Surveillance of antibiotic resistance in *Neisseria gonorrhoeae* in the WHO Western Pacific and South East Asian Regions, 2010

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Abstract

The World Health Organization (WHO) Gonococcal Antimicrobial Surveillance Programme (GASP) has conducted continuous surveillance of antimicrobial resistance in *Neisseria gonorrhoeae* in the WHO Western Pacific Region (WPR) to optimise antibiotic treatment and control of gonococcal disease since 1992. From 2007, this has been enhanced by the inclusion of data from the WHO South East Asian Region (SEAR). Over time, there has been recruitment of additional centres in both regions. This report provides an analysis of antimicrobial resistance in *N. gonorrhoeae* in the WHO WPR and SEAR derived from results of the 2010 GASP surveillance. In 2010 there were 9,744 *N. gonorrhoeae* isolates examined for their susceptibility to one or more of the antibiotics used for the treatment of gonorrhoea, incorporating External Quality Assurance controlled methods, from reporting centres in 19 countries and/or jurisdictions. A high proportion of penicillin and quinolone resistance was again detected amongst isolates tested in the 'Asian' countries of WHO WPR and SEAR. In contrast, lower levels of penicillin and quinolone resistance were reported from the Pacific Islands of Fiji and New Caledonia. The proportion of gonococci reported as having 'decreased susceptibility' to the third-generation cephalosporin antibiotic ceftriaxone varied widely, ranging from 1.3% to 55.8%. There is a continued 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, and to relate these to treatment outcome. Azithromycin resistance was very low in most countries reporting, except in Mongolia where it was 34%. 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 underlines the importance of the maintenance and expansion of surveillance programs such as GASP, which are essential for disease control. *Commun Dis Intell* 2012;36(1):95–100.

Keywords: annual reports; antimicrobial resistance; *Neisseria gonorrhoeae*, World Health Organization, Western Pacific Region, South East Asia Region

Introduction

The progressive development of antimicrobial resistance (AMR) in *Neisseria gonorrhoeae* within and across antibiotic classes has, over many years, compromised the treatment and public health management of gonococcal disease in the World Health Organization (WHO) Western Pacific Region (WPR) and South East Asian Region (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 single-dose treatment regimens of the third-generation cephalosporin agents, predominantly the injectable ceftriaxone, however there are a wide range of dosing regimens used. The oral third-generation cephalosporin most commonly used is cefixime, but dosing regimens are more uniform. Other injectable and oral cephalosporins are also used in some jurisdictions.[1]

Resistance to penicillin, early generation cephalosporin and quinolone antibiotics in the 'Asian' group of WPR and in SEAR countries is widespread.[2,3] However, in the 'Pacific Island' or 'Oceania' group of countries within the WHO WPR, there are a small number of settings where antibiotic resistance continues to be low and the penicillin group of agents continues to be the recommended treatment.[2]

Other antibiotics such as spectinomycin and azithromycin are recommended and used in some countries, although availability and cost limits 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]

It is recommended by the WHO[4] and others[5,6] that therapeutic regimens be supported by data from

surveillance of AMR in *N. gonorrhoeae,* and further that routine use of an antibiotic for treatment be discontinued when treatment failure occurs 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]

Significant concerns have been expressed following the appearance and spread of gonococci with 'decreased-susceptibility' to the later-generation cephalosporins in the WHO WPR.[8–11] This was followed by reports of treatment failures with several oral third-generation cephalosporins.[8,10,12] The gonococci involved 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 and SEAR derived from the results of the GASP surveillance for the calendar year 2010. The difficulties currently experienced with reliable detection and reporting of gonococci with altered susceptibility to cephalosproins[4] and strategies implemented to address this in these settings are discussed.

