Antimicrobial Susceptibility of Neisseria gonorrhoeae Isolates From Three Caribbean Countries: Trinidad, Guyana, and St. Vincent

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Background: The percentage of *Neisseria gonorrhoeae* isolates resistant to antimicrobial agents commonly used for treatment is unknown in many Caribbean countries.

Goal: To determine the antimicrobial susceptibility of N gonorrhoeae isolates from Trinidad (144 isolates), Guyana (70 isolates), and St. Vincent (68 isolates) so baseline data can be established for further studies, and to assist in establishing effective treatment guidelines.

Study Design: Consecutive urethral and endocervical specimens from several clinics were collected and identified as N gonorrhoeae. Isolates of N gonorrhoeae were tested for their susceptibility to penicillin, tetracycline, ceftriaxone, ciprofloxacin, spectinomycin, and azithromycin. The presumptive identification of penicillinase-producing N gonorrhoeae and/or tetracycline-resistant N gonorrhoeae isolates based on MIC was confirmed by plasmid and tetM content analysis.

Results: High percentages of penicillin and/or tetracycline resistance were observed in *N gonorrhoeae* isolates from Guyana (92.9%), St. Vincent (44.1%), and Trinidad (42.4%). Isolates from all three countries were susceptible to ceftriaxone, ciprofloxacin, and spectinomycin. One penicillinase-producing *N gonorrhoeae*/tetracycline-resistant *N gonorrhoeae* from Guyana had an MIC of 0.5 μ g/l to ciprofloxacin. This and nine other isolates from Guyana also were resistant to azithromycin (defined as MIC \geq 2.0 μ g/ml) as well as penicillin and tetracycline. A reduced susception

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tibility to azithromycin was displayed by 16% of the isolates from St. Vincent and 72% of the isolates from Guyana (MIC, 0.25–1.0 μ g/ml). Most penicillinase-producing N gonorrhoeae isolates carried Africa-type plasmids (61/90), with 28 of 90 having Toronto-type plasmids and a single isolate carrying an Asia-type plasmid. The *tet*M determinant in tetracycline-resistant N gonorrhoeae isolates was predominantly of the Dutch type (68/91).

Conclusions: The high prevalence of *N gonorrhoeae* isolates from 3 of 21 English- and Dutch-speaking Caricom countries in the Caribbean with either plasmid-mediated or chromosomal resistance to penicillin and tetracycline supports international observations that these drugs should not be used to treat gonococcal infections. The detection of isolates with reduced susceptibility to drugs such as azithromycin, which currently are recommended for treatment in the region, attest to the importance of the continued monitoring of gonococcal antimicrobial susceptibility for the maintenance of effective treatment guidelines.

THE PROPORTION OF *Neisseria gonorrhoeae* isolates that are resistant to antimicrobials has increased worldwide.^{1–5} Resistant gonococcal strains have been reported sporadically from the Caribbean Basin, where gonorrhea remains an important source of morbidity.^{6–9} Therefore, laboratory-based surveillance of the antimicrobial susceptibility of circulating gonococci is a key component in gonorrhea programs.^{2,3}

Despite certain regional differences, protracted worldwide trends of gonococcal resistance to antibiotics include high percentages of isolates with plasmid-mediated resistance to penicillin (penicillinase-producing *N gonorrhoeae* [PPNG]), tetracycline (tetracycline-resistant *N*

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gonorrhoeae [TRNG]), or both (PP/TRNG).^{2–4,10} In addition, gonococcal isolates also may carry chromosomal resistance to penicillin, tetracycline, and other antibiotics, either singly or in combination.^{2,5} Consequently, neither penicillin nor tetracycline have been recommended for the treatment of gonococcal infections for well over a decade.

The current antibiotics recommended for the treatment of *N* gonorrhoeae by the World Health Organization (WHO) and various individual countries include thirdgeneration cephalosporins, fluoroquinolones, and spectinomycin.^{11–13} Most strains of *N* gonorrhoeae remain susceptible to third-generation cephalosporins. However, fluoroquinolone-resistant isolates have been increasingly reported worldwide.^{2,14–19} Spectinomycin-resistant *N* gonorrhoeae isolates continue to be sporadically isolated worldwide as well.^{3–5} Recently, a disturbing study from China¹⁹ reported gonococcal resistance to several drugs currently recommended for treatment. Ceftriaxone-resistant bacteria accounted for 16.5% of the isolates tested, whereas 11.1% of the isolates were resistant to spectinomycin and 59.3% to ciprofloxacin.

