRNG in 2009, and up to 70% of gonococci exhibited this form of resistance. The proportion of TRNG has been high in some parts of the WPR for many years, and between 35% and 70% of all strains in Brunei, China, Hong Kong, Malaysia, Singapore and Vietnam were TRNG; with proportions between 10% and 34% in Australia, India, Korea and New Zealand, Papua New Guinea, and the Philippines. The number of strains tested in the countries and jurisdictions mentioned above are shown in Tables 1 and 2.

The need for more and better quality surveillance of gonococcal antibiotic resistance in the WHO WPR and SEAR is evident.[4–6] Increasing surveillance of resistance to include other antibiotics is imperative. As an example, azithromycin is used either as a primary treatment for gonorrhoea or as adjunctive treatment for other pathogens and resistance to this antibiotic is known to occur in the WHO WPR. However, substantive surveillance data are not yet available. There are recent reports elsewhere of high-level azithromycin resistance following widespread use of this antibiotic.[21]

Given the past history of the emergence and spread of antibiotic resistant gonococci from the WHO WPR and SEAR to other parts of the world,[4] there is a high likelihood that, unless better disease control becomes a reality, new forms of resistance will continue to appear and spread well beyond these regions. A suggested approach to the closely related issues of gonococcal disease control and AMR control in *N. gonorrhoeae* has recently been published from WHO sources.[4] Implicit in these recommendations is the availability of reliable and verifiable antibiotic resistance surveillance data.

Acknowledgements

Vale Professor John W Tapsall AM: As this report goes to press we remember our colleague and mentor Professor John Tapsall AM (1945–2010) who contributed greatly to the establishment and maintenance of surveillance in these WHO regions to aid in the control of this disease.

This project was supported by means of a Technical Services Agreement between the WHO Collaborating Centre for STD, Sydney; the WHO Western Pacific Regional Office, Manila; the WHO South East Asia Regional Office, New Delhi; and WHO Headquarters, Geneva.

Members of the WHO Western Pacific and South East Asian Gonococcal Antimicrobial Surveillance Programmes for 2009 are: JW Tapsall, EA Limnios and MM Lahra, Australia; D Dorji, Bhutan; Hjh Mahani Hj Abu Bakar, Brunei Darussalam; B Guillard and Hem Sopheak, Cambodia; Yin Yue Ping, China; EM Buadromo, P Kumar and S Singh, Fiji; J Lo, Hong Kong; M Bala, India; T Deguchi, M Tanaka and Y Watanabe, Japan; K Lee and Y Chong, South Korea; S Noikaseumsy and T Phouthavane, Lao PDR; I-Ching Sam, Malaysia; O Tundev, Mongolia; KM Lwin and PH Eh, Myanmar; C Goarant and R Goursaud, New Caledonia; T Bathgate and M Brokenshire, New Zealand; P Toliman, Mition Yoannes, L Latorre and E Velemu, Papua New Guinea; C Carlos, M Lagrada, S Leano and EO Telan, Philippines; SS Goh, ST Koh, C Ngan and AL Tan, Singapore; S Mananwatte, Sri Lanka; N Piyanoot, S Lokpichat and P Sirivongranson, Thailand; M Fakahau and H Sitanilei, Tonga; Le Van Hung, Vietnam.

Author details

Correspondence: Dr M Lahra, WHO Collaborating Centre for STD, Department of Microbiology, SEALS The Prince of Wales Hospital, RANDWICK NSW 2031. Facsimile: +61 2 9382 9310. Email monica.lahra@sesiahs.health.nsw.gov.au

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