Annual reports

Surveillance of antibiotic resistance in *Neisseria gonorrhoeae* in the WHO Western Pacific and South East Asian Regions, 2007–2008

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. In 2007 and 2008, this Gonococcal Antimicrobial Surveillance Programme (GASP) was enhanced by the inclusion of data from the South East Asian Region (SEAR) and recruitment of additional centres within the WPR. Approximately 17,450 *N. gonorrhoeae* were examined for their susceptibility to one or more antibiotics used for the treatment of gonorrhoea by external quality controlled methods in 24 reporting centres in 20 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, but much lower rates of penicillin resistance and little quinolone resistance was present in most of the Pacific Island countries. The proportion of gonococci reported as 'resistant', 'less susceptible' or 'non-susceptible' gonococci to the third-generation cephalosporin antibiotic ceftriaxone lay in a wide range, but no major changes were evident in cephalosporin minimal inhibitory concentration (MIC) patterns in 2007–2008. Altered cephalosporin susceptibility was 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 a form of plasmid mediated high level resistance to tetracyclines. The continuing emergence and spread of antibiotic resistant gonococci in and from the WHO WPR and SEAR supports the need for gonococcal antimicrobial resistance surveillance programs such as GASP to be maintained and potentially expanded. *Commun Dis Intell* 2010;34:1–7.

Keywords: annual reports; antimicrobial resistance; *Neisseria gonorrhoeae*

Introduction

The World Health Organization (WHO) Western Pacific (WPR) and South East Asian Regions (SEAR) have a continuing high incidence of gonorrhoea, but treatment and public health management of gonococcal disease in both regions have been severely compromised over many years by increasing antimicrobial resistance (AMR) in *Neisseria gonorrhoeae*. Currently, treatment of gonorrhoea in the public sector of 'Asian' countries in the WHO WPR and in the WHO SEAR is substantially based on the use of 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 remains 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 use of an antibiotic for routine 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 since 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, including penicillins and quinolones 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 years 2007 and 2008, 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 cephalosporin 'non-susceptible' gonococci[4] are discussed.

Methods

The methods used by the WHO WPR GASP have been published[7] and provide full details of the source of isolates, sample populations, laboratory test methods and quality assurance programs (EQAS) used to generate data. These general principles were unaltered in 2007–2008 and were also applied to centres in the WHO SEAR. However, there has been a continuing expansion of the *N. gonorrhoeae* comprising the panel strains used in WHO WPR and SEAR EQAS programmes so as to reflect the impact of emerging resistance initially to the quinolones and, latterly, the third-generation cephalosporins and issues related to the detection of these forms of resistance.[13,14]

Results and discussion

A total of 17,458 *N. gonorrhoeae* isolates were examined for their susceptibility to one or more antibiotics used for the treatment of gonorrhoea by EQAS controlled methods in the 2 years 2007–2008 in 24 reporting centres in 20 countries and jurisdictions: 16 in the WHO WPR and four in SEAR countries. There are important limitations that apply to data generated from surveys of this kind. Inevitably, low sample numbers only were available in some centres. This is for several reasons, including abandonment of laboratory-based diagnostic culture facilities where syndromic management is used and, more recently, substitution of diagnostic nucleic amplification assays for culture based approaches. Additionally, resource limitations restrict the capacity for susceptibility testing based on minimal inhibitory concentration (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 surveillance is conducted over extended periods under the same conditions, this series has provided reliable trend data for the WHO WPR as a whole.

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

Tables 1–4 show the patterns of resistance to the quinolone and penicillin groups of antibiotics by jurisdiction for each year of the surveillance period. The WHO recommendation that an antibiotic should be removed from standard treatment schedules when the proportion of resistant isolates reaches 5% or more provides guidance for the interpretation of these data. The previously described patterns of resistance to these groups of antibiotics across the WHO WPR[2,7] were again evident in 2007–2008. A high proportion of both penicillin and/or quinolone resistance was detected amongst isolates tested in North Asia and the WHO SEAR, but much lower rates of penicillin resistance and little quinolone resistance was present in most of the Pacific Island countries. In 2007, quinolone resistance or reduced susceptibility was in excess of 90% of all *N. gonorrhoeae* isolates examined in China, the Hong Kong SAR, Mongolia, India, Thailand and Sri Lanka and between 75% and 90% of all isolates in Brunei, Japan, Korea, Malaysia, Singapore and Vietnam. Similarly, high proportions of quinolone resistant gonococci (QRNG) were found in these centres and also in Myanmar in 2008. Lower, but still substantial, proportions of QRNG were present in Australia, the Lao PDR, New Zealand and the Philippines in both years. Penicillin resistance rates were lower than those for the quinolone antibiotics, but followed a similar pattern in WPR and SEAR centres in both 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 have also been shown to have decreased susceptibility to third-generation cephalosporins for a number of