In the Caribbean region, most studies describing the prevailing antimicrobial susceptibility of N gonorrhoeae isolates have been reported mainly in local publications or regional conferences. Various reports, primarily covering different years in the early 1990s, indicate that high percentages of isolates have exhibited both chromosomal and plasmid-mediated resistance to penicillin in St. Lucia (10-11%),²⁰ Suriname (18-76%),²¹ Barbados (44-72%),²² Jamaica (11.2-62.9%),^{8,23} and Puerto Rico (7.5%).²⁴ Countries in the Caribbean region often report high percentages of tetracycline-resistant isolates as well. For example, during different years, 4% to 54% of the isolates in Barbados were reported as resistant to tetracycline.²² Also, in Jamaica, 32% to 74.2% of the isolates were resistant to this antibiotic.8,23 Despite evidence of widespread resistance to penicillin and tetracycline, these antibiotics still were being used to treat gonococcal infections in some Caribbean regions.

The CARICOM countries comprise 21 English- and Dutch-speaking countries in the Caribbean region with agreements between them relating to health and other issues. The Caribbean Epidemiology Center (CAREC), based in Port-of-Spain, Trinidad, acts as a public health reference center for these countries. In this study, susceptibility to penicillin, tetracycline, ciprofloxacin, azithromycin, and ceftriaxone was analyzed in isolates of *N gonorrhoeae* from three CARICOM countries. Guyana and St. Vincent have not previously published baseline data on gonococcal susceptibility. The data from Trinidad were generated to confirm and extend preliminary baseline screening data.⁹

Methods

Isolation, Growth, and Identification of Neisseria gonorrhoeae Isolates

Isolates were collected initially in different clinics where presumptive identifications were carried out on the basis of Gram stain, colony morphology, and oxidase testing.²⁵ The isolates were stored at -70 °C in brain heart infusion broth (Difco, Detroit, MI) with 20% glycerol and then shipped to CAREC. Subsequently, N gonorrhoeae were grown either on modified Thayer Martin medium or GC Medium Base (Difco) containing 1% Kellogg's defined supplement and incubated at 35 °C for 18 to 24 hours in a humid environment with 5% CO₂. The identity of the isolates was reconfirmed at CAREC. At the same time, β -lactamase testing and antimicrobial susceptibility testing for isolates from Trinidad were performed.25 Thereafter, the isolates were forwarded to the Coordinating Center for the Gonococcal Antimicrobial Surveillance Program (GASP) in the Americas and the Caribbean in Ottawa for determination of the minimum inhibitory concentration (MIC), plasmid content, and *tet*M type.

Altogether, 294 patients attending the Georgetown Hospital STD Clinic in Guyana during 1994 and 1995 were screened. The positivity rate was 86/175 for men and 22/119 for women. Of the 108 consecutive isolates collected, 70 were available for further antimicrobial susceptibility testing, reflecting the difficulty in transporting these strains to remote sites. In addition, 76 consecutive N gonorrhoeae isolates were collected from patients attending sexually transmitted disease (STD) clinics in St. Vincent during 1996, and 68 were recovered for antimicrobial susceptibility testing. In Trinidad, 1502 patients (929 women and 573 men) were screened in seven STD clinics from May to November 1992, and 518 isolates were recovered. On the basis of the initial, local, antimicrobial susceptibility testing results,9 all the Trinidadian isolates initially classified as resistant to penicillin, tetracycline, or other antibiotics, and 20% of the susceptible isolates were sent to the GASP-Ottawa Center for confirmation of the MIC and resistance phenotype. Of the 161 isolates shipped, 144 were viable. Nevertheless, and fortuitously, the ratio of resistant to sensitive isolates was maintained.

Antimicrobial Susceptibility Testing and Plasmid and tetM Content Analysis

The MICs were determined for penicillin (Wyeth-Ayerst Canada Inc., St. Laurent, QC), tetracycline (Pfizer Canada Inc., Pte Claire, QC), ciprofloxacin (Bayer Inc., Etobicoke, ON), ceftriaxone (Hoffman-LaRoche, Mississauga, ON), spectinomycin (Upjohn Co. of Canada, Don Mills, ON), and azithromycin (Pfizer Canada Inc.). These studies were conducted in duplicate by the agar dilution method using GC medium base (Difco) containing 1% Kellogg's defined supplement and serial twofold dilutions of antibiotic. The meth-

Country		N gonorrhoeae Isolates, n (%)								
	No. of isolates tested, n (%)	Susceptible	TRNG	PPNG	PP/TRNG	PPNG/CMTR	CMTR	CMRNG		
Trinidad	144 (100)	83 (57.6)	16 (11.1)	4 (2.8)	6 (4.2)	16 (11.1)	16 (11.1)	3 (2.1)		
Guyana	70 (100)	5 (7.1)	14 (20)	3 (4.3)	40 (57.1)	8 (11.4)	0	0		
St. Vincent Total	68 (100) 282	38 (55.9) 126 (44.7)	13 (19.1) 43 (15.2)	1 (1.5) 8 (2.8)	2 (2.9) 48 (17.0)	10 (14.7) 34 (12.1)	4 (5.9) 20 (7.1)	0 3 (1.1)		

