Antimicrobial resistance in gonococci, WHO Western Pacific Region, 1996

The WHO Western Pacific Region Gonococcal Antimicrobial Surveillance Programme[1]

Abstract

The World Health Organization (WHO) Western Pacific Region Gonococcal Antimicrobial Surveillance Programme is a multicentric long term programme for continuous surveillance of the antimicrobial susceptibility of *Neisseria gonorrhoeae*. In 1996 the programme examined the susceptibility of 8,421 isolates of gonococci to various antimicrobials in 17 focal points. A trend toward increased resistance noted in earlier years continued. The proportion of quinolone resistant gonococci reported from most centres either remained stable or increased. More than 50% of isolates in Hong Kong, China, Korea, Cambodia and the Philippines had altered quinolone susceptibility. Resistance to the penicillins was again widespread, and chromosomal mediated resistance was of increasing importance. Penicillinase producing *Neisseria gonorrhoea* were present in all but one centre. All isolates were sensitive to the third generation cephalosporins and only a very few isolates were spectinomycin resistant. A high proportion of isolates in a number of centres had high level tetracycline resistance, but the proportion of tetracycline resistant *Neisseria gonorrhoea* in most centres was less than 10%. *Comm Dis Intell* 1997;21:349-53

Introduction

Information on gonococcal susceptibility patterns can be used to introduce, modify or make more appropriate antimicrobial regimens for treatment of gonococcal disease. Proper treatment of gonorrhoea benefits the individual by preventing complications, and the community at large by ultimately decreasing the total disease burden. Other data suggest that a decrease in the prevalence of gonorrhoea also assists in reducing the transmission of HIV.[1] The World Health Organization (WHO) has sought to establish a global surveillance network to monitor antimicrobial resistance in *Neisseria gonorrhoeae*; the Gonococcal Antimicrobial Surveillance Programme (GASP). The GASP network is useful not only for the individual contributing countries and Regions, but also has wider application as an indicator of emerging global resistance in the gonococcus.

The WHO Western Pacific Region (WPR) GASP commenced in 1992. Annual reports of WPR GASP findings have been published in a number of publications to disseminate the data as widely

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Table 1. Penicillin resistance in *Neisseria gonorrhoeae* in the WHO Western Pacific Region, 1996, by country of isolation

Country	Number of strains tested	Penicillinase mediated resistance (PPNG)		Chromosomal resistance (CMRNG)		All penicillin resistance (PPNG & CMRNG)	
		Number	%	Number	%	Number	%
Australia	2,753	161	6	271	10	432	16
Brunei	23	-	-	-	-	18	78
Cambodia	100	79	79	-	-	-	-
China	464	39	8	342	74	361	82
Hong Kong	1,976	180	9	1,212	61	1,392	70
Fiji	845	30	4	9	1	39	5
Japan	72	4	6	0	0	4	6
Korea	199	140	70	40	20	180	90
Malaysia	17	8	47	2	12	10	59
New Caledonia	17	1	6	0	0	1	6
New Zealand	437	21	5	18	4	39	9
Papua New Guinea	505	47	9	0	0	47	9
Philippines	59	45	76	1	2	46	78
Singapore	707	381	54	13	2	394	56
Tonga	45	13	29	7	16	20	44
Vanuatu	116	0	0	-	-	-	-
Vietnam	93	91	98	-	-	-	-

as possible.[2-8] This report deals with data generated in the calendar year 1996.

Methods

Data were generated by participants in focal points in various countries throughout the WHO WPR and collated in the regional reference laboratory. Participating countries included those with a small geographic area, for example Singapore and Hong Kong, where isolates were examined in a single centre. Data from other centres represents an analysis of strains referred from around a country to a central laboratory, as in Malaysia. Other countries (for example, Australia and 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.[7] In summary, participants were encouraged to examine the susceptibility of gonococci to a recommended 'core' list of antimicrobials using one of the standard methods nominated by the programme. A programme-specific quality assurance programme was 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 were examined for susceptibility to all antimicrobials by all participants. Most strains examined were from non-selected STD clinic patients, but

Table 2. Quinolone resistance in *Neisseria gonorrhoeae* in the WHO Western Pacific Region, 1996, by country of isolation

Country	Number of strains tested	Less susceptible		Resistant	
		Number	%	Number	%
Australia	2,753	56	2	72	3
Brunei	29	-	-	3	10
Cambodia	100	-	-	53	53
China	340	236	69	46	14
Fiji	845	0	0	0	-
Hong Kong	1,976	1,090	55	475	24
Korea	199	76	38	31	16
Malaysia	17	0	0	0	0
New Caledonia	17	2	12	0	0
New Zealand	437	13	3	3	1
Papua New Guinea	448	0	0	29	7
Philippines	59	0	0	39	66
Singapore	707	46	7	25	4
Vietnam	89	5	6	5	6

some were obtained as a result of case finding.

