Correlates of Gonococcal Infection and of Antimicrobial-Resistant *Neisseria gonorrhoeae* among Female Sex Workers, Republic of the Philippines, 1996–1997

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From 1994 to 1997, the proportion of *Neisseria gonorrhoeae* highly resistant to ciprofloxacin (MIC ⩾4 μg/mL) increased substantially among female sex workers (FSWs) in the Philippines. Among 1499 Filipina FSWs, we evaluated factors associated with gonococcal infection and with gonococcal antimicrobial resistance. By multivariate analysis, gonococcal infection was associated with sex with a new client, self-prescribed prophylactic antimicrobial use, work in a brothel, and inconsistent condom use and was negatively associated with registration status and vaginal hygiene practices. Factors associated with ciprofloxacin-resistant gonococci included: marital status, living alone, duration of sex work, and clinic site. Further, gonococci highly resistant to ciprofloxacin were isolated from 10 (11.5%) of 87 FSWs reporting self-prescribed antimicrobial use versus 44 (3.4%) of 1295 reporting no antimicrobial use ($P < .001$). Self-prescribed prophylactic antimicrobial use and inconsistent condom use could be important factors in the continued emergence of gonococcal antimicrobial resistance in the Philippines.

From 1988 to 1996, several reports from the Republic of the Philippines described decreased susceptibility of isolates of *Neisseria gonorrhoeae* to various antimicrobials, including quinolones [1–3]. From 1994 to 1996–1997, the percentage of gonococci highly resistant to ciprofloxacin (MIC ⩾4 μg/mL) increased suddenly from 9% to 49% among female sex workers (FSWs) in Metropolitan Manila and Cebu City [4]. A 1994 survey in the Philippines found that 31% of FSWs had used antimicrobials, predominantly penicillin and ampicillin, as prophylaxis in the previous 2 weeks [5]. Goh et al. [6] found prophylactic use of penicillin associated with penicillinase-production among gonococci isolated from FSWs in Singapore; Zenilman et al. [7] made similar observations in sexually transmitted disease (STD) clinic patients in Dade County, Florida.

To assess prophylactic use of antimicrobials and other potential risk factors for infection with antimicrobial-resistant gonococci, we surveyed FSWs undergoing screening for uncomplicated gonorrhea and compared survey results with gonococcal culture results and antimicrobial susceptibilities of gonococcal isolates.

Methods

From August 1996 to January 1997, FSWs attending three social hygiene clinics in metropolitan Manila and one social hygiene clinic in Cebu City were recruited for a trial of treatment of uncomplicated gonorrhea. All women underwent a standardized face-to-face interview, during which data on demographic and employment characteristics and practices regarding sexual behavior, reproductive health, medication-taking, and vaginal hygiene were obtained. FSWs were classified into "registered" or "unregistered" on the basis of current registration status with the social hygiene clinic.

All women had endocervical samples cultured on modified Thayer-Martin media for *N. gonorrhoeae.* Isolates identified by Gram's stain and oxidase reaction were confirmed by sugar utilization tests and then stored in trypticase-soy broth containing 20% glycerol at −70°C until transport to the University of Washington. β-lactamase production was determined by standard methods. Agar dilution was performed in Seattle to determine susceptibilities of 86 gonococci to ciprofloxacin, penicillin, and tetracycline according to guidelines of the National Committee for Clinical Laboratory Standards. For 27 isolates not available for testing at University of Washington, the E test performed in the Philippines was used to determine susceptibilities to ciprofloxacin (AB Biodisk, Solan, Sweden). Isolates were categorized into four levels of susceptibility, based on the MIC of ciprofloxacin: susceptible (⩽.064

Received 27 May 1998; revised 26 November 1998.

Informed consent was obtained from study participants.

Financial support: NIH STD Cooperative Research Center (AI-31448); unrestricted research grant from Bristol-Myers Squibb Corporation; International Core of the University of Washington Center for AIDS Research (NIH, AI-27757); United States Agency for International Development (USAID) as part of the Family Health International's AIDS Control and Prevention Project (HRN-5972-C-K00-4001-00).

The content of this report does not necessarily reflect the views or policies of USAID.

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The Journal of Infectious Diseases 1999; 179:729–33

0022-1899/99/7903-0031$02.00

g/mL), decreased susceptibility (0.125–0.5 μg/mL), low-level resistance (≥0.64–<4.0 μg/mL), and high-level resistance (≥4.0 μg/mL).

Characteristics of women were compared by gonococcal infection status, and for those infected, by level of gonococcal susceptibility to ciprofloxacin, using the *t* test, χ^2 test, and Fisher's exact test. All variables in the univariate analyses that significantly distinguished between the groups at $P < .10$ were used to develop a multivariate model using backwards conditional stepwise logistic regression (SPSS 8.0 for Windows, SPSS, Chicago). From this model, adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were calculated.