Methods

The methods used by the WHO WPR GASP and more recently by WHO SEAR, have been publishedand provide full details of the source of isolates, sample populations, laboratory test methods and quality assurance programs (EQA) used to generate these data.[7] These general principles were unaltered in 2010. The expansion of the reference panel of *N. gonorrhoeae* control strains used in WHO WPR and SEAR EQA programs continues.[13] This is to monitor the impact of emerging resistance (initially with the quinolones and, latterly, the third-generation cephalosporins) and address issues related to the detection of these forms of resistance.[13,14]

Results

In 2010, there were 9,744 *N. gonorrhoeae* examined for their susceptibility to one or more antibiotics used for the treatment of gonorrhoea using EQA controlled methods. These were reported from 21 centres in 19 countries and jurisdictions; 15 in the WHO WPR and 4 from the WHO SEAR. Other centres were unable to supply data for 2010 but maintained contact with the program through participation in the EQA program. In 2010, data were not available from Laos, Papua New Guinea, Tonga and Myanmar.

Quinolone resistant *Neisseria gonorrhoeae*

In 2010, quinolone resistance (QRNG)or reduced susceptibility was in excess of 90% of all *N. gonorrhoeae* examined in Brunei, Cambodia, China, Hong Kong SAR, Korea, the Philippines and Vietnam (WHO WPR) and in Bhutan, India, Sri Lanka and Thailand (WHO SEAR). Rates between 70% and 90% were reported from Japan, Malaysia and Singapore. Lower, but still substantial, proportions of QRNG were present in Australia, Mongolia, and New Zealand. Quinolone resistance remained below 1% in Fiji and New Caledonia (Table 1).

Penicillin resistance

Penicillin resistance rates were lower than those for the quinolone antibiotics, and in a similar pattern to that of previous years. Not all jurisdictions monitored penicillin resistance because treatment of gonorrhoea with this group of antibiotics has long been discontinued. Even where this surveillance was performed, it was sometimes limited to detection of beta-lactamase production (Table 2).

Decreased susceptibility and resistance to third-generation cephalosporins

Regionally, 9,282 isolates of *N. gonorrhoeae* were examined for cephalosporin susceptibility in 2010, and WHO EQA validated data were available for 7,024 of these isolates at the time of this report. Most of these centres tested isolates for susceptibility to ceftriaxone only and the proportion of gonococci reported with 'decreased susceptibility' to ceftriaxone varied widely. Singapore reported 1.3% and Australia reported 4.8% of isolates with decreased susceptibility to ceftriaxone; whereas China (55.8%), Korea (29.3%), Japan (20.3%), Hong Kong SAR (23.3%) and India (10.8%) reported gonococci with decreased susceptibility to ceftriaxone in much larger proportions. There were no EQA validated data reporting resistance in either region.

Spectinomycin resistance

In 2010, as in previous years, there were only a few sporadic cases of resistance to spectinomycin from a limited number of settings reported from the 15 centres testing 9,315 isolates for resistance to this antibiotic. There were low numbers of isolates (12 or less) with *in vitro* resistance or decreased susceptibility to spectinomycin reported from Mongolia; China and Bhutan, similar to the GASP data for 2009.

Tetracycline resistant *Neisseria gonorrhoeae*

Tetracyclines are not a recommended treatment for gonorrhoea in the WHO WPR or SEAR, but historical data on the spread of high-level plas-

mid mediated tetracycline resistant *N. gonorrhoea* (TRNG) continues to be monitored in some countries. Fifteen centres tested gonococci for TRNG in 2010, 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, with Brunei reporting TRNG in the percentage range of 71%–100%. Mongolia, China, Hong Kong SAR, Singapore and Vietnam reported proportions of TRNG in the range 35%–70%. Proportions in the range 10%–34% were reported from Australia, India, Korea and New Zealand, Papua New Guinea, Sri Lanka and the Philippines. The number of strains tested in the countries and jurisdictions mentioned above are shown in Tables 1 and 2.

Azithromycin resistance

Azithromycin AMR data are reported for the first time in this GASP report. This antibiotic can be 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. In 2010, 6 countries (four in the WPR and two in SEAR) tested 5,295 *N. gonorrhoea* isolates for susceptibility. There was no resistance (0%) reported from Cambodia; Vietnam and India and very low rates (< 1%) from Australia. In contrast 34% resistance was reported from Mongolia.