Results

Approximately 8,400 isolates were examined in 17 focal groupings in 1996. Cambodia joined the programme in 1996, and data were not available from the Solomon Islands in this period. About 35,000 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 more mechanisms ranged between 4.6% (Fiji) and 97.5% (Vietnam) of isolates in the 17 contributing centres. Particularly high levels of penicillin resistance were also recorded (Table 1) in Korea (90%), China (82.1%), Cambodia (79%) and Brunei (78.3%).

The programme seeks to identify separately the extent of penicillin resistance manifest through plasmid-mediated penicillinase production (penicillinase producing *N. gonorrhoea*, PPNG) or through chromosomally controlled intrinsic resistance (chromosomally mediated resistant *N. gonorrhoea*, 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 1996. Vanuatu was the only centre not recording the presence of any PPNG, but the proportion of PPNG was below 10% in many centres. A steady increase in the proportion of PPNG has been noted in some countries since the inception of this programme. In Vietnam the proportion of PPNG has increased from 55% to 97.5 % since 1992. An increasing proportion of CMRNG has also been detected over the life of the programme. In Hong Kong isolates of this type now represent 72.6% of all isolates while the proportion of PPNG has declined to 4.9%.

Quinolone antibiotics

About 8,000 isolates were examined for quinolone susceptibility in 14 centres in 1996 and quinolone resistant *N.gonorrhoea* (QRNG) were detected in 12 of these. Separate categories of 'less susceptible' and 'resistant' were included in Table 2 because of their epidemiological relevance in long term studies of the evolution of antimicrobial resistance. The pattern of increased quinolone resistance first described in the WPR in 1993 and reinforced in 1994 and 1995 was maintained in 1996.

While the proportion of 'less susceptible' isolates has increased significantly in many centres since 1992, there was little further change in 1996. The proportion of 'less susceptible' strains remained particularly high in China (69.4%), Hong Kong (55.2%) and Korea (38%) in 1996. However, only Korea showed an increased proportion of less susceptible QRNG, with the proportion in 1996 (38%) being more than double the 15.6% observed in 1995. In a large sample in Fiji and a small sample in Malaysia, no QRNG were detected.

However, many centres either reported an increase in the proportion of resistant isolates in 1996, or maintained the high numbers seen in 1995. The highest proportion of resistant isolates was again seen in the Philippines (66%). Fifty-three per cent of isolates from Cambodia were QRNF. Fully developed resistance appeared in 24% of Hong Kong isolates (up from 7.7% in 1995) and 15.6% of isolates in Korea. In other centres the increase in fully developed QRNG was slower. In Singapore the proportion has increased from 0.3% to 3.5% since 1993 and in Australia from 0.1% to 2.6% since 1992. In Australia however, the more populous centres have much higher rates of QRNG. Sydney, for example, had in excess of 10% of strains exhibiting high level quinolone resistance.

Ceftriaxone

This third generation cephalosporin was used as the representative agent for this group of antimicrobials in this programme. No resistance to this agent was evident amongst the 5,287 strains tested in 13 centres. As in

Table 3. Spectinomycin resistance in *Neisseria gonorrhoeae* in the WHO Western Pacific Region, 1996, by country of isolation

Country	Number of strains tested	Resistant	
		Number	%
Australia	2,743	0	-
Brunei	25	0	-
Cambodia	100	0	-
China	353	1	0.3
Japan	72	0	-
Korea	179	0	-
Malaysia	17	0	-
New Caledonia	16	0	-
Papua New Guinea	162	3	1.8
Singapore	368	0	-
Vietnam	89	0	-

Table 4. High level tetracycline resistance (TRNG) in *Neisseria gonorrhoeae* in the WHO Western Pacific Region, 1996, by country of isolation

Country	Number of strains tested	Resistant	
		Number	%
Australia	2743	136	5
Cambodia	100	74	74
China	353	23	7
Fiji	462	0	0
Korea	199	2	1
Malaysia	17	13	77
New Caledonia	17	1	6
New Zealand	437	8	2
Papua New Guinea	472	72	15
Philippines	59	6	10
Singapore	707	526	74
Tonga	21	0	0
Vietnam	93	46	49

previous years, some evidence of increasing minimum inhibitory concentration (MIC) levels was evident in some centres.

Spectinomycin

Just over 4,000 isolates were examined in 11 centres in 1996 (Table 3). A small number of resistant isolates were seen only in China (1) and Papua New Guinea (3). In particular, all 179 isolates tested in Korea were susceptible to this agent.

High level tetracycline resistance

About 5,700 isolates were examined in 1996 in 13 countries, and high level tetracycline resistant *Neisseria gonorrhoea* (TRNG) were present in 11 of these centres. Particularly high proportions of TRNG were seen in Singapore (74%), Malaysia (76%) and Vietnam (49%) continuing a pattern observed in earlier years. Cambodia, reporting for the first time, noted the presence of 74% TRNG. Fifteen per cent of isolates in Papua New Guinea and 10% in the Philippines were TRNG, but in all other centres the proportion was less than 10%.

