

Resistance in gonococci isolated in the WHO Western Pacific Region to various antimicrobials used in the treatment of gonorrhoea, 1997

(Prepared by the WHO Western Pacific Gonococcal Antimicrobial Surveillance Programme - WHO WPR GASP)

Summary

The World Health Organization Western Pacific Region Gonococcal Antimicrobial Surveillance Programme (WHO WPR GASP) is a multicentric long term programme of continuous surveillance of the antibiotic susceptibility of *Neisseria gonorrhoeae*. In 1997 the programme examined the susceptibility of 8,594 isolates of gonococci to various antimicrobials in 15 focal points.

The trend toward increased antimicrobial resistance noted in earlier years continued. The proportion of quinolone resistant gonococci reported from most centres was either maintained or else increased. More than half of the isolates tested in China - Hong Kong, China, Japan, Korea, and the Philippines had altered quinolone susceptibility and increases in the number and percentage of quinolone resistant strains were noted in most, but not all, of the other centres.

Resistance to the penicillins was again widespread, and chromosomally mediated resistance was a significant factor. Penicillinase-producing *Neisseria gonorrhoeae* (PPNG) were present in all centres.

All isolates were sensitive to the third generation cephalosporins and only a very few isolates in China were spectinomycin resistant.

High level tetracycline resistance was concentrated in a number of centres including Singapore, Malaysia, the Philippines and Vietnam. The proportion of tetracycline resistant *Neisseria gonorrhoeae* (TRNG) in most of the remaining centres was less than 10 per cent.

Introduction

Effective treatment of gonorrhoea remains a priority for well founded reasons including prevention of morbidity in individual patients and reduction in the total disease burden associated with the disease. It is now also established that the rate of HIV transmission increases by three to five times in the presence of gonorrhoea.¹ With proper treatment HIV transmission rates can be reduced by up to 40 per cent.²

Appropriate antibiotic regimens for treatment of gonococcal disease may be established, modified and made more relevant by data on gonococcal susceptibility patterns. The WHO has sought to establish a global surveillance network to monitor antibiotic resistance in the gonococcus - the Gonococcal Antimicrobial Surveillance Programme (GASP). Such a GASP network is useful not only for the individual contributing countries and the

Regions, but also has wider application as an indicator of emerging global resistance in *Neisseria gonorrhoeae*.³

The WHO WPR GASP commenced in 1992. Annual reports of WPR GASP findings have been published in a variety of sources designed to disseminate the data as widely as possible.⁴⁻¹⁰ This report deals with data generated in the calendar year 1997.

Methods

Data were generated by participants in focal points in various countries throughout the WHO WPR and collated in the regional reference laboratory. A list of participating members of the programme is contained in the acknowledgements. These include countries with a small geographic area e.g. Singapore and China - Hong Kong where isolates were examined in a single centre. Data from other centres represents an analysis of strains referred throughout a country to a central setting as in Malaysia. Other countries (e.g. Australia, China) have a network of contributors supplying data from a national surveillance scheme. A full description of the methods used in the WPR GASP is available.⁹ Briefly, participants were encouraged to examine susceptibility of gonococci to a recommended 'core' list of antibiotics using one of the standard methods nominated by the programme. A programme-specific quality assurance programme is conducted annually and a series of reference strains pertinent to the regional patterns of resistance were made available. Because of resource limitations, not all isolates are examined for sensitivity to all agents by all participants. Most strains examined are from non-selected sexually transmissible disease (STD) clinic patients, but some are obtained as a result of case finding.

Results

Approximately 8,600 isolates were examined in 15 focal groupings in 1997. Other centres were unable to supply data but maintained contact with the programme through participation in the quality assurance (QA) programme. Mongolia joined the programme in 1997, but data were not available from Brunei, Cambodia, Papua New Guinea or the Solomon Islands in this period. About 44,000 strains have been examined in this programme since 1992. The sensitivity of isolates to selected antimicrobials is shown in Tables 1 - 4.

Penicillins

The proportion of isolates resistant to the penicillin group by one or mechanisms ranged between 3.5 per cent (Japan) and 95 per cent of isolates (Philippines) in the 15

Table 1. Penicillin sensitivity of strains of *Neisseria gonorrhoeae* isolated in countries in the WHO WPR in 1997.

Country	Number tested	PPNG		CMRNG		All Pen R	
		No	%	No	%	No	%
Australia	2,817	180	6.4	36	12.8	541	19.2
China	908	101	11.0	406	44.0	507	55.0
Fiji	522	29	5.5	13	2.5	42	8.0
Hong Kong (China)	2,435	125	5.2	1,492	61.2	1,617	66.4
Japan	85	2	2.3	1	1.2	3	3.5
Korea	382	303	79.0	47	12.3	350	91.3
Malaysia	51	21	41.0	NT			
Mongolia	20	4	20.0	NT			
New Caledonia	16	0		1	6.0	1	6.0
New Zealand	309	23	7.4	22	7.1	45	14.5
Philippines	22	18	81.8	3	13.6	21	95.4
Singapore	691	424	61.3	5	1.0	429	62.3
Tonga	9	2	22.0	2	22.0	4	44.0
Vanuatu	171					28	16.4
Vietnam	156	100	64.1	20	12.8	120	76.9

contributing centres. Particularly high levels of penicillin resistance were also recorded in Korea (91.3%), China - Hong Kong (66.4%), Vietnam (76.9%) and Singapore (62.3%) (Table 1).