TABLE 1. Susceptibility of Neisseria gonorrhoeae Isolates to Penicillin and Tetracycline

TRNG = tetracycline-resistant *N* gonorrhoeae; PPNG = penicillinase-producing *N* gonorrhoeae; PP/TRNG = PPNG and TRNG; CMTR = chromosomally mediated tetracycline resistance; CMRNG = chromosomally resistant to multiple antibiotics.

ods and inoculum (10⁴ cfu/ml) were those recommended by the National Committee for Clinical Laboratory Standards (NCCLS).²⁶ Control strains included WHO III, WHO V, WHO VII, and ATCC 49226.²⁶

The MIC interpretive criteria recommended by NCCLS were used for each antibiotic.²⁶ The MIC was defined as the concentration of antibiotic completely inhibiting growth.26 Isolates were classified as chromosomally resistant to multiple antibiotics (i.e., CMRNG) if their MICs for both penicillin and tetracycline were 2 μ g/ml or more (these isolates could be resistant also to other antibiotics), and if they were not classified as either TRNG (i.e., MIC $\geq 16 \ \mu g/ml$) or PPNG (i.e., β-lactamase-producing). If isolates were not PPNG and their MICs were 2 μ g/ml or more, they were classified as having chromosomal resistance to penicillin (i.e., CMPR). If the MICs of non-TRNG isolates were 2 to 8 μ g/ml, they were regarded as carrying chromosomally mediated resistance to tetracycline (i.e., CMTR). Although breakpoints have not been established for third-generation cephalosporins, isolates were considered susceptible if ceftriaxone MICs were 0.25 μ g/ml or less.²⁶ Isolates with an MIC of 1 µg/ml or more were considered resistant to ciprofloxacin.²⁶ Although breakpoints describing resistance to azithromycin have not yet been established, the published data suggest that values of 0.25 to 1 μ g/ml describe decreased susceptibility, and that values $\geq 2 \ \mu g/ml$ denote resistance.^{27–32} Therefore, an MIC of 2 μ g/ml or more was used to classify resistance to azithromycin.

Plasmid profile analysis and *tet*M typing were performed to confirm the presumptive identification of isolates as PPNG

and/or TRNG on the basis of MIC tests, as described previously.³³⁻³⁵

Results

Susceptibility to Penicillin

Penicillinase-producing isolates were the predominant source of penicillin resistance in Guyana and St. Vincent. In Guyana, 72.8% of 70 isolates were PPNG (11 PPNG and 40 PP/TRNG; Table 1). In St. Vincent 19.1% of 68 isolates were PPNG (11 PPNG and 2 PP/TRNG; Table 1). No chromosomal resistance to penicillin was detected in either Guyana or St Vincent, although it is understood that the high penicillin MICs of PPNG isolates may mask chromosomal resistance. In Trinidad, 29 of the 144 isolates tested (20.1%) were resistant to penicillin. Of these 29 isolates, 26 (89.6%) were penicillinaseproducing, including 20 PPNG and 6 PP/TRNG (Table 1), and 3 were CMRNG. Because Trinidad submitted only a portion of all the isolates collected initially (i.e., all the resistant isolates and 20% of the susceptible isolates), the actual percentage of penicillin-resistant isolates from the original sample was about 6% (29/508).

Susceptibility to Tetracycline

All three countries had high percentages of tetracyclineresistant isolates. In Trinidad, chromosomal and/or plasmidmediated resistance to tetracycline was observed in 57 of 144 isolates (Table 1). This represented 39.6% of the isolates

TABLE 2. Plasmid and tetM Content of Isolates From Trinidad, Guyana, and St. Vincent

Country		No. of Isolates With Plasmid and/or tetM Type												
	PPNG				PP/TRNG	TRNG								
	Toronto	Africa	Total	African/Dutch	African/American	Asian/Dutch	Total	Dutch	American	Total				
Trinidad	11	9	20	5	1	0	6	16	0	16				
Guyana	6	5	11	23	17	0	40	10	4	14				
St. Vincent	11	0	11	1	0	1	2	12	1	13				
Total	28	14	42	29	18	1	48	38	5	43				

PPNG = penicillinase-producing Neisseria gonorrhoeae; PP/TRNG = PPNG and TRNG; TRNG = tetracycline-resistant N gonorrhoeae.