Discussion

The WPR GASP consolidated further in 1996. Although there was a slight change in the composition of focal points, with Cambodia joining, and the Solomon Islands not participating in this period, the majority of the focal points have contributed data continuously for a number of years.[7] Data from Brunei was again available this year. This continuous surveillance has facilitated analysis of the trends in gonococcal susceptibility in the region. The number of isolates examined in 1996 (8,421) was the highest number tested since the programme began.

Particular interest is centred on emerging gonococcal resistance to the quinolone group of antibiotics. In 1995 the situation with regard to QRNG in the WPR was summarised as a steady increase in the proportion of resistant isolates since 1992,[5] when very few resistant isolates were observed. The change manifest 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 also the pattern in 1996. The widespread dispersal of QRNG in the WPR was also confirmed by the data from Cambodia, where 53% of isolates were QRNG. It should be remembered that quinolone resistance is chromosomally mediated, and levels of resistance increase incrementally due to a number of complementary alterations in the organism. The first clinically manifest resistance observed was at a low MIC level and was accommodated by increasing the recommended dose of antimicrobial administered. These strains, where identified, were those classified as ‘less susceptible’ in Table 2. Subsequently, strains with higher MICs were detected and these were not amenable to therapy with currently available quinolones, even with higher dose regimens. These isolates are shown in Table 2 as the ‘resistant’ group. In 1996, one particular feature has been the increase or maintenance of high numbers of strains with fully developed quinolone resistance.

Some interest remains in the extent and type of resistance to the penicillins. The decrease in the previously high levels of PPNG in centres such as Hong Kong has been noted previously,[9] and the continuing increase in PPNG in Vietnam also continued. The clinical usefulness of this group of antimicrobials has decreased significantly in the WPR, but this group of agents was still used effectively in a number of specific settings.

There was no resistance detected to the later generation cephalosporins and little to the injectable agent spectinomycin. Significant levels of spectinomycin resistance were recorded in the region some years ago, but only sporadic resistance is now observed and in very few isolates. The inappropriate use of antimicrobials in the informal health sector has been a contributor to the development of antibiotic resistance in the past. In theory at least, the availability of oral third generation cephalosporins increases the chances of inappropriate use. For these reasons continuing surveillance of these antimicrobials is needed, and is of greater importance now that the usefulness of the quinolones is rapidly declining.

As tetracyclines must be administered as a multiple dose treatment for gonorrhoea, they are not a recommended therapy for compliance reasons. However, a particular form of high level plasmid mediated tetracycline resistant *Neisseria gonorrhoea*, TRNG, has been recognised for a number of years, and the programme has monitored the spread of TRNG in the region. Considerable regional variation in the distribution of TRNG was again noted. Singapore, Malaysia and Vietnam continue to have high numbers of TRNG and the same pattern was revealed in Cambodia.

The trend towards a decrease in susceptibility of gonococci to various antimicrobials in the WPR has now been observed over a number of years, and 1996 saw a continuation of this shift. This situation poses additional problems for successful treatment of gonococcal disease in the region.

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An outbreak of hepatitis A associated with a spa pool

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Introduction

The Victorian Infectious Diseases Unit received three notifications of hepatitis A between 17 and 20 October 1997 from a general practitioner in the eastern suburbs of Melbourne. The three cases were all young males who attended the same primary school, but were also members of the local junior football club. An earlier case notified was also a member of the football club, but attended a different school. Active surveillance was initiated through the club and the affected schools.

Methods

Using the National Health and Medical Research Council (NHMRC) case definition (anti-HAV IgM positive or demonstration of a clinical case of hepatitis, and epidemiologically linked to a serologically confirmed case), seven cases in six families were identified. All cases were young males (age range 8 to 15 years) and dates of onset ranged from 31 August to 13 October (Figure 1).

Using a standard questionnaire that elicited data on potential sources of infection including food and water, it was found that all cases had attended a presentation at the football club on 31 August 1997. Families attending the presentation brought their own food, although sausages were cooked on a public barbecue and canned drinks were served.

After the presentation, all the cases attended a private function at one of the case's homes. Food and drinks were shared, and all of the cases used a spa pool. At this private function the index case felt ill and left early; his illness was subsequently confirmed serologically as hepatitis A. Excluding the case and his two siblings, 27 other children and adolescents and an unknown number of adults attended the function. Of these, 17 were males ranging in age from 8 to 16 years, and 10 were females ranging in age from 3 to 17 years. Some males including the index case, but none of the females, used the spa pool. Whilst in the pool, 'whale spitting' was performed, in which mouthfuls of spa water were spat in a projectile fashion.

Discussion

Six of the 17 young males became ill with hepatitis A. None of the adults or young females became ill. It is believed the gender difference in cases of hepatitis A observed after this private function is best explained by the hypothesis that hepatitis A virus was shed by the index case whilst in the spa pool, and subsequently ingested by other participants, all male, who became secondary cases. The break in notifications observed after the index case on 31 August (Figure 1) is consistent with the known incubation period for hepatitis A. Other modes of transmission such as sharing of food

Figure 1. Notifications of hepatitis A, by week of onset