Surveillance of antibiotic resistance in *Neisseria gonorrhoeae* in the WHO Western Pacific Region, 2004

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 10,000 isolates of *Neisseria gonorrhoeae* from 15 countries for resistance to antibiotics in 2004. Treatment options for gonorrhoea in the Region are limited by persisting high rates of resistance to penicillins and quinolones. There were infrequent instances of spectinomycin resistance and the presence of gonococci with decreased susceptibility to third generation cephalosporins was again noted in several centres. *Commun Dis Intell* 2006;30:129–132.

Keywords: antimicrobial resistance, disease surveillance, gonococcal, Neisseria gonorrhoeae, *World Health Organization Western Pacific Region*

Introduction

The World Health Organization (WHO) Western Pacific Region (WPR) has continuing and increasing problems with antimicrobial resistance in *Neisseria gonorrhoeae*. This has been documented by its Gonococcal Antimicrobial Surveillance Programme (WPR GASP). Penicillin resistance emerged and spread in the 1970s with the appearance of penicillinase-producing *N. gonorrhoeae* (PPNG) and gonococci resistant to penicillins by chromosomally mediated resistance (CMRNG). Since its inception in 1994, the WPR GASP has reported on the progressive increase in quinolone resistance in gonococci in the Region.[1,2] The rates of resistance to both of these antibiotic groups have been so high for so long that they should now only be used in programmatic treatments for infections acquired in this Region in specific situations where their efficacy is clearly demonstrated. Other established treatments for gonorrhoea have also suffered a loss of efficacy at different periods. Gonococci with high-level plasmid-mediated resistance to tetracyclines (TRNG) are frequently encountered in many centres,[2] spectinomycin resistance emerged rapidly when used widely in Korea in the 1980s[3] and more recently, there have been reports of the spread of gonococci with decreased susceptibility to third generation cephalosporins in Japan.[4]

Laboratory assessment of *in vitro* resistance to antibiotics in *N. gonorrhoeae* provides a reliable indication of the likely clinical efficacy of different treatment regimens. This report provides an analysis of antimicrobial resistance in *N. gonorrhoeae* in the WHO WPR derived from the results of the WHO WPR GASP surveillance for 2004.

Methods

The methods used by the WHO WPR GASP have been published[1] 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 2004. As a guide to the interpretation of the following data, a WHO expert committee has recommended that treatment regimens be altered once resistance to a particular antibiotic reaches 5 per cent.[5,6]

Results

Just over 10,000 gonococcal isolates were examined for susceptibility to one or more antibiotics in 15 participating countries in 2004.

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Quinolone antibiotics

Table 1 shows the distribution of quinolone-resistant *N. gonorrhoeae* (QRNG) in 13 countries that examined a total of 9,470 isolates in 2004. The proportion of QRNG found in isolates tested ranged from 2 per cent in New Caledonia and Papua New Guinea to nearly 100 per cent in the Hong Kong SAR and China. QRNG represented about 20 per cent of all gonococci tested in Australia and New Zealand, about 50 per cent were QRNG in Brunei, the Philippines and Singapore and 85 per cent or more in Japan, Korea, Laos and Viet Nam. These rates were in general higher than in previous years although decreases were noted in New Caledonia, the Philippines and Brunei when comparisons were made with 2003 data. Most of the resistance was at the higher level MICs (ciprofloxacin MIC ≥ 1 mg/L) that are associated with high rates of treatment failure.

Cephalosporins

Strains with some decrease in susceptibility to third generation cephalosporins were again detected in isolates from Australia, Brunei, China, and Papua New Guinea in 2004. Because of some methodological differences in testing, MIC values are not directly comparable between centres, but values ranged up to 0.25 mg/L.

Spectinomycin

A small number of spectinomycin resistant strains were reported from China. Only very small numbers of spectinomycin resistant gonococci have been reported in recent years in WPR GASP surveys.

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 or a combination of chromosomally mediated mechanisms. Table 2 shows the penicillin susceptibility of 9,983 gonococci in 15 WHO WPR centres. Little change was seen in 2004 from the generally high levels seen in previous years. There was an increase of note in PPNG in Brunei from 55 per cent in 2003 to 85 per cent, and a decrease in the Philippines from 78 per cent in 2003 to 37 per cent. The proportion of PPNG in Fiji increased to 6.4 per cent from the 3 per cent detected in 2003.

Tetracyclines

Tetracycline antibiotics are still widely available in the WPR. About 6,300 isolates were examined for one particular form of resistance, namely, that high-level plasmid-mediated form referred to as TRNG, in 10 countries in 2004 (Table 3). Again, rates of resistance, expressed as a percentage of all isolates tested, were similar to those found in 2003, except for increases in New Zealand where the proportion doubled in 2004 to 17.9 per cent, and Singapore (58% in 2003 and 72% in 2004), and a decrease in the Philippines from 29 per cent to 8 per cent. Low proportions of TRNG (< 10%) were found in Japan, Korea, New Caledonia, Papua New Guinea and the Philippines. The proportions of TRNG were from 14 to 34 per cent in isolates from Australia, China, New Zealand and Viet Nam while in Singapore TRNG were 72 per cent of 160 isolates tested.