	Ceftriaxone			Ciprofloxacin			Spectinomycin			Azitromycin		
Country	MIC Range*	MIC ₉₀ S	MIC ₉₀ R	MIC Range	MIC ₉₀ S	MIC ₉₀ R	MIC Range	MIC ₉₀ S	MIC ₉₀ R	MIC Range	MIC ₉₀ S	MIC ₉₀ R
Trinidad Guyana St. Vincent	0.0005–0.032 0.002–0.016 0.00025–0.016	0 0 0	0.02 0.02 0.02	0.002-0.063 0.004-0.5 [†] 0.002-0.032	0 0 0	0.03 0.02 0.02	ND [‡] 0.125–16.0 8–32	ND 16 16	ND 16 16	ND 0.063–8 [‡] 0.032–1	ND 0.5 0.25	ND 2 0.5

TABLE 3. Susceptibility of Neisseria gonorrhoeae Isolates to Ceftriaxone, Ciprofloxacin, Spectinomycin, and Azithromycin

*MICs in µg/ml.

[†]One isolate had an MIC of 0.5 μ g/ml.

[‡]Eight isolates had an MIC of 2 μ g/ml and 2 isolates had an MIC of 8 μ g/ml.

S = susceptible to penicillin and/or tetracycline; R = resistant to penicillin and/or tetracycline; ND = not done.

submitted for the current study, but approximately 11% of the isolates initially screened. Of these isolates, 22 (38.6%) carried plasmid-mediated resistance (16 TRNG and 6 PP/TRNG; Table 2), whereas chromosomally mediated resistance (3 CM-RNG, 32 CMTR) was observed in 61.4% of the isolates. Of the CMTR isolates from Trinidad, 16 were also PPNG (Table 1). In Guyana, 62 of 70 isolates (88.6%) were tetracycline resistant, and 54 of these isolates (87.1%) were TRNG (40 PP/TRNG and 14 TRNG; Table 1). Eight isolates from Guyana were chromosomally resistant to tetracycline (i.e., CMTR) and also PPNG (Table 1). Of 68 isolates from St. Vincent, 29 (42.6%) were resistant and 15 (51.7%) TRNG. Of the tetracycline-resistant isolates from St. Vincent, 12 were PPNG (2 PP/TRNG and 10 PPNG and CMTR; Table 1).

The total burden of resistance to penicillin and/or tetracycline in isolates tested from Guyana was 92.9% (65/70). Of the isolates from St. Vincent, 44.1% (30/68) were resistant to one or both of these antibiotics (Table 1). In the case of isolates from Trinidad submitted for confirmatory testing, 42.4% (61/144) were resistant to one or both antibiotics, representing approximately 12% of the original number of isolates screened (a slight underestimate given that some strains did not survive transport or revival).

The identification of isolates as PPNG and TRNG based on MIC was confirmed by plasmid content and *tet*M analysis of all the isolates (Table 2). Of the 42 PPNG non-TRNG isolates, 28 carried Toronto-type plasmids (3.05 MDa). The remaining 14 PPNG carried Africa-type plasmids (3.2 MDa). Conversely, 47 of 48 PP/TRNG isolates carried the Africa-type plasmid (Table 2) and 1 carried an Asia-type plasmid (4.4. MDa). Most *tet*M determinants (68 of 91) were of the Dutch type (38 of 43 TRNG and 30 of 48 PP/TRNG; Table 2), whereas the American-type *tet*M determinant was found in 5 TRNG and 18 of 48 PP/TRNG.

Susceptibility to Spectinomycin, Ceftriaxone, Ciprofloxacin, and Azithromycin

All the isolates from Trinidad, Guyana and St. Vincent were susceptible to ceftriaxone (MIC ranges: Trinidad, 0.0005–0.032 μ g/ml; Guyana, 0.002 - 0.016 μ g/ml; and St. Vincent 0.00025–0.16 μ g/ml; Table 3). Except for one PP/TRNG isolate from Guyana with decreased susceptibility to ciprofloxacin (MIC, 0.5 μ g/ml), isolates from all three countries were susceptible to this antibiotic (MIC range, 0.002–0.063 μ g/ml). All the isolates from St. Vincent and Guyana were also susceptible to spectinomycin (Table 3).

A comparison of the MIC_{90} of ceftriaxone, ciprofloxacin, spectinomycin, and azithromycin for isolates classified as susceptible or resistant to penicillin, tetracycline, or both is summarized in Table 3. Most penicillin- and tetracycline-resistant strains had two- to fourfold higher MICs for ceftriaxone, azithromycin, and ciprofloxacin than their susceptible counterparts (Table 3). There was no difference in their MICs for spectinomycin.

