Surveillance of antibiotic resistance in *Neisseria gonorrhoeae* in the WHO Western Pacific Region, 2005

The WHO Western Pacific Gonococcal Antimicrobial Surveillance Programme

Abstract

The World Health Organization Western Pacific Region Gonococcal Antimicrobial Surveillance Programme examined about 8,700 isolates of *Neisseria gonorrhoeae* from 15 countries for resistance to antibiotics in 2005. High to very high rates of resistance to penicillins and quinolones persisted in most centres. Increasing numbers of gonococci with decreased susceptibility to third generation cephalosporins were found in several countries. There were infrequent instances of spectinomycin resistance. *Commun Dis Intell* 2006;30:430–433.

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

Introduction

Antimicrobial resistance in *Neisseria gonorrhoeae* has been a major problem in the World Health Organization (WHO) Western Pacific Region (WPR), and has impacted adversely on treatment and control of gonococcal disease for many years. The WPR Gonococcal Antimicrobial Surveillance Programme (WPR GASP) has monitored this resistance in gonococci at a regional level from 1992 onwards.[1] High levels of penicillin resistance had emerged in the 1970s and the WPR GASP has also reported on a progressive increase in quinolone resistance in gonococci in the region[1,2] as well as resistance to other established agents for the treatment of gonorrhoea. In recent years, increasing numbers of gonococci with decreased susceptibility to oral and injectable third generation cephalosporins have been detected, particularly in Japan.[3,4]

Laboratory assessment of *in vitro* resistance to antibiotics in *N. gonorrhoeae* is undertaken with the aim of optimising treatments, and thereby preventing the complications of gonococcal disease and assisting in its control.[5] The WHO recommends that a standard or programmatic treatment regimen should be altered once resistance is found in 5 per cent or more of isolates from a general population.[5,6] 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 2005.

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 2005.

Results

About 8,700 gonococcal isolates were examined for susceptibility to one or more antibiotics in 15 participating countries in 2005.

Quinolone antibiotics

Table 1 shows the distribution of quinolone-resistant *N. gonorrhoeae* (QRNG) in 13 countries that examined a total of 8,233 isolates in 2005. The proportion of QRNG found in isolates tested ranged from 2 per cent in New Caledonia to nearly 100 per cent in the Hong Kong SAR and China. QRNG represented 20 per cent or more of all gonococci tested in the centres other than New Caledonia and 50 per cent or more isolates were QRNG in Brunei, Japan, Laos, Korea, the Philippines, Singapore and Vietnam. When compared to earlier data, these rates were in general higher than in previous years. Most isolates with altered quinolone susceptibility had ciprofloxacin MICs that are associated with high rates of treatment failure (≥1 mg/L).

Correspondence: Associate Professor John Tapsall, WHO Collaborating Centre for STD and HIV, Department of Microbiology, The Prince of Wales Hospital, Randwick, NSW 2031. Telephone: +61 2 9298 9084. Facsimile: + 61 2 9398 4275. Email j.tapsall@unsw.edu.au

Table 1. Quinolone resistance strains of *Neisseria gonorrhoeae* isolated in 13 countries in the WHO WPR, 2005

Country	Tested	Less susceptible		Resistant		All QRNG	
		n	%	n	%	n	%
Australia	3,886	77	2	1,113	28.6	1,190	30.6
Brunei	116	14	12	64	55.2	78	67.2
China	1,442	47	3.2	1,384	96	1,431	99.2
Hong Kong SAR	1,887	67	3.6	1,794	95.1	1,871	98.7
Japan	26	1	3.8	20	76.9	21	80.8
Korea	48	5	10.4	39	81.2	44	91.7
Lao PDR	29					19	65.5
Malaysia	17	3	17.6	2	11.7	5	29.3
New Caledonia	55	0		1	1.8	1	1.8
New Zealand	310	0	0	60	19.4	60	19.4
Philippines	94					37	39.3
Singapore	160	13	8.1	95	59.4	108	67.5
Vietnam	163	35	21.5	96	58.9	131	80.4
Total	8,233	262		4,668		4,996	

Cephalosporins

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

Spectinomycin

Only very small numbers of spectinomycin resistant gonococci have been reported in recent years in WPR GASP surveys. Of the 6,000 isolates tested in eight countries in 2005, three isolates in China and one each in Malaysia and the Philippines were spectinomycin resistant.