Results

During the study period, 1499 women were interviewed and had cervical samples cultured for *N. gonorrhoeae.* One-third used no birth control, and one-fifth reported an STD in the past month. FSWs reported an average of 4 commercial sex partners, including 2.5 new commercial sex partners, during the week before the study. Gonococcal infection prevalence varied by clinic site: in metropolitan Manila (3 sites), 27 (13.1%) of 206, 12 (5.1%) of 237, and 19 (8.8%) of 215; in Cebu, 55 (6.5%) of 841 ($P < .01$ by χ^2 2×4 table). Gonococcal infection prevalence was 4-fold greater among unregistered (19%) than among registered (4.5%) FSWs ($P < .001$).

Condom use was reported with only 28% of boyfriends, 60% of regular clients, and 92% of new clients during the previous week. Reported condom use with husbands, boyfriends, and regular clients was not significantly associated with risk of gonorrhea. Among 881 women with a new client in the past month, however, the prevalence of gonococcal infection among women who reported 100% condom use was 57 (8%) of 718, versus 38 (23%) of 163 among women with new clients who reported <100% condom use ($P < .001$). Table 1 shows the number and percent of patients infected with *N. gonorrhoeae* by various characteristics of patients. Factors associated with gonococcal infection included younger age, not having a boyfriend or husband, having less than a high school education, reporting inconsistent (<100%) condom use with new clients, not being registered with a social hygiene clinic, working in a brothel, having larger numbers of regular or new clients, using prophylactic antimicrobials in the past month, using self-prescribed prophylactic antimicrobials during the past week, and not practicing vaginal hygiene.

Some of these risk factors were interrelated; therefore, a multivariate analysis was done, adjusting for all of the above variables. The multivariate model showed gonococcal infection significantly associated with having had sex with a new client in the past month (aOR, 3.8; CI, 2.7–5.5), using self-prescribed prophylactic antimicrobials in the past week (aOR, 2.5; CI, 1.8–3.7), working in a brothel (aOR, 1.8; CI, 1.4–2.5), inconsistent condom use by new clients (aOR, 1.7; CI, 1.3–2.2), practicing vaginal hygiene (aOR, 0.5; CI, 0.4–0.6), and being registered with a social hygiene clinic (aOR, 0.4; CI, 0.3–0.5).

MICs of antimicrobials determined by the E test correlated well with MICs determined by agar dilution ($r = 0.75$). Gonococci with decreased susceptibility or resistance to ciprofloxacin (MIC ≥0.125 μg/mL) were most common among FSWs using self-prescribed prophylactic antimicrobials (85%), least common among those taking prophylactic antimicrobials prescribed by physicians (25%), and intermediate in frequency for those using no antimicrobials (75%) ($P < .05$). High-level gonococcal resistance to ciprofloxacin (MIC ≥4.0 μg/mL) was significantly associated with clinic attendees in metropolitan Manila (39 [67%] of 58) and with FSWs living alone but being married (16 [89%] of 18). In a multivariate model, correlates of high-level ciprofloxacin resistance among infected FSWs included clinic site in metropolitan Manila (aOR, 4.9; CI, 3.2–7.4) and working as a FSW <12 months (aOR, 2.4; CI, 1.5–3.7). Self-prescribed prophylactic antimicrobial use was only weakly associated with an increased risk of high-level resistance (aOR, 1.3; 95% CI, 0.7–2.5).

Figure 1 shows gonococcal prevalence by antimicrobial use and prescription source and by MIC of ciprofloxacin. Gonococci with MICs of ciprofloxacin ≥4.0 μg/mL were isolated from 10 (11.5%) of 87 FSWs reporting self-prescribed antimicrobial use versus 44 (3.4%) of 1295 reporting no antimicrobial use ($P < .001$). This difference was attributable both to increased prevalence of gonorrhea and to the slightly increased proportion of gonococci resistant to ciprofloxacin among these 87 FSWs.

Fifty-six (90%) of 62 penicillin-resistant isolates (MIC ≥2.0 μg/mL) among 86 tested produced β-lactamase. Among infected FSWs, 13 of 13 who reported use of penicillin or ampicillin in the past week were infected with penicillin-resistant gonococci, versus 5 (62%) of 8 who reported use of antimicrobials other than penicillin or ampicillin (Fisher's exact $P < .05$). Tetracycline resistance (MIC ≥2 μg/mL) was also associated with recent use of tetracycline, but the association was not statistically significant.