As shown in Table 4, 10 isolates from Guyana were resistant to azithromycin. Nine of these isolates were PPNG, and one carried reduced susceptibility to penicillin. Eight of the azithromycin-resistant isolates from Guyana displayed

TABLE 4. Susceptibility of Isolates from Guyana and St. Vincent to Azithromycin*

Country	No. (Cumulative %) Isolates With MICs											
	0.032 n (C%)	0.063 n (C%)	0.125 n (C%)	0.25 n (C%)	0.5 n (C%)	1 n (C%)	2 n (C%)	4 n (C%)	8 n (C%)			
Guyana St. Vincent	1 (1.5)	1 (1.4) 4 (7.5)	8 (13.0) 45 (74.6)	48 (82.6) 6 (83.6)	2 (85.5) 9 (97)	0 2 (100)	8 (97.1)	0	2 (100)			

*Azithromycin MICs of isolates from Trinidad were not determined. C% = cumulative percentage.

chromosomal resistance to tetracycline, and the two other isolates were TRNG: one with an American-type and one with a Dutch-type *tet*M determinant. The PP/TRNG isolate with reduced susceptibility to ciprofloxacin, mentioned earlier, was also resistant to azithromycin. A further 50 (72%) isolates from Guyana displayed MICs for azithromycin in the range 0.25 - 0.5 μ g/ml. In St. Vincent, 17 of 68 isolates had reduced susceptibility to azithromycin (Table 4).

Discussion

The main purpose for undertaking the surveillance of the antimicrobial susceptibility of *N gonorrhoeae* is to inform public health planners and physicians of trends in resistance so they can recommend effective antimicrobial regimens for the treatment of gonococcal diseases. In many developing countries, the absence of appropriate financial and human resources, as well as a variety of technical challenges, limits the possibility of periodically monitoring the antimicrobial susceptibility of gonococcal isolates.

To improve national STD programs, the CARICOM countries have developed protocols for a laboratory-based surveillance program for gonococcal antimicrobial susceptibility. This program is linked to the broader regional Gonococcal Antimicrobial Surveillance Program (GASP) in the Americas and the Caribbean. Regrettably, there is not yet a systematic, periodic collection of *N gonorrhoeae* isolates in the region. Additionally, both the regional surveillance programs and the broader GASP program have been restricted in their scope and periodicity by capricious underfunding.

The current retrospective study was designed to generate and recover information on the antimicrobial susceptibility of *N gonorrhoeae* isolates in three CARICOM countries. In doing so, a database has been created that will serve as a baseline for future studies, providing a rational basis for better treatment guideline recommendations.

The high prevalence of both plasmid-mediated and chromosomally-mediated resistance to penicillin and tetracycline in isolates of *N gonorrhoeae* from Trinidad, Guyana, and St. Vincent precludes the use of these antibiotics for the treatment of gonococcal infections.^{3,4} The frequency of tetracycline-resistant strains found in these countries, particularly in Guyana (77.1%), was unusually high. Only a few countries (e.g., Singapore with 63.8% and Portugal with 52.2%) report such high percentages of TRNG.^{4,36}

A study of centers in the United States reported that 0% to 30.4% of isolates were TRNG.¹⁷ In Canada, TRNG increased overall from 2.3% of reported gonorrhea cases in 1990 to a peak of approximately 20% of reported cases in 1995 (Ng and Dillon, manuscript in preparation). In Uruguay, 4% of the isolates tested between 1989 and 1994 were reported to be TRNG.³⁷ It is notable also that most of the TRNG isolates from Guyana were PP/TRNG (57.1%). High

percentages (47.4%) of PP/TRNG also have been reported from Jamaica.⁸ The percentage of PP/TRNG isolates in Canada was reported as 20% of TRNG tested as early as 1989,^{38,39} whereas in the United States, PP/TRNG isolates remained below 4% of the isolates tested between 1988 and 1998.⁴⁰

In the current study, one fourth of the TRNG isolates carried the American-type *tet*M determinant.^{34,35} This differs from other studies in Latin America, which found that most or all isolates carried a Dutch-type *tet*M determinant.^{37,41}

A 1988 report suggested that PPNG was common in coastal South America, with hyperendemic foci on the continent's western coast. In ports along the Pacific ocean, 35% of the isolates were PPNG, as were 8% of the isolates in certain ports along the Atlantic.42 A report from Uruguay showed that 54% of 213 isolates collected between 1989 and 1994 were β -lactamase positive, and that this proportion rose to 58% of the isolates tested between 1994 and 1997.37,43 In 1989, the prevalence of PPNG was 60% in Honduras⁴⁴ and 78% in Nicaragua.⁴⁵ A study in Jamaica during 1990-1991 reported that 58.6% of the isolates were PPNG.8 In the Bahamas, more than 70% of the gonococcal isolates have been PPNG since 1992 (L. Everingham, personal communication, February 1994). A multicenter study in 1990 also reported very high percentages of penicillinaseproducing isolates in Antigua (90.3% of 31 isolates) and Dominica (60% of 20 isolates; P. Prabhakar, unpublished data). Suriname reported a high percentage of PPNG isolates (76% in 1993 and 54% in 1994).²¹ In Barbados, the percentage of *β*-lactamase-producing gonococci rose from 30% in 1990 to 50% in 1994.22 A report from Puerto Rico indicated that the percentage of PPNG between 1982 and 1994 is approximately 50% of the isolates.46

