Surveillance of antibiotic resistance in *Neisseria gonorrhoeae* in the WHO Western Pacific Region, 2006

The WHO Western Pacific Gonococcal Antimicrobial Surveillance Programme

Abstract

The World Health Organization Western Pacific Region Gonococcal Antimicrobial Surveillance Programme (WHO WPR GASP) examined approximately 8,400 isolates of *Neisseria gonorrhoeae* from 16 countries for resistance to relevant antibiotics in 2006. Antimicrobial resistance was at record levels in the region and poses major problems for the management of this important disease. High rates of resistance to penicillins and quinolones persisted. Gonococci 'non-susceptible' to third generation cephalosporins were found in several centres. There were infrequent instances of spectinomycin resistance. *Commun Dis Intell* 2008;32:48–51.

Keywords: disease surveillance, *Neisseria gonorrhoeae*, Western Pacific Region

Introduction

The impact of increasing antimicrobial resistance (AMR) in *Neisseria gonorrhoeae* (GC), in terms of rendering treatment for gonorrhoea ineffective for infected individuals and compromising wider disease control efforts for gonococcal disease, is all-too familiar in the World Health Organization (WHO) Western Pacific Region (WPR). This undesirable outcome is increasingly evident in many parts of the world where the progressive loss of therapeutic effectiveness of the penicillins, tetracyclines, macrolides (including azithromycin), spectinomycin and, most recently, quinolone antibiotics is well documented over many years.[1] The WHO recommends that use of an antibiotic for routine treatment be discontinued when therapeutic failure reaches a level of 5%.[2] Currently in the WHO WPR, rates of gonococcal resistance to some of the above antibiotics are well in excess of 50%. The WPR Gonococcal Antimicrobial Surveillance Programme (WPR GASP) has documented the emergence and spread of this resistance in gonococci at a regional level from 1992 onwards[3,4] to provide information for action and to optimise the antibiotic treatment for gonorrhoea.

Because of the progressive loss of effectiveness of other antibiotics, in parts of the WPR treatment for gonorrhoea has become increasingly reliant on use of injectable (ceftriaxone) and oral (cefixime, ceftibuten, cefpodoxime, cefdinir and cefropozan) later-generation cephalosporins. Worryingly, the appearance and spread of GC 'non-susceptible' to these later-generation cephalosporins (and usually also resistant to other antibiotics[4,5]) has been documented over several years and in an increasing number of countries in the WPR, and is sometimes accompanied by evidence of treatment failure.[6]

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 2006.

Methods

The methods used by the WHO WPR GASP have been published[3] and provide full details of the source of isolates, sample populations, laboratory test methods and quality assurance programs used to generate data. These methods were unaltered in 2006.

Results

A total of 8,374 isolates of *N. gonorrhoeae* were examined for susceptibility to one or more antibiotics in 16 participating countries in 2006.

Quinolone antibiotics

Table 1 shows the distribution of quinolone-resistant *N. gonorrhoeae* (QRNG) in 14 countries that examined a total of 7,954 isolates in 2006. The proportion of QRNG in most of these centres was high to very high. The exceptions were New Caledonia where there were no QRNG detected, and Papua New Guinea where only a single QRNG was found. Very high rates of quinolone resistance (more than 80% of isolates tested) were present in Brunei, China, Hong Kong, Japan, Korea, Laos and Vietnam. The proportion of QRNG found in isolates from Malaysia (62%), the Philippines (69%) and Singapore (70%) was also high, while those from Australia (38%) and New Zealand (14%) while lower, were still substantial. When compared to earlier data, these rates were in general as high or higher as rates in previous years although a lower rate was noted in New Zealand.