Discussion

This study describes risk factors for gonococcal infection and for infection with antimicrobial-resistant *N. gonorrhoeae* among a large sample of young FSWs from metropolitan Manila and Cebu City. By multivariate analysis, factors associated with gonococcal infection included sex with a new client in the past month, <100% condom use by new clients, self-prescribed prophylactic antimicrobial use, working in a brothel, not practicing vaginal hygiene, and being unregistered with a social hygiene clinic. Factors associated with gonococcal resistance to ciprofloxacin included being married but living alone, less work experience, and clinic site in metropolitan Manila. In addition, self-prescribed antimicrobial use was associated with a significant increase in the overall risk of infection with highly resistant gonococci. Penicillin use was associated with infection

Table 1. Prevalence of infection with *N. gonorrhoeae* by various characteristics of patients, in Manila and Cebu, the Philippines, 1996–1997.

	No. infected/total	%	*P*
Characteristics of patients, all	113/1499	8	
Demographics			
Clinic site			
Manila	58/658	9	
Cebu City	55/841	7	.12
Age			
<26 years	77/750	10	
≥26 years	36/749	5	<.001
Living alone			
Yes	99/1228	8	
No	14/271	5	.13
Husband or boyfriend			
Yes	37/639	6	
No	96/880	11	.03
Married			
Yes	22/228	10	
No	91/1271	7	.19
Education			
High school	29/627	5	
Less than high school	84/872	10	<.001
Reproductive health history			
Condom use with new clients, past month			
Always	57/718	8	
Almost always	8/42	19	
Sometimes	20/91	22	
Rarely	3/10	30	
Never	7/20	35	<.001[a]
STD during past month			
Yes	18/273	7	
No	95/1226	8	.59
Uses oral contraceptive pill only	7/154	5	
Uses no oral contraceptive pill	106/1345	8	.14
Commercial sex work history			
Registered with social hygiene clinic			
Yes	53/1189	4	
No	60/310	19	<.001
Brothel-based			
Yes	36/152	24	
No	77/1347	6	<.001
No. of regular clients during past month			
None	18/618	3	
≥1	95/881	11	<.001
No. of new clients during past week			
<2	56/1008	6	
≥2	57/491	12	<.001
Oral antimicrobial use, past month			
No	87/1208	7	
Yes, as STD treatment only	9/182	5	.26[b]
Yes, as STD prophylaxis only	14/99	14	<.05[b]
Oral antimicrobial use, past week			
No	89/1295	7	
Yes, as physician-prescribed STD treatment	3/52	6	1.0[b]
Yes, as physician-prescribed STD prophylaxis	5/65	8	.80[b]
Yes, as self-prescribed STD treatment	2/9	22	.13[b]
Yes, as self-prescribed STD prophylaxis	14/73	19	<.001[b]
Antimicrobials used during past week			
Penicillins	16/120	13	
Tetracyclines	3/40	8	
Quinolones	3/28	11	
Sulfonamides	1/8	13	
Other antimicrobials	1/8	13	.87[c]
Vaginal hygiene practices during past week			
None	56/415	13	
Toothpaste, soap, lactate, or betadine wash	52/991	5	<.001[b]
Douche	3/50	6	.13[b]
Suppository or internal cream	2/42	5	.11[b]

[a] χ^2 for trend.
[b] χ^2 test for comparison with no characteristic.
[c] Fisher's exact test for 2×5 table.

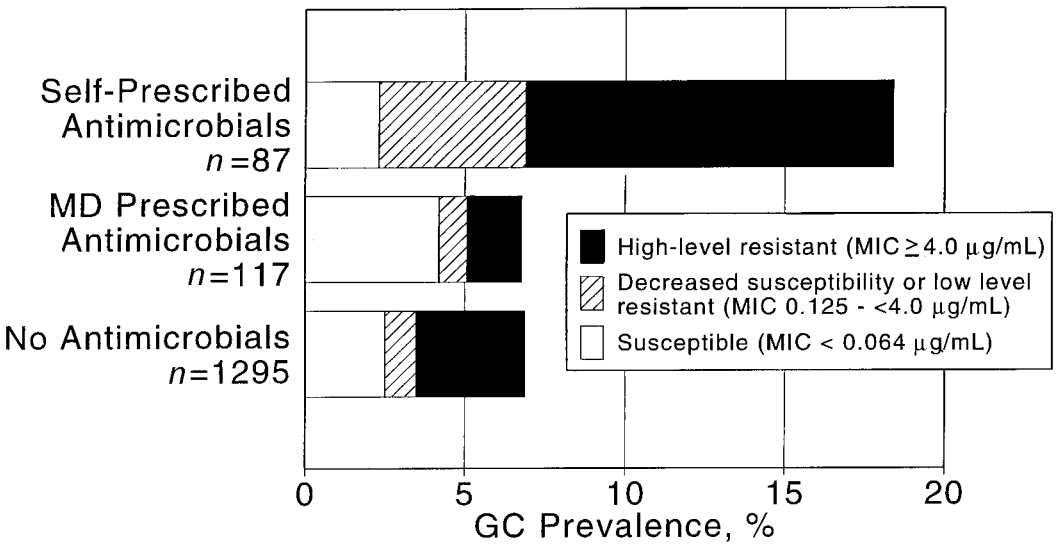

Figure 1. Gonococcal (GC) prevalence in Filipina sex workers by antimicrobial use and prescription source and level of susceptibility to ciprofloxacin, 1996–1997.