Because the proportion of isolates resistant to penicillin and tetracycline reported from around the world is high, it has long been established that these agents should no longer be used for treatment.11 Regrettably, in many developing countries, these two drugs continue to be used for a number of reasons. In the absence of reliable data on treatment failure, the assumption is made that these drugs remain effective. Furthermore, in developing countries, the low cost of traditional antibiotics such as penicillin and tetracycline is sometimes given as the reason why these drugs are purchased in bulk for the treatment of gonococcal disease instead of more expensive but effective drugs. The ready availability of these drugs over the counter in pharmacies and their black market sale in other venues also account for their continued use. This indicates that, under circumstances in which it is highly unlikely that antibiotics will be treated as controlled substances, simple education programs on appropriate therapies, directed both to consumers and the pharmacists serving them, might be beneficial.

The current international recommended therapies for gonorrhea include fluoroquinolone drugs (e.g., ciprofloxacin), third-generation cephalosporins (e.g., ceftriaxone or cefixime), and spectinomycin.11,12 Gonococcal isolates from Trinidad, Guyana, and St. Vincent were susceptible to these drugs, although there is an indication that susceptibility to ciprofloxacin should be monitored closely given the resistance to fluoroquinolones reported from countries in the Western Pacific and elsewhere.^{15–19} In 1992, the recommended treatment regimens for N gonorrhoeae in Trinidad were spectinomycin and ceftriaxone. However, at the time of the current study, the treatment recommended in Guyana for uncomplicated gonorrhea was amoxicillin with probenecid or tetracycline. As a result of the findings from this study, recommendations for the treatment of these infections in Guyana were changed to ceftriaxone and spectinomycin. The current recommended treatment for uncomplicated gonococcal infections in St. Vincent is ceftriaxone. At the time when the gonococcal strains for the current study were collected, ciprofloxacin was considered too expensive for federally funded STD programs in many Caribbean countries, although this antimicrobial agent is now used extensively by physicians in the private sector.

Currently, azithromycin, a modified macrolide active against both N gonorrhoeae and Chlamydia trachomatis, is commonly recommended for the treatment of coexisting chlamydial infections in some countries, and for the primary treatment of gonococcal infections in some Latin American countries.13,28 Gonococcal resistance to azithromycin has been reported already,27,29 and cross-resistance between azithromycin and erythromycin has been documented.30 The azithromycin-resistant isolates reported from Guyana and those with decreased susceptibility reported from St. Vincent in this study foreshadow a potential problem. Because azithromycin is not used commonly in Guyana, azithromycin-resistant isolates may have been selected because of selective pressures exerted through the more common use of erythromycin to treat other types of infection. Furthermore, the true prevalence of azithromycin-resistant isolates may in fact be underestimated because breakpoints correlated with treatment failures have not been established.

One goal of the GASP program in the Americas is to improve the laboratory-based surveillance of antimicrobial susceptibility in Latin America and the Caribbean by ensuring data comparability through standardized methods, by encouraging periodic or ongoing surveillance, and by encouraging better, more complete regional reporting. These activities should be reflected ultimately in the implementation of effective treatment guidelines in each country. The current study has established baseline data in three countries, allowing allowed better-informed decisions to be made regarding the treatment of gonococcal infections. This study should be followed with sustained antimicrobial surveillance programs in the region, coupled with a more comprehensive epidemiologic analysis.