Table 1. Quinolone resistance in 7,954 strains of *Neisseria gonorrhoeae* isolated in 14 countries in the WHO Western Pacific Region, 2006

Country	Number of isolates	Less susceptible		Resistant		All QRNG	
		n	%	n	%	n	%
Australia	3,850	42	1.2	1,413	36.7	1,455	37.8
Brunei	208	50	24	120	57.7	170	81.7
China	1,134	61	5.4	1,068	94.2	1,129	99.6
Hong Kong SAR	1,622	32	2	1,554	95.8	1,586	97.8
Japan	211	16	7.6	160	75.8	176	83.4
Korea	47	7	14.9	35	74.5	42	89.4
Lao PDR	9					9	100
Malaysia	29	5	17.2	13	44.8	18	62
New Caledonia	93	0	0	0	0	0	0
New Zealand	284	0	0	39	13.7	39	13.7
Papua New Guinea	53	0	0	1	1.8	1	1.8
Philippines	42	0	0	29	69	29	69
Singapore	160	13	8.2	99	61.8	112	70
Vietnam	212	54	25.5	120	56.6	174	82.1

Cephalosporins

Strains 'non-susceptible' to ceftriaxone and/or other later generation cephalosporins were again reported amongst isolates from Australia and Brunei and were especially prominent in China. The correlation between clinical outcomes and *in vitro* tests for 'resistance' to this group of antibiotics has not been reliably performed to date so that published parameters for decreased sensitivity to ceftriaxone and oral agents remains arbitrary. Because of this and some other methodological issues, minimal inhibitory concentrations (MIC) values are not directly comparable between different centres.

Spectinomycin

Only very small numbers of spectinomycin resistant gonococci have been reported in recent years in WPR GASP surveys and these sporadically, and this continued to be the case in 2006.

Penicillins

Resistance to penicillins has been widespread and at high levels for many years in the WPR, and may be the result of penicillinase production (PPNG) or aggregation of a number of chromosomally mediated mechanisms (CMRP). These mechanisms may co-exist in the one strain. Table 2 shows the penicillin susceptibility of 8,374 gonococci isolated in 16 WHO WPR centres in 2006. Because the penicillins have not been used for treatment of gonorrhoea for many years in some WPR countries, only testing for PPNG is performed in these centres. For example, China found 48% PPNG, but did not test for chromosomally mediated resistance. Once again penicillin resistance was widespread and, although less than that for quinolone antibiotics in most centres, was present in a high proportion of isolates in most countries. Rates of resistance to the penicillins above 50% in decreasing order of magnitude, were Laos, 100% (in a small sample), the Philippines 78%, Korea 69%, Brunei 64%, Hong Kong 63% and Singapore 59%. Rates ranging between 34% in Malaysia and Australia, 30% in Vietnam to 23% in Japan and 21.5% in New Zealand, were also recorded. In previous reports, some Pacific Island states have consistently reported low levels of penicillin resistance. In Fiji, 12% of 409 gonococci were penicillin resistant in 2006 with 7% of all isolates being PPNG. Papua New Guinea currently monitors AMR in GC every two years, and 43% of isolates tested from a number of centres in 2006 were PPNG. In Tonga, 9% of 32 gonococci tested were penicillin resistant, but no penicillin resistance was observed in New Caledonia.

Tetracyclines

These antibiotics are still widely available in the WPR. Approximately 7,650 isolates in 10 countries in 2006 were examined for one particular form of resistance, namely, the high-level plasmid-mediated form referred to as TRNG (Table 3). The highest rates of TRNG were reported from Singapore (77%), Hong Kong (49%), China (35%) and the Philippines (31%). Only low numbers were present in Japan and New Caledonia. Low proportions of TRNG (at or around 10%) were found in Korea and Australia, and slightly higher rates were found in New Zealand (25%) and Vietnam (16.5%).