The programme seeks to identify separately the extent of penicillin resistance manifested through plasmid-mediated penicillinase production (PPNG) or through chromosomally controlled intrinsic resistance [chromosomally-mediated resistant *Neisseria gonorrhoeae* (CMRNG)]. Both forms of resistance may exist simultaneously in the one isolate, but the latter type may be masked in PPNG.

PPNG were widely distributed throughout the WPR in 1997 but the proportion of PPNG was below 10% in a number of centres. PPNG were especially prominent in the Philippines (81.8% of isolates), Korea (79%) Singapore (61.3%) Vietnam (64.1%) and Malaysia 41%). An increasing proportion of CMRNG has also been detected over the life of the programme. In Hong Kong isolates of this type now represent 61.2 per cent of all isolates while the proportion of PPNG has declined to 5.2 per cent.

Quinolone antibiotics

About 8,400 isolates were examined for susceptibility to second generation quinolones in 12 centres in 1997 and quinolone resistant gonococci (QRNG) were detected in 10. Separate categories of "less sensitive" and "resistant" (to the second generation agents) are included in Table 2 because of their epidemiological relevance in long term studies of the evolution of quinolone resistance. The pattern of increasing quinolone resistance in gonococci first described in the WPR in 1993 and reinforced from 1994 to 1996 was present again in 1997.

The proportion of 'less sensitive' isolates has increased significantly in many centres since 1992, but there was little further change in 1997. The proportion of 'less sensitive' strains remained particularly high in China (51.5%), Hong Kong (42.1%) and Korea (46.8%) in 1997.

In a large sample in Fiji and in a small one in Malaysia, no QRNG were detected.

Many centres reported an increase in the proportion of resistant isolates in 1997 or else maintained the high numbers seen in 1996. The highest proportions of fully quinolone resistant isolates were seen in the Philippines (50%), Japan (41.2%), China - Hong Kong (38.6%), China (28.5%) and Korea (20.4%). In other centres the increase in fully developed QRNG was slower. In Australia resistant strains account for 5.6 per cent of all isolates but most of these were concentrated in one city. The proportion of QRNG more than doubled in New Zealand in 1997.

Table 2. Quinolone resistance in strains of *Neisseria gonorrhoeae* isolated in countries in the WHO WPR in 1997

Country	Number tested	Less susceptible		Resistant	
		No.	%	No.	%
Australia	2,817	46	1.6	158	5.6
China	903	468	51.5	257	28.5
Fiji	522	0	0	0	0
Hong Kong (China)	2,435	1,026	42.1	939	38.6
Japan	85	17	20.0	35	41.2
Korea	382	179	46.8	78	20.4
Malaysia	9	0		0	0
New Caledonia	16	3	18.0	0	0
New Zealand	309	18	5.8	6	1.9
Philippines	22	0	0	11	50.0
Singapore	691	33	4.8	26	3.8
Vietnam	152	5	3.3	5	3.3

Ceftriaxone

This third generation cephalosporin was used as the representative agent for this group of antibiotics in this programme. No resistance to this agent was evident in 1997. As in previous years, some evidence of increasing MIC levels was present in some centres.

Spectinomycin

Just over 5,000 isolates were examined in 10 centres in 1997. Only in China was there a small number of resistant isolates. In particular, all 382 isolates tested in Korea were sensitive to this agent (Table 3).

High level tetracycline resistance (TRNG)

About 5,400 isolates were examined in 1997 in 10 countries and TRNG were present in all of these centres. Particularly high proportions of TRNG were again seen in Singapore (82%), Malaysia (55%) and Vietnam (35.9%) continuing a pattern observed in earlier years. In all other centres except the Philippines (45.4%) and New Caledonia

(12.5%), the proportion of TRNG was below 10 per cent of isolates tested (Table 4).

Discussion

There was a slight change in the composition of the focal points of the WHO WPR in 1997 with Mongolia joining the group. The Solomon Islands and Papua New Guinea were unable to supply data in 1997 but will do so in 1998. Data from Brunei and Cambodia were not available. However the majority of the focal points have contributed data continuously for a number of years. This continuous surveillance has facilitated analysis of the trends in gonococcal susceptibility in the region. The number of isolates examined in 1997 was the highest number tested since the programme began.