References

- Backman M, Jacobson K, Ringertz S. The virgin population of *Neisseria gonorrhoeae* in Stockholm has decreased, and antimicrobial resistance is increasing. Genitourin Med 1995; 71:234–238.
- Dillon JR, Pagotto F. Importance of drug resistance in gonococci: from mechanisms to monitoring. Curr Opin Infect Dis 1999; 12:35–40.
- Ison CA, Dillon JR, Tapsall JW. The epidemiology of global antibiotic resistance among *Neisseria gonorrhoeae* and *Haemophilus ducreyi*. Lancet 1998; 351(suppl III):8–11.
- Tapsall JW. Antimicrobial resistance in gonococci: WHO Western Pacific region, 1995. Comm Dis Intel 1996; 20:425–428.
- Fox KK, Wittington WL, Levine WC, et al. Gonorrhea in the United States, 1981–1996: demographic and geographic trends. Sex Transm Dis 1998; 25:386–396.
- Pan Am Health Organization. AIDS/HIV and STD Annual Surveillance Report for the Region of the Americas–1992. Washington DC: Pan American Health Organization 1994; 109:42–45.
- King SD, Brathwaite AR, Dillon JR. Treatment of gonorrhoea and susceptibility to antimicrobials of PPNG and non-PPNG strains in Jamaica. Genitourin Med 1987; 63:365–370.
- Knapp JS, Brathwaite AR, Hinds A, Duncan W, Rice RJ. Plasmidmediated antimicrobial resistance in *Neisseria gonorrhoeae* in Kingston, Jamaica, 1990–1991. Sex Transm Dis 1995; 22:155–159.
- Swanston WH, Fimls A, Mahabir MB, Prabhakar P, Basraj S, George J. Antibiotic susceptibility of *Neisseria gonorrhoeae* in Trinidad and Tobago. West Ind Med J 1997; 46:107–110.
- Trees DL, Fakile Y, Neal SW, Knapp JS. Prevalence and *tetM* subtype of tetracycline-resistant *Neisseria gonorrhoeae* in Ohio, 1994. Sex Transm Dis 2000; 27:46–48.
- Moran JS, Levine WC. Drugs of choice for treatment of uncomplicated gonococcal infections. Clin Infect Dis 1995; 20(suppl 1):S47–S65.
- Centers for Disease Control and Prevention (CDC). Guidelines for treatment of sexually transmitted diseases: gonococcal infection. MMWR Morb Mortal Wkly Rep 1998; 47:59–69.
- Division of STD Prevention and Control, Health Protection Branch, Health Canada. Gonococcal Infection. In: Canadian STD Guidelines. 1998 ed. Division of STD Prevention and Control, Health Protection Branch, Health Canada, Ottawa, ON. 1998:115–124.
- Knapp JS, Fox KK, Trees DL, Whittington WL. Fluoroquinolone resistance in *Neisseria gonorrhoeae*. Emerg Infect Dis 1997; 3:33– 39.
- Tapsall JW, Phillips EA, Shultz TR. Quinolone-resistant *Neisseria* gonorrhoeae isolated in Sydney, Australia, 1991–1995. Sex Transm Dis 1996; 23:425–428.
- Knapp JS, Mesola VP, Neal SW, et al. Molecular epidemiology in 1994 of *Neisseria gonorrhoeae* in Manila and Cebu city, Republic of Philippines. Sex Transm Dis 1997; 24:2–10.
- Fox KK, Knapp JS, Holmes KK, et al. Antimicrobial resistance in Neisseria gonorrhoeae in the United States, 1988–1994: the emergence of decreased susceptibility to the fluoroquinolones. J Infect Dis 1997; 175:1396–1403.
- Harnett N, Brown S, Riley G, et al. Analysis of *Neisseria gonorrhoeae* in Ontario, Canada, with decreased susceptibility to quinolones by pulsed-field gel electrophoresis, auxotyping, serotyping, and plasmid content. J Med Microbiol 1997; 46:383–390.
- Li GM, Chen Q, Wang SC. Resistance of *Neisseria gonorrhoeae* epidemic strains to antibiotics. Sex Transm Dis 2000; 27:115–118.
- King S, Grandison-Didier M, Scott N, et al. Status of cultured STDs in St. Lucia. Caribb Lab Action News 1993; 3:6–7.
- Sadal S. Antibiotic resistance of *Neisseria gonorrhoeae* in Suriname. Presented at the XI Meeting of the International Society for STD Research; August 27–30, 1995; New Orleans, LA; 237.
- Levett PN. Antibiotic sensitivity of *Neisseria gonorrhoeae* isolates in Barbados: longitudinal surveillance 1990–1994. West Ind Med J 1995; 44:130–132.
- King SD, Brathwaite AR, Dillon JR. Treatment of gonorrhoea and susceptibility to antimicrobials of PPNG and non-PPNG strains in Jamaica. Genitourin Med 1987; 63:365–370.
- 24. Kouri YH, Gonzalez L, Perez M, et al. Effect of penicillin and spectinomycin given for urethritis and cervicitis with *Neisseria gon*-

orrhoeae: high prevalence of penicillin-resistant isolates. Genitourin Med. 1989; 65:342–346.