Discussion

This paper reports the findings of the WHO Gonococcal Antimicrobial Surveillance Programme for the Western Pacific and South East Asian Regions for 2010. In this calendar year there were 9,744 *N. gonorrhoeae* isolates examined for their susceptibility to one or more of the antibiotics used for the treatment of gonorrhoea, incorporating external quality assurance controlled methods, from reporting centres in 19 countries and/or jurisdictions. Important limitations apply to data generated from surveys of this kind. Inevitably, only low sample numbers were available in some centres for reasons including the absence, abandonment or inability to perform laboratory-based diagnostic culture and where syndromic management is used. Further, there is increasing substitution of diagnostic nucleic amplification assays replacing culture. Resource restrictions in many settings in the region limit the capacity for the 'gold standard' of susceptibility testing based on minimum inhibitory concentra-

Table 1: Quinolone resistant *Neisseria gonorrhoeae* (QRNG) in the World Health Organization Western Pacific Region and the South East Asia Region, 2009 (n = 9,744 strains)

		Less susceptible		Resistant		All QRNG	
Country	n	n	%	n	%	n	%
Western Pacific Region							
Australia	3,997	43	1.1	1,342	33.6	1,385	34.7
Brunei	396	127	32.1	242	61.1	369	93.2
Cambodia	76	2	2.6	73	96.1	75	98.7
China	1,398	38	2.7	1,250	89.4	1,288	92.1
Fiji	336	0	0.0	2	0.6	2	0.6
Hong Kong SAR	947	18	1.9	916	96.7	934	98.6
Japan	403	3	0.7	292	72.5	295	73.2
Korea	82	2	2.4	76	92.7	78	95.1
Malaysia	17	3	17.6	12	70.6	15	88.2
Mongolia	690	7	1.0	231	33.5	238	34.5
New Caledonia	197	0	0.0	1	0.5	1	0.5
New Zealand	72	0	0.0	21	29.2	21	29.2
Philippines	59	0	0.0	57	96.6	57	96.6
Singapore	160	2	1.3	117	73.1	119	74.4
Vietnam	86	3	3.5	83	96.5	86	100.0
South East Asia Region							
Bhutan	179	0	0.0	172	96.1	172	96.1
India	37	1	2.7	36	97.3	37	100.0
Sri Lanka	72	0	0.0	65	90.3	65	90.3
Thailand	540	111	20.6	416	77.0	527	97.6
Total	9,744	360	3.7	5,404	55.5	5,764	59.2

Table 2: Penicillin resistance in *Neisseria gonorrhoeae* in the World Health Organization Western Pacific Region and the South East Asia Region, 2010 (n = 9,702 strains)

Country	n	PPNG		CMRP		All penicillin resistance	
		n	%	n	%	n	%
Western Pacific Region							
Australia	3,997	462	11.6	699	17.5	1,161	29.0
Brunei	397	210	52.9	71	17.9	281	70.8
Cambodia	76	–	–	–	–	59	77.6
China	1,398	534	38.2	NS	–	NS	–
Fiji	336	16	4.8	12	3.6	28	8.3
Hong Kong SAR	947	304	32.1	182	19.2	486	51.3
Japan	403	1	0.2	158	39.2	159	39.5
Korea	82	14	17.1	29	35.4	43	52.4
Malaysia	17	1	5.9	3	17.6	4	23.5
Mongolia	605	–	–	–	–	361	59.7
New Caledonia	197	1	0.5	0	0.0	1	0.5
New Zealand	72	0	0.0	13	18.1	13	18.1
Philippines	59	57	96.6	0	0.0	57	96.6
Singapore	160	57	35.6	22	13.8	79	49.4
Vietnam	86	27	31.4	15	17.4	42	48.8
South East Asia Region							
Bhutan	179	–	–	–	–	178	99.4
India	37	14	37.8	4	10.8	18	48.6
Sri Lanka	43	28	65.1	4	9.3	32	74.4
Thailand	611	503	82.3	88	14.4	591	96.7
Totals	9,702	2,229	23.0	1,300	13.4	3,593	37.0

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

tions (MIC) methodology, even when gonococcal isolates are available, so that disc testing procedures with methods incorporating standardised control strains remain the only practical means of *in vitro* assessment of gonococcal antibiotic susceptibility in many situations.[14] Despite this, in the absence of other surveillance data sources, the WHO WPR GASP has been conducted for more than 20 years, under the same conditions and the annual WHO WPR gonococcal surveillance reports continue to provide reliable trend data for the region as a whole. Since 2007, the addition of quality controlled information has been available from the WHO SEAR. The consistent results that have been obtained over time in similar countries in the WPR reinforce the significance of the findings. This allows inferential extrapolation of the data obtained to those countries that are unable to participate fully in each surveillance period.