Particular interest is once more centred on emerging gonococcal resistance to the quinolone group of antibiotics. In 1995 the position with regard to QRNG in the WPR was summarised as a steady increase in the proportion of resistant isolates since 1992 when very few resistant isolates were observed.⁷ The change was manifested as an increasing number of centres reporting the presence of these strains, an increasing number of strains showing quinolone resistance in those centres and increasing MICs in resistant isolates. This was again the pattern in 1997 and QRNG are now widely dispersed throughout the region.

It should be remembered that resistance to the quinolones in gonococci is chromosomally mediated and levels of resistance increase incrementally due to a number of complementary alterations in the organism. The first clinically manifested resistance observed was at a low MIC level and was accommodated by increasing the recommended dose of antibiotic administered. These strains, where identified, were those classified as less sensitive in Table 2. Subsequently strains with higher MICs were detected and these were not amenable to therapy with then available quinolones, even with higher dose regimens. These isolates are shown in Table 2 as the 'resistant' group. In 1997, one particular feature has been the increase or maintenance of high numbers of strains with fully developed quinolone resistance.

The data shown apply to resistance to the group of quinolones now called 'second generation' agents.¹¹ Newly released quinolones with activity against some of strains resistant to second generation agents are now available. Their activity and potential for use in the WHO WPR will need to be assessed.

Some interest remains within and without the region in the extent and type of resistance to the penicillins. Because of the very high levels of resistance, the clinical usefulness of this group of antibiotics has decreased significantly in the WPR. Consequently the testing for susceptibility to the penicillins is a decreasing priority. However this group of agents is still used effectively in a number of specific settings, and the data generated in the WPR continues to be of interest to other regions.

There was no resistance detected to the later generation cephalosporins and very little to the injectable agent spectinomycin. Significant levels of spectinomycin resistance were recorded in parts of the region some years ago. The inappropriate use of antibiotics, and availability of

Table 3. Spectinomycin resistance in isolates of *Neisseria gonorrhoeae* in countries in the WHO WPR in 1997

Country	Number tested	Number resistant
Australia	2817	0
China	905	4 (0.045%)
Japan	85	0
Korea	382	0
Malaysia	9	0
New Caledonia	9	0
Philippines	22	0
Singapore	691	0
Vietnam	156	0

Table 4. High level tetracycline resistance - TRNG - in strains of *Neisseria gonorrhoeae* isolated in 10 countries in the WHO WPR in 1997

Country	Number Tested	Number TRNG	% TRNG
Australia	2817	162	5.8
China	901	21	2.3
Japan	85	1	1.2
Korea	382	4	1.0
Malaysia	9	5	55.0
New Caledonia	16	2	12.5
New Zealand	309	17	5.5
Philippines	22	10	45.4
Singapore	691	567	82.0
Vietnam	156	56	35.9

agents in the informal health sector have both contributed to the development of antibiotic resistance in the past. The increasing availability of oral third generation cephalosporins and the consequent risk of inappropriate use suggests that continuing surveillance of these agents is prudent. Such surveillance is of greater importance now that the usefulness of the quinolones is rapidly declining in the WPR.

Tetracyclines are a multiple dose treatment for gonorrhoea and are not a recommended therapy for gonorrhoea. However the presence of a particular form of high level plasmid mediated tetracycline resistance - TRNG - has been recognised. The programme has therefore monitored the spread of TRNG in the region. Considerable regional variation in the distribution of TRNG was again noted. Singapore, Malaysia, the Philippines and Vietnam in particular have high numbers of TRNG.

The trend towards a decrease in susceptibility of gonococci to various antimicrobials in the WPR has continued over a number of years poses additional problems for successful treatment of gonococcal disease in the region.

Acknowledgements

Dr. G. Pomeroy Regional Adviser STD, WHO Regional Office for the Western Pacific, Manila, Philippines;

J. W. Tapsall, Area co-ordinator, Sydney, Australia.

The following supplied data in 1997 for the WPR GASP:

Members of the Australian gonococcal surveillance programme throughout Australia;

Ye Shunzhang and Su Xiaohong, Nanjing, China;

M. Shah, Suva, Fiji;

K. M. Kam, Hong Kong;

Toshiro Kuroki, Yokohama Japan;

K. Lee and Y. Chong, Seoul, Korea;

Rohani MD Yasin, Kuala Lumpur, Malaysia;

Chimgee Erdenechimeg, Ulaanbaatar, Mongolia

P. Duval, and B. Gentile, Noumea, New Caledonia;

M. Brett, Wellington and M. Brokenshire, Auckland, New Zealand;

C. C. Carlos, Manila, Philippines;

A. E. Ling, Singapore;

Ane Tone Ika, Nuku'alofa, Tonga;

H. Wamle and D. Kalorib, Vanuatu;

Le Thi Phuong, Hanoi, Vietnam.

The regional reference laboratory is supported by a technical services grant from the WHO.

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