- Knapp JS, Rice RJ. *Neisseria* and *Branhamella*. In: Baron EJ, Pfaller MA, Tenover FC, Yolken RH, eds. Manual of Clinical Microbiology. 6th ed. Washington DC: ASM Press, 1995:324–340.
- 26. National Committee for Clinical Laboratory Standards. Approved Standard M100-S9. Performance Standards for Antimicrobial Susceptibility Testing. Ninth Informational Supplement. Wayne, PA: National Committee for Clinical Laboratory Standards, 1999.
- Tapsall JW, Shultz TR, Limnios EA, et al. Failure of azithromycin therapy in gonorrhea and discorrelation with laboratory test parameters. Sex Transm Dis 1998; 25:505–508.
- Zarantonelli L, Borthagaray G, Lee EH, Shafer WM. Decreased azithromycin susceptibility of *Neisseria gonorrhoeae* due to mtrR mutations. Antimicrob Agents Chemother 1999; 43:2468–2472.
- Ehret JM, Nims LJ, Judson FN. A clinical isolate of *Neisseria gonor-rhoeae* with in vitro resistance to erythromycin and decreased susceptibility to azithromycin. Sex Transm Dis 1996; 23:270–272.
- Young H, Moyes A, McMillan A. Azithromycin and erythromycin resistant *Neisseria gonorrhoeae* following treatment with azithromycin. Int J STD AIDS 1997; 8:299–302.
- Mehaffey PC, Shannon DP, Barrett MS, Jones RN. Evaluation of in vitro spectra of activity to azithromycin, clarithromycin, and erythromycin tested against strains of *Neisseria gonorrhoeae* by reference agar dilution, disk diffusion, and E test methods. J Clin Microbiol 1996; 34:479–481.
- 32. Ohye R, Lee V, Whiticar P, et al. Fluoroquinolone resistance in *Neisseria gonorrhoeae*, Hawaii, 1999, and decreased susceptibility to azithromycin in *N. gonorrhoeae*, Missouri, 1999. MMWR Morb Mortal Wkly Rep 2000; 49:833–837.
- Pagotto F, Aman A-T, Ng L-K, Yeung K-H, Brett M, Dillon J-AR. Sequence analysis of the family of penicillinase-producing plasmids of *Neisseria gonorrhoeae*. Plasmid 2000; 43:24–34.
- Ison CA, Tekki N, Gill MJ. Detection of the *tetM* determinant in Neisseria gonorrhoeae. Sex Transm Dis 1993; 20:329–333.
- Xia M, Pang Y, Roberts MC. Detection of two groups of 25.2 Mda tetM plasmids by polymerase chain reaction of the downstream region. Mol Cell Probes 1995; 9:327–332.

- Ferreira E, Louro D, Gomes JP, Catry MA, Vaz Pato MV. High-level tetracycline-resistant *Neisseria gonorrhoeae* isolated in Portugal. Pathol Biol 1997; 45:371–375.
- Marquez C, Minsheng X, Borthagaray G, et al. The first molecular characterization of tetracycline-resistant *Neisseria gonorrhoeae* from Uruguay. J Antimicrob Chemother 1996; 37:839–841.
- Dillon JR, Carballo M. Molecular epidemiology and novel combinations of auxotype, serovar, and plasmid content in tetracyclineresistant *Neisseria gonorrhoeae* isolated in Canada. Can J Microbiol 1990; 36:64–67.
- Bureau of HIV/AIDS, STD, TB. Sexually transmitted diseases in Canada: 1996 surveillance report. Laboratory Centre for Disease Control, Health Canada. 1997. Available at: http://www.hc-sc.gc.ca/ hpb/lcdc. Accessed Summer 2000.
- 40. Available at: http://www.cdc.gov.ncidod.dastir/gedir/resist/annrep98.
- Dillon JR, Rubabaza J-PA, Benzaken AS, et al. Reduced susceptibility to azithromycin and high percentages of penicillin and tetracycline resistance in *Neisseria gonorrhoeae* isolates from Manaus, Brazil, 1998. Sex Transm Dis 2001; 28:521–526.
- Escamilla J, Bourgeois AL, Gardiner CH, Kilpatrick ME. Penicillinase-producing *Neisseria gonorrhoeae* in various seaport cities of Latin America. Sex Transm Dis 1988; 15:141–143.
- 43. Borthagaray G, Marquez C, Acevedo A, Zarantonelli I. Gonococcal Antimicrobial Susceptibility Surveillance in Uruguay. Presented at the XII Meeting of the International Society for STD Research; October 19–27, 1997; Seville, Spain; 85.
- Venegas VS, Villafranca P, Madrid JP, Cosenza H, Bygdeman S. Gonorrhoea and urogenital chlamydial infection in female prostitutes in Tegucigalpa, Honduras. Int J STD AIDS 1991; 2:195– 199.
- Castro I, Bergeron MG, Chamberland S. Characterization of multiresistant strains of *Neisseria gonorrhoeae* isolated in Nicaragua. Sex Transm Dis 1993; 20:314–320.
- 46. Torres-Bauza LJ. Characterization of Penicillinase-Producing *Neisse-ria gonorrhoeae* From Puerto Rico, 1982–1994. Presented at the XI Meeting of the International Society for STD Research; August 27–30, 1995; New Orleans, Louisiana; 234.