The patterns of resistance to the quinolone and penicillin groups of antibiotics by jurisdiction for the year 2010 are shown in Tables 1 and 2. The WHO recommends that use of an antibiotic for routine treatment be removed from standard treatment schedules when therapeutic failure reaches a level of 5%. The previously described patterns of resistance to these groups of antibiotics across the WHO WPR and SEAR[2,7] were again evident in 2010. Whilst a high proportion of both penicillin and quinolone resistance was detected amongst isolates tested in most reporting centres, from the Pacific Island states, New Caledonia continues to report low levels of both penicillin and quinolone resistance and Fiji low levels of quinolone resistance and low but increased penicillin resistance.

N. gonorrhoeae in the WPR and SEAR with decreased susceptibility to third-generation cephalosporins have been reported for a number of years.[4,7–12] This has been accompanied by reports of treatment failure with oral third-generation cephalosporins in a significant number of cases.[6,8,10,12] Regionally, surveillance of gonococcal AMR to the third-gener-

ation cephalosporins (ESCs) focuses on ceftriaxone because of its widespread use,[1] and data reported in 2010 are based primarily on testing of the *in vitro* susceptibility of gonococcal isolates to ceftriaxone. However, there are ongoing concerns regarding assessment of *N. gonorrhoeae* with altered susceptibility to the ESCs. The mechanisms of resistance in *N. gonorrhoeae* to the ESCs are multiple and complex, involving the aggregation and expression of a number of different genes within *N. gonorrhoeae,*[15–17] and further, other important mechanisms of gonococcal cephalosporin resistance exist, but are yet to be fully elucidated.[16] The effects of the 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, indicating that susceptibility data for ceftriaxone cannot reliably predict the outcomes of treatment with oral cephalosporins.[4,12] To address this there is ongoing 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 through WHO working groups.[4] In 2010, with the use of the WHO reference panel[13] in particular 'WHO K' the ceftriaxone control for decreased susceptibility, laboratories have the measure to correctly interpret MIC results of test isolates, however, some limitations continue to be evident in reporting AMR and in EQA performance data.[14]

In 2010, the revised panel of *N. gonorrhoeae* WHO control strains was further developed and distributed in the WPR and SEAR and widespread incorporation of these has better defined '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 sites is also more difficult, e.g. extra-genital tract infections are harder to eradicate.[19] The 2010 data are indicative of a well documented increase in the MIC values of cephalosporins in gonococci found in both regions[15–17] and are alarming in terms of the proportion of isolates with decreased susceptibility and the absence of alternative therapies on the horizon. 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 reported in GASP from the WPR and latterly the SEAR. 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. The availability of spectinomycin as a treatment option has been significantly reduced following a lack of reliable supplies of the drug. Spectinomycin resistance has not been detected in WHO WPR or SEAR for many years and overall resistance to this antibiotic remains low in both regions.

In the 6 countries reporting testing for azithromycin AMR there was low or no resistance reported from Cambodia; Vietnam, India and Australia, and 34% resistance was reported from Mongolia. There are recent reports elsewhere of high-level azithromycin resistance following widespread use of this antibiotic [21] and it is now recommended as part of a dual therapy strategy in the United Kingdom National Guideline for treatment of gonorrhoea in adults.[22] Azithromycin has not been a part of the WHO GASP core group of antibiotics tested in the past, however it is evident that its inclusion is necessary and AMR data will be reported where available in the GASP.

Increased and improved surveillance of gonococcal antibiotic resistance in the WHO WPR and SEAR is urgently required and this has long been evident.[4–6] Further to this, expanding surveillance of resistance to include other antibiotics is imperative as therapeutic options diminish, and enhancement of surveillance should also include test of cure studies, which are crucial to determine both the clinical correlates of surveillance data, and for disease control. The emergence and spread of antibiotic resistant gonococci from the WHO WPR and SEAR to other parts of the world has been documented,[4] and 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.

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