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 (CMRNG). These mechanisms may co-exist in the one strain. Table 2 shows the penicillin susceptibility of 8,722 gonococci in 15 WHO WPR centres. Once again penicillin resistance was widespread and found in a high proportion of isolates in most centres. The highest rates of resistance to the penicillins were found in China and Laos. In previous reports, some Pacific Island states have consistently reported low levels of penicillin resistance, but there has been a shift towards resistance in recent years. In Fiji, for example, 16 per cent of 328 gonococci were penicillin resistant in 2005 with 10 per cent of all isolates PPNG. In 2003, only three per cent of isolates were penicillin resistant and in 2004, 6.4 per cent of isolates were penicillin resistant.

Tetracyclines

These antibiotics are still widely available in the WPR. About 7,800 isolates were examined for one particular form of resistance, namely, high-level plasmid-mediated form (TRNG), in 10 countries in 2005 (Table 3). The highest rates of TRNG were reported from Singapore (78%) and Hong Kong (42%). Only low numbers were present in Malaysia and New Caledonia. Low proportions of TRNG (at or around 10%) were found in Japan, Korea, Australia and Vietnam, and slightly higher rates in China (28%) and the Philippines (30%).

Discussion

Despite limitations, surveys of this kind provide the best available indication of antimicrobial resistance (AMR) in *N. gonorrhoeae* in the WHO WPR. Additionally, they have a particular value in being able to follow trends in AMR over time. Little comfort can be taken from this latest report of resistance rates in *N. gonorrhoeae* in the WHO WPR. High rates of resistance to cheaper oral agents such as the quinolones have continued and the few situations where penicillins remained a viable treatment, such as some Pacific Island centres, are showing sustained upward trends in resistance to this group of antibiotics.

Table 2. Penicillin resistance strains of *Neisseria gonorrhoeae* isolated in 15 countries in the WHO WPR, 2005

Country	Tested	PPNG		CMRNG		All Pen R	
		n	%	n	%	n	%
Australia	3,886	410	10.5	738	19	1,148	29.5
Brunei	194					111	57.2
China	1,474	556	37.7	289			
China SH/GD*	298	126	42.2	163	54.7	289	96.9
Fiji	328	33	10	20	6	53	16
Hong Kong SAR	1,887	586	31	529	28	1115	59
Japan	26	2	7.7	11	42.3	13	50
Korea	48	7	14.6	22	45.8	29	60.4
Lao PDR	29	16	55	13	45	29	100
Malaysia	17	4	23.5	2	11.7	6	35.2
New Caledonia	55	1	1.8	0	0	1	1.8
New Zealand	310	6	1.9	28	9	34	10.9
Philippines	94					64	68
Singapore	160	81	50.6	16	10	97	60.6
Tonga	48					10	20.8
Vietnam	166	57	34.3	1	0.6	58	34.9
Total	8,722†	1,885		1,832		3,057	

* A sample of 298 gonococci examined for both lactamase production and chromosomal resistance in Shanghai and Guandong; elsewhere isolates were examined for penicillinase production only.

† Total excludes the 298 gonococci examined in Shanghai and Guandong.

Table 3. High-level tetracycline resistance in strains of *Neisseria gonorrhoeae* isolated in 10 countries in the WHO WPR, 2005

Country	Tested	n	%
Australia	3,886	534	13.7
China	1,442	405	28.1
Hong Kong SAR	1,887	791	41.9
Japan	26	2	7.7
Korea	48	5	10.4
Malaysia	17	1	5.8
New Caledonia	55	1	1.8
Philippines	94	28	29.7
Singapore	160	124	77.5
Vietnam	162	16	9.9
Total	7,777	1,907	

Decreased susceptibility to alternative agents is also a concern. One group of antibiotics now widely used is the third generation cephalosporins, either as an oral preparation such as cefixime or cefdinir or in the form of the injectable ceftriaxone. At different times Australia, Cambodia, Brunei, China, Japan, Korea, Malaysia, New Zealand, Papua New Guinea, Singapore and Tonga have reported the presence of gonococci with decreased susceptibility to these agents. This reduced susceptibility to later generation cephalosporins was associated with the presence of a number of mosaic *penA* genes,[7] but this is probably not the full explanation of this phenomenon.[8,9] Those gonococci with this decreased susceptibility to cephalosporins are often multi-resistant, and exhibit high-level quinolone resistance as well as resistance to other beta-lactam antibiotics. These strains have now spread beyond the WHO WPR.[10,11]

The current situation is one where the provision of effective treatment for individuals and disease control efforts are compromised by high and increasing levels of AMR. This has considerable health and economic consequences in the WHO WPR. The combination of high disease rates and general problems of antibiotic resistance means that control of gonorrhoea is unlikely to be achieved in the immediate future unless concerted long-term efforts are applied.