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 2 years of surveillance reported here. There are however concerns in regard to assessments 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 emphasised the assessment of ceftriaxone susceptibility because of its wide use throughout both regions[1] so that the MIC data reported here were based mostly on assessment of the *in vitro* susceptibility of gonococcal isolates to the injectable agent ceftriaxone. 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 predict reliably 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 aggregate over time 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 2007 and 2008, these limitations were evident in reporting and in EQAS data.[14] In 2009, a revised panel of 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 will better define 'decreased susceptibility', 'non-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 improved and more complete examination of gonococci isolated from documented treatment failures. Additionally, different jurisdictions may employ different treatment doses, especially for ceftriaxone[1]

Table 1: Quinolone resistance in 8,376 strains of *Neisseria gonorrhoeae* in the World Health Organization Western Pacific Region and the South East Asia Region, 2007

Country	n	Less susceptible		Resistant		All QRNG	
		n	%	n	%	n	%
Western Pacific Region *(n = 7,507)*							
Australia	3,042	37	1.2	1,456	47.9	1,493	49.1
Brunei	208	50	24.0	120	57.7	170	81.7
China	1,163	41	3.5	1,108	95.3	1,149	98.8
Fiji	320	0	0.0	3	0.9	3	0.9
Hong Kong SAR	1,478	15	1.0	1,437	97.2	1,452	98.2
Japan	329	16	4.9	241	73.3	257	78.1
Korea	56	9	16.1	37	66.1	46	82.1
Lao PDR	9	NS	NS	3	33.0	3	33.0
Malaysia	41	5	12.2	29	70.7	34	82.9
Mongolia	10	4	40.0	6	60.0	10	100.0
New Caledonia	108	0	0.0	0	0.0	0	0.0
New Zealand	301	1	0.3	48	15.9	49	16.3
Papua New Guinea	54	0	0.0	0	0.0	0	0.0
Philippines	99	1	1.0	71	71.7	72	72.7
Singapore	160	12	7.5	122	76.3	134	83.8
Vietnam	129	45	34.9	70	54.3	115	89.1
South East Asian Region *(n = 869)*							
India	36	8	22.2	28	77.8	36	100.0
Sri Lanka	115	12	10.4	94	81.7	106	92.2
Thailand	718	217	30.2	480	66.9	697	97.1

NS Not specified

Table 2: Quinolone resistance in strains of *Neisseria gonorrhoeae* isolated in the World Health Organization Western Pacific Region and the South East Asia Region, 2008

Country	n	Less susceptible		Resistant		All QRNG	
		n	%	n	%	n	%
Western Pacific Region							
Australia	3,110	34	1.1	1,651	53.1	1,685	54.2
Brunei	353	92	26.1	168	47.6	260	73.7
China	1,403	53	3.8	1,348	96.1	1,401	99.9
Hong Kong SAR	1,393	12	0.9	1,362	97.8	1,374	98.6
Japan	328	14	4.3	240	73.2	254	77.4
Korea	141	29	20.6	106	75.2	135	95.7
Lao PDR	9	NS	NS	1	11.0	1	11.0
Malaysia	43	6	14.0	29	67.4	35	81.4
Mongolia	91	35	38.5	34	37.4	69	75.8
New Caledonia	152	2	1.3	3	2.0	5	3.3
New Zealand	258	2	0.8	53	20.5	55	21.3
Papua New Guinea	32	0	0.0	0	0.0	0	0.0
Philippines	84	4	4.8	68	81.0	72	85.7
Singapore	160	10	6.3	119	74.4	129	80.6
Vietnam	153	5	3.3	147	96.0	152	99.3
South East Asian Region							
India	60	10	16.7	50	83.3	60	100.0
Myanmar	12	4	33.3	6	50.0	10	83.3
Sri Lanka	34	0	0.0	26	76.5	26	76.5
Thailand	754	162	21.5	570	75.6	732	97.1

NS Not specified

that may alter MIC/outcome correlates. It is also established that elimination of *N. gonorrhoeae* from some infected sites is also more difficult, e.g. extragenital tract infections are harder to eradicate.[19] The following data are therefore indicative of a well documented increase in the MICs of cephalosporins in gonococci found in both regions. Sixteen centres examined *N. gonorrhoeae* for cephalosporin susceptibility in 2007 and 15 in 2008. The proportions of 'resistant', 'less susceptible' or 'non-susceptible' gonococci lay over a wide range in both years. A large number of centres including Australia, Fiji, India, Japan, Hong Kong, Korea, Laos, Malaysia, New Zealand, Papua New Guinea, the Philippines, Singapore, Thailand, Tonga 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, Myanmar and Mongolia all reported ceftriaxone 'resistant' or 'less susceptible' gonococci in much larger proportions. The number of strains tested in the countries and jurisdictions mentioned above approximates those shown in Tables 1–4. 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 other reports of unexplained low level resistance or decreased susceptibility also occur. Fourteen centres examined gonococci for spectinomycin susceptibility in each year. Only a few sporadic cases of resistance to spectinomycin were found and in a limited number of settings in 2007–2008. Low numbers of isolates (10 or less) with *in vitro* resistance or decreased susceptibility to spectinomycin were found in Brunei, China, Japan, Laos, New Caledonia, Papua New Guinea and Thailand. The number of strains tested in the countries and jurisdictions mentioned above approximates those shown in Tables 1–4. The availability of spectinomycin as a treatment option has been significantly reduced following 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