with penicillin-resistant gonococci, which were mostly β-lactamase–producing.

Reported 100% condom use by FSWs with new clients was associated with a reduced prevalence of gonococcal infection (72% reduction by unadjusted analysis, 40% by adjusted analysis). This important finding deserves emphasis, because condoms are an inexpensive and widely available method for reducing STD transmission in the Philippines. Increased condom use would decrease transmission of antimicrobial-resistant gonococci and reduce transmission of other STDs, yet condom use for human immunodeficiency virus infection/STD prevention in the Philippines has remained controversial, with opposition from the Catholic Church [8].

Our results extend previous studies demonstrating the high prevalence of prophylactic antimicrobial use among commercial sex workers and the potential contribution of this practice to the development of antimicrobial-resistant gonococci [5–7, 9]. In our current study, 14% and 19% of FSWs had used antimicrobials in the past week and month, respectively—intermediate between the 6% recently reported in Thailand [9] and the 31% previously reported in the Philippines [5]. This study further characterized the nature of antimicrobial use by reason and source of prescription. Use of self-prescribed antimicrobials was associated not only with an increased risk of gonococcal infection, but also with a >3-fold increased risk of infection with ciprofloxacin-resistant gonococci (figure 1).

The somewhat paradoxical association of self-prescribed prophylactic antimicrobial use with increased prevalence of gonorrhea persisted after adjustment for potential confounders. A suggested mechanism by which regular antimicrobial use might increase the risk of gonococcal infection is through its effect on the vaginal microenvironment. Ampicillin suppresses vaginal lactobacilli [10], and repeated use could eliminate H_2O_2-producing lactobacilli from the vagina. In a recent prospective study, the absence of such lactobacilli predicted the acquisition of gonococcal infection [11].

The observation that routine vaginal hygiene practices were associated with reduced risk of gonococcal infection could be related to previous work showing that some microbicides reduced the risk of gonococcal infection [12, 13]. Although most FSWs reported vaginal hygiene practices during the past week, douching was relatively uncommon compared with vaginal washing with household items such as toothpaste, laundry detergent, and soap, as well as with over-the-counter lactate-containing solutions. New investigations into the acceptability, safety, and effectiveness of simple, inexpensive approaches to vaginal cleansing in commercial sex are warranted.

Registration status was also associated with significantly reduced risk of gonococcal infection. Women working in entertainment establishments are required to register with a social hygiene clinic. Registered FSWs in the Philippines undergo regular gynecologic examinations that include cervical Gram's stain but not culture of specimens; this is scheduled weekly in Cebu and biweekly in metropolitan Manila. Although a recent study failed to show effectiveness of a similar control program in Lima, Peru [14], our findings suggest some effectiveness of this control program in the Philippines.

This study had several strengths and limitations. We specifically designed the study to measure antimicrobial use and personal hygiene behaviors and correlate these behaviors with infection with resistant gonococci. We consecutively enrolled women at the four social hygiene clinics. A reference laboratory

used standard methods to determine gonococcal antimicrobial resistance. The cross-sectional design of this study, however, precluded strong inferences of causality for any of the observed associations. The association of antimicrobial use and gonococcal infection is unlikely to be explained, however, primarily by gonococcal infection leading to increased antimicrobial use, since the associations were noted among prophylactic users and not among those using antimicrobials for treatment.

The first reported isolates of penicillinase-producing *N. gonorrhoeae* were in the Philippines, ultimately making penicillin-based therapy for gonococcal infection obsolete. Subsequently, the Philippines produced some of the first reports of high-level gonococcal resistance to ciprofloxacin, rendering quinolones unreliable for gonorrhea therapy in this country [1–3]. As a result of our studies, cefixime is now the recommended treatment of gonococcal infection in the Philippines [4, 15]. To prevent emergence of gonococcal resistance to yet another important class of antimicrobials in the Philippines, reducing prophylactic use of antimicrobials and increasing condom use in the commercial sex industry could be an important strategy. The role of vaginal hygiene practices in preventing gonococcal infection warrants further study.

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