Table 2. Penicillin resistance in 8,374 strains of *Neisseria gonorrhoeae* isolated in 16 countries in the WHO Western Pacific Region, 2006

Country	Number of isolates	PPNG		CMRP		All Pen R	
		n	%	n	%	n	%
Australia	3,850	342	9	964	25	1,306	34
Brunei	308	119	38.6	79	25.6	198	64.2
China	1,013	483	47.7				
Fiji	409	30	7.3	20	4.9	50	12.2
Hong Kong SAR	1,622	553	34.1	464	28.6	1,017	62.7
Japan	211	2	0.9	46	21.8	48	22.7
Korea	47	5	10.6	30	63.8	35	74.5
Lao PDR	9					9	100
Malaysia	29					10	34.4
New Caledonia	93	0	0	0	0	0	0
New Zealand	284	3	1	58	20.4	61	21.5
Papua New Guinea	53	23	43.4			53	43.4
Philippines	42	21	50	12	28.5	33	78.5
Singapore	160	79	49.4	16	10	95	59.4
Tonga	32	2	6	1	3	3	9
Vietnam	212	65	30.7	1	0.5	66	30.2

Table 3. High-level tetracycline resistance in 7,654 strains of *Neisseria gonorrhoeae* isolated in 10 countries in the WHO Western Pacific Region, 2006

Country	Number of isolates	Number of TRNG	% TRNG
Australia	3,850	462	12
China	1,133	399	35.2
Hong Kong SAR	1,622	793	48.9
Japan	211	2	0.9
Korea	47	4	8.5
New Caledonia	93	2	2.1
New Zealand	284	71	25
Philippines	42	13	31
Singapore	160	123	76.8
Vietnam	212	35	16.5

Discussion

The now well-documented picture of increasing antimicrobial resistance in *Neisseria gonorrhoeae* to many of the antibiotics used for treatment of gonorrhoea in the WHO WPR was reinforced by data obtained in this survey. As in previous surveys,[3,4] there were considerable differences in rates of resistance to several important groups of antibiotics across the WHO WPR, with a high proportion of both penicillin and quinolone resistance amongst isolates tested in north Asia, but much lower rates of penicillin resistance and little if any quinolone resistance present in Pacific Island states.

While the situation in regard to resistance to penicillins and quinolones was little changed, concerns continue over increasing numbers of isolates 'non-susceptible' to later-generation cephalosporins. This has been manifested as a rise in the MICs for these cephalosporins,[7] and at least some of this increase in MICs has been shown to be due to alterations in PBP2, the site of action of these antibiotics.[8–10] Particular attention has been paid to 'mosaic' *penA* genes that encode these PBP2 alterations. In gonorrhoea caused by GC with altered PBP2, treatment failures have been reported following therapy with a number of oral cephalosporins,[6] but so far not with the injectable agent ceftriaxone. However, there is much that is still unclear regarding these GC that are cephalosporin 'non-susceptible' in regard to the resistance mechanisms involved, the differential effect of these mechanisms on the various cephalosporin agents and how these phenomena affect treatment outcomes. Further clarification regarding the correlations between laboratory and clinical findings, and the extent of spread of GC with these alterations in the region is required before the longer term implications that arise from these events can be fully elucidated.

Surveys of this kind suffer from a number of limitations. The most obvious of these is that low sample numbers only are available in some centres, for several reasons, and the resource limitations that restrict capacity for testing, even when isolates are available. Other antibiotics, such as azithromycin, are being used either as a primary treatment or as adjunctive treatment for other pathogens, but sub-

stantive data on emerging azithromycin resistance in WPRO is not available. Some incomplete data suggest that azithromycin resistance is present, albeit in low proportions. Despite these limitations, in the absence of other data sources, and when conducted over extended periods under the same conditions, this series provides reasonably reliable guides to AMR trends in the region. The difficulties associated with surveillance in the WHO WPR GASP have increased and become more complex over time, but the ongoing need to meet these challenges is shown in the continuing problems posed by AMR in GC. Further, given the past history of the spread of antibiotic resistant GC from the WPR to other parts of the world,[1] there is a high likelihood that, unless better disease control becomes a reality, they will continue to spread well beyond the region.

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