Table 3: Penicillin resistance in strains of *Neisseria gonorrhoeae* isolated in the World Health Organization Western Pacific Region and the South East Asia Region, 2007

Country	n	PPNG		CMRP		All Pen R	
		n	%	n	%	n	%
Western Pacific Region							
Australia	3,042	369	12.1	796	26.2	1,165	38.3
Brunei	308	119	51.3	79	25.6	198	64.3
China	1,163	435	37.4	NS	ND	NS	NS
Fiji	345	22	6.4	12	3.4	34	9.8
Hong Kong SAR	1,478	498	33.7	384	26.0	882	59.7
Japan	329	4	1.2	53	16.1	57	17.3
Korea	56	7	12.5	24	42.9	31	55.4
Lao PDR	9	NS	NS	NS	NS	7*	78.0
Malaysia	41	11	26.8	5	12.2	25	61.0
Mongolia	10	0	0.0	7	70.0	7	70.0
New Caledonia	108	0	0.0	0	0.0	0	0.0
New Zealand	301	5	1.7	60	19.9	65	21.6
Papua New Guinea	54	40	74.1	0	0.0	40	74.1
Philippines	99	89	89.9	0	0.0	89	89.9
Singapore	160	83	51.9	7	4.4	90	56.3
Tonga	55	NS	NS	NS	NS	9*	16.4
Vietnam	129	48	37.2	0	0.0	48	37.2
South East Asian Region							
India	36	13	36.1	4	11.1	17	47.2
Sri Lanka	39	24	61.5	2	5.1	26	66.7
Thailand†	815	701	86.0	16/22	72.7	NS	NS

ND Gonococci in China were examined for penicillinase production only.

NS Not specified

* Laos, Tonga – mechanism of penicillin resistance not specified.

† Thailand, a subset of 22 non-PPNG strains were tested for chromosomal resistance.

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 1 form of tetracycline resistance, namely a high level plasmid mediated type (TRNG), continues to be monitored in some countries. Eleven centres tested gonococci for this form of resistance in 2007 and 12 in 2008. In 2007 and 2008, up to 50% of gonococci examined 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 55% of all strains in China, Hong Kong, Malaysia, the Philippines, Papua New Guinea, Singapore, Sri Lanka and Vietnam were TRNG, with proportions between 10% and 34% in Australia, India, Korea and New Zealand. The number of strains tested in the countries and jurisdictions mentioned above approximates those shown in Tables 1–4.

The complexities associated with surveillance in the WHO WPR and SEAR GASP have increased as the need for more and better quality surveillance of gonococcal antibiotic resistance has become more obvious.[4–6] Resistance to other antibiotics, such as azithromycin, that are being used either as a primary treatment for gonorrhoea or as adjunctive treatment for other pathogens, is known to occur in the WHO WPR, but substantive data are not yet available. Of concern are recent reports elsewhere of high level azithromycin resistance following widespread use of this antibiotic.[21]

Given the past history of emergence and spread of antibiotic resistant gonococci identified in the WHO WPR and SEAR to other parts of the world,[4] there is a high likelihood that, unless better disease

Table 4: Penicillin resistance in strains of *Neisseria gonorrhoeae* isolated in the World Health Organization Western Pacific Region and the South East Asia Region, 2008

Country	n	PPNG		CMRP		All Pen R	
		n	%	n	%	n	%
Western Pacific Region							
Australia	3,110	373	12.0	994	32.0	1,367	44.0
Brunei	351	201	70.5	44	12.5	245	69.8
China	1,403	543	38.7	ND	NS	NS	NS
Fiji	320	20	6.3	11	3.4	31	9.7
Hong Kong SAR	1,393	434	31.2	169	12.1	603	43.3
Japan	328	2	0.6	88	26.8	90	27.4
Korea	141	18	12.8	77	54.6	95	67.4
Lao PDR	9	NS	NS	NS	NS	7*	78.0
Malaysia	43	23	53.5	0	0.0	23	53.5
Mongolia	91	NS	NS	3	3.3	3	3.3
New Caledonia	152	0	0.0	2	1.3	2	1.3
New Zealand	258	6	2.3	57	22.1	63	24.4
Papua New Guinea	32	20	62.5	2	6.3	22	68.8
Philippines	84	76	90.5	0	0.0	76	90.5
Singapore	160	90	56.3	12	7.5	102	63.8
Tonga	14	1	7.1	0	0.0	1	7.1
Vietnam	153	40	26.1	9	5.9	49	32.0
South East Asian Region							
India	60	20	33.3	5	8.3	25	41.7
Myanmar	12	2	16.7	8	66.7	10	83.3
Sri Lanka	34	18	52.9	1	2.9	19	55.9
Thailand†	733	592	80.8	45/53	84.9	NS	NS

ND Gonococci in China were examined for penicillinase production only.

NS Not specified

* Laos – mechanism of penicillin resistance not specified.

† Thailand, a subset of 53 non-PPNG strains were tested for chromosomal resistance.

control becomes a reality, new forms of resistance will continue to appear and spread. 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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