Acknowledgements

Members of the WHO Western Pacific Gonococcal Antimicrobial Surveillance Programme in 2005: JW Tapsall and EA Limnios, Australia; Hjh Mahani

Hj Abu Bakar, Brunei Darussalam; Yin Yue Ping, China; EM Buadromo and S Singh, Fiji; J Lo, Hong Kong; Yuko Watanabe, Japan; K Lee and Y Chong, South Korea; T Phouthavane, Lao PDR; N Ahmad, Malaysia; R Goursaud, New Caledonia; M Brokenshire, New Zealand; CC Carlos and D Agdamag, Philippines; Cecilia Ngan and M Yuen, Singapore, M Fakahau, Tonga, Le Thi Phuong, Hanoi, Vietnam.

References

1. WHO Western Pacific Region Gonococcal Surveillance Programme. Surveillance of antibiotic susceptibility of *Neisseria gonorrhoeae* in the WHO Western Pacific Region 1992–4. *Genitourin Med* 1997;73:355–361.

2. The WHO Western Pacific Gonococcal Antimicrobial Surveillance Programme. Surveillance of antibiotic resistance in *Neisseria gonorrhoeae* in the WHO Western Pacific Region, 2003. *Commun Dis Intell* 2005;29:62–64.

3. Ito M, Deguchi T, Mizutani KS, Yasuda M, Yokoi S, Ito S, *et al.* Emergence and spread of *Neisseria gonorrhoeae* clinical isolates harbouring mosaic-like structure of penicillin-binding protein 2 in Japan. *Antimicrob Agent Chemother* 2005;49:137–143.

4. The WHO Western Pacific Gonococcal Antimicrobial Surveillance Programme. Surveillance of antibiotic resistance in *Neisseria gonorrhoeae* in the WHO Western Pacific Region, 2004. *Commun Dis Intell* 2006;30:129–132.

5. Tapsall JW. Antimicrobial resistance in *Neisseria gonorrhoeae.* WHO/CDS/CSR/DRS/2001.3. World Health Organization, Geneva, Switzerland, 2001. Available from: http://www.who.int/entity/drugresistance/Antimicrobial_resistance_in_Neisseria_gonorrhoeae.pdf Accessed December 2006

6. Management of sexually transmitted diseases. World Health Organization 1997; Document WHO/GPA/TEM94.1 Rev.1 p 37.

7. Ameyama S, Onodera S, Takahata M, Minami S, Maki N, Endo K, *et al*. Mosaic-like structure of penicillin-binding protein 2 gene (*penA*) in clinical isolates of *Neisseria gonorrhoeae* with reduced susceptibility to cefixime. *Antimicrob Agents Chemother* 2002;46:3744–3749.

8. Takahata S, Senju N, Osaki Y, Yoshida T, Ida T. Amino acid substitutions of mosaic penicillin-binding protein 2 associated with reduced susceptibility to cefixime in clinical isolates of *Neisseria gonorrhoeae*. *Antimicrob Agents Chemother* 2006;50:3638–3645.

9. Whiley DM, Limnios EA, Ray S, Sloots TP, Tapsall W. Further questions regarding the role of mosaic *penA* sequences in conferring reduced susceptibility to ceftriaxone in *Neisseria gonorrhoeae. Antimicrob Agents Chemother* 2007; Epub ahead of print, November 2006.

10. Wang SA, Lee MV, O'Connor N, Iverson CJ, Ohye RG, Whiticar PM, *et al.* Multidrug-resistant *Neisseria gonorrhoeae* with decreased susceptibility to cefixime—Hawaii, 2001. *Clin Infect Dis* 2003;37:849–852.

11. Hoffman SH, Lambertson L, Berthelsen L, Cowan S. *Neisseria gonorrhoeae* with increasing cetriaxon MIC in Denmark in 2004: serotyping, bi-locus sequence typing and sexual preference. In: *Proceedings of the 16th Biennial Meeting of the International Society for STD Research*, Amsterdam, 2005: Abstract WP-035.