Table 1. Quinolone resistance in strains of *Neisseria gonorrhoeae* isolated in 13 countries in the World Health Organization Western Pacific Region, 2004

Country	Tested	Less susceptible		Resistant		All QRNG	
	n	n	%	n	%	n	%
Australia	3,542	68	1.9	757	21.4	825	23.3
Brunei	113	15	13.3	46	40.7	61	54.0
China	1,203	60	4.9	1,135	94.3	1,195	99.2
Hong Kong SAR	2,811	144	5.1	2,647	94.2	2,627	99.3
Japan	261	16	6.1	213	81.6	239	91.6
Korea	93	17	18.2	65	70.0	82	88.2
Lao PDR	48	4	8.0	42	88.0	46	96.0
New Caledonia	43	0	0.0			1	2.3
New Zealand	773	14	1.8	148	19.1	162	20.9
Papua New Guinea	92	1	1.0	1	1.0	2	2.0
Philippines	175	2	1.1	83	47.4	85	48.5
Singapore	160	10	6.2	80	50.0	90	56.2
Viet Nam	156	49	31.4	82	52.5	131	83.9

QRNG Quinolone-resistant *Neisseria gonorrhoeae*.

Table 2. Penicillin resistance in 9983 strains of *Neiserria gonorrhoeae* isolated in 15 countries in the World Health Organization Western Pacific Region, 2004

Country	Tested	PPNG		CMRNG		All Pen R	
	n	n	%	n	%	n	%
Australia	3,542	393	11.1	377	10.6	770	21.7
Brunei	111	95	85.6	0		95	85.6
China	1,002 for PPNG	489	48.8		26.4		75.2
Fiji	606	39	6.4				
Hong Kong SAR	2,811	857	30.5	646	23.0	1,503	53.5
Japan	261	8	3.0	60	23.0	68	26.0
Korea	93	23	24.7	49	52.7	72	77.4
Lao PDR	48	40	83.0	8	17.0	48	100
New Caledonia	43					3	7.0
New Zealand	773	29	3.7	16	2.0	45	5.8
Papua New Guinea*	52 for PPNG 92 for all pen R	27	51.9			45	48.9
Philippines	175	65	37.1			90	51.4
Singapore	160	78	48.7	3	1.8	81	50.5
Tonga	110	3	2.7	6	5.4	9	8.1
Viet Nam	156	47	30.1	2	1.3	49	31.4

Papua New Guinea tested 52 of 92 isolates for lactamase production.

PPNG Penicillinase–producing *Neisseria gonorrhoeae*.

CMRNG Chromosome–mediated resistance *Neisseria gonorrhoeae*.

Table 3. High-level tetracycline resistance in strains of *Neisseria gonorrhoeae* isolated in 10 countries in the World Health Organization Western Pacific Region, 2004

Country	Number tested	TRNG n	TRNG %
Australia	3,542	490	13.8
China	1,202	411	34.2
Japan	261	6	2.3
Korea	93	2	2.1
New Caledonia	43	1	2.3
New Zealand	584	105	17.9
Papua New Guinea	92	4	4.3
Philippines	175	14	8.0
Singapore	160	115	71.9
Viet Nam	150	30	20.0

TRNG Tetracycline resistant *Neisseria gonorrhoeae*.

Discussion

Attempts to treat and control gonorrhoea are compromised by the emergence and spread of antibiotic-resistant *N. gonorrhoeae*. The data from 2004 indicate that the problems of providing efficacious treatment for gonorrhoea in the WHO WPR continue. The WHO recommends that standard treatment schedules should be changed when resistance to an antibiotic reaches a level of 5 per cent or more.[6] Resistance rates for the recommended cheaper oral agents such as the penicillins or quinolones remained well above this 5 per cent level in many centres and show no signs of decreasing. It is highly unlikely that effective newer derivatives from these antibiotic families will be developed.[7,8]

Alternative treatments are available but these either require intramuscular injection or else are more expensive than traditional agents. One group of antibiotics now widely used is the third generation cephalosporins, either as an oral preparation such as cefixime or cefdinir or the injectable ceftriaxone. The slow spread of gonococci with decreased susceptibility to third generation cephalosporins continues in the WHO WPR. After first reports from Japan, from 2000 onwards a small number of isolates with altered susceptibility to third generation cephalosporins has been reported each year in WHO WPR surveys in various countries. At different times Australia, Cambodia, Brunei, China, Japan, Korea, Malaysia, New Zealand, Papua New Guinea and Singapore have reported their presence. The reduced susceptibility is associated with the presence of a number of mosaic *penA* genes[4] and these gonococci are often

multi-resistant due to the aggregation of different resistance mechanisms.[9] These strains have now spread beyond the WHO WPR.[10,11]

Over-reliance on antibiotic treatment as a principal mechanism of gonococcal disease control in the absence of other important measures to decrease disease rates has undoubtedly contributed to the problem of antimicrobial resistance in *N. gonorrhoeae.*[12] The combination of high gonococcal disease rates and general problems of antibiotic resistance in the WHO WPR will continue without concerted efforts that simultaneously address the linked, but separate, issues of control of sexually transmitted diseases and containment of antimicrobial resistance.[8,12] Surveillance of antimicrobial resistance is an essential component of local, regional and international efforts for control of gonorrhoeae.

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