MAJOR ARTICLE

Prevalence of and Associated Risk Factors for Fluoroquinolone-Resistant *Neisseria gonorrhoeae* in California, 2000–2003

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(See the editorial commentary by DeMaria on pages 804–7)

Background. Rates of fluoroquinolone-resistant *Neisseria gonorrhoeae* (QRNG) are increasing worldwide and in California.

Methods. As a supplement to established surveillance, the investigation of QRNG in California included expanded surveillance in southern California, with in-depth interviews of patients (who had QRNG during the period of January 2001–June 2002) and a cross-sectional study of patients at 4 sexually transmitted diseases clinics with gonococcal isolates that underwent susceptibility testing (for the period of July 2001–June 2002).

Results. The rate of QRNG increased from <1% in 1999 to 20.2% in the second half of 2003. The 2001–2002 expanded surveillance demonstrated that 66 (4.9%) of 1355 isolates were resistant to fluoroquinolones; the majority of these infections occurred after August 2001. Cross-sectional analysis of 952 patients with gonorrhea revealed that the prevalence of QRNG varied geographically during 2001–2002, with the highest rate being in southern California (8.9%) and the lowest being in San Francisco (3.6%). The QRNG prevalence was 8.6% among men who have sex with men (MSM), 5.1% among heterosexual men, and 4.3% among women. Although risk factors for QRNG varied by clinic, multivariate analysis demonstrated independent associations with race/ethnicity, recent antibiotic use, and MSM.

Conclusions. The emergence and spread of QRNG in California appeared to evolve from sporadic importation to endemic transmission among both MSM and heterosexuals. Monitoring of both the prevalence of and risk factors for QRNG infections is critical for making treatment recommendations and for developing interventions to interrupt transmission.

Neisseria gonorrhoeae infection is the second most commonly reported communicable disease in the United States [1]. *N. gonorrhoeae* infects urethral, cervical, rectal, and pharyngeal sites; causes myriad complications; and increases the risk of HIV transmission [2]. *N. gonorrhoeae* develops antimicrobial resistance through a variety of molecular mechanisms [3–6]. Penicillinase-producing *N. gonorrhoeae* was first identified in the United States in 1976, and by 1987, penicillin was no longer recommended for treatment of gonorrhea [7, 8]. Resistance to tetracyclines developed throughout the 1970s and 1980s. High rates of fluoroquinolone-resistant *N. gonorrhoeae* (QRNG) have been identified in southeast Asia and the Pacific Islands, including Hawaii [9]. Before 2000, only sporadic cases of QRNG infection had been reported in the continental United States [10–13].

The Centers for Disease Control and Prevention (CDC) recommends antibiotic treatment for gonorrhea

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Received 9 March 2005; accepted 10 May 2005; electronically published 12 August 2005.

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Clinical Infectious Diseases 2005; 41:795–803

1058-4838/2005/4106-0005$15.00

that includes cephalosporins (cefixime and ceftriaxone) and fluoroquinolones (ciprofloxacin, ofloxacin, and levofloxacin) [14]. According to the CDC, fluoroquinolone regimens can be used with confidence to treat gonorrhea, as long as QRNG strains constitute <1% of isolated gonococcal strains [15]. In 1999, the prevalence of QRNG was <0.5% nationwide [16].

From July through September 2000, six QRNG cases were identified at a sexually transmitted diseases (STD) clinic in Orange County, California, an increase in prevalence from the previous 5 years, during which only 1 case had been identified at this clinic [17]. To identify risk factors for infection, to monitor the prevalence of QRNG, and to develop evidence-based gonorrhea treatment recommendations for California, a multiple-phase investigation was launched.

METHODS

Gonococcal Isolate Surveillance Project (GISP). GISP is the US national surveillance system established in 1986 to monitor gonococcal resistance. As part of GISP, sentinel site STD clinics in northern California (San Francisco) and southern California (Long Beach, Orange County, and San Diego) submit up to 25 gonococcal isolates recovered from male urethral culture specimens each month. Antimicrobial susceptibility testing is performed by GISP Regional Laboratories, and the results are confirmed by the CDC using standard agar dilution methods [18]. Resistance to ciprofloxacin is defined as an MIC of $\geqslant$1.0 μg/mL, intermediate resistance is defined as an MIC of 0.125–0.5 μg/mL, and susceptibility is defined as an MIC of $\leqslant$0.06 μg/mL [19]. QRNG was defined as *N. gonorrhoeae* that is resistant to either ciprofloxacin or ofloxacin, according to nationally recognized susceptibility test interpretations [20, 21].

Expanded antimicrobial resistance surveillance and case series, Southern California, January 2001 through June 2002. In addition to ongoing GISP surveillance in the southern California (Long Beach, Orange County, and San Diego) STD clinics, local public health laboratories in Orange County and San Diego conducted susceptibility testing of all gonococcal isolates from STD clinic patients, including isolates from women, from nonurethral sites, and in Orange County, from incarcerated patients. In addition, the Kaiser Permanente Southern California regional laboratory, which serves >90 clinic sites in 6 southern California counties (Kern, Los Angeles, Orange, Riverside, San Bernardino, and San Diego counties) tested all gonococcal isolates submitted during the period of February through April 2001. Disk diffusion methods were used to determine susceptibility to ciprofloxacin by the Orange County public health and Kaiser Permanente Southern California regional laboratories and to determine susceptibility to ofloxacin by the San Diego County public health laboratory [20, 21]. Fluoroquinolone resistance was confirmed by subsequent testing at a GISP Regional Laboratory using agar dilution methods described above. Patients infected with QRNG were interviewed in person or via telephone by trained disease investigators. Demographic characteristics, medical and STD history, and symptom data were abstracted from medical records.

Cross-sectional study, Northern and Southern California, July 2001 through June 2002. To determine the prevalence of QRNG infection among different risk groups and risk factors for acquisition of QRNG infection, we conducted a medical record review of male and female patients with viable gonococcal isolates from any anatomic site tested for fluoroquinolone resistance at any of the 4 California GISP STD clinics (in Long Beach, Orange County, San Diego, and San Francisco) during the period of July 2001 through June 2002. The San Francisco GISP site (in northern California) was included to determine whether the prevalence of and risk factors for QRNG infection differed across the state.

Statistical methods. All data were analyzed using SAS statistical software (SAS Institute) [22]. Men who reported having only male sex partners or having both male and female sex partners were categorized as men who have sex with men (MSM); men who reported having only female sex partners were categorized as men who have sex with women only (MSW). Fisher's exact tests were used to calculate *P* values, and standard asymptotic methods were used to calculate 95% CIs.

For the cross-sectional data analysis, prevalence ratios (PRs) were calculated to compare different demographic and risk categories with regard to the prevalence of QRNG infection. To control for possible confounding or effect-modifying factors, a logistic regression model using backward stepwise elimination was created. The model was restricted to male subjects and included the following variables: GISP clinic site, age, race/ethnicity (white, Asian/Pacific Islander, or other), sexual orientation, HIV infection status, whether there had been multiple partners in prior 6 months, symptoms at site of infection, antibiotic use in prior month, commercial sex exposure, and injection drug use, as well as an interaction term between sexual orientation and clinic. Female subjects were excluded because no cases of QRNG infection were reported from 2 clinics, and travel history was excluded because data on it were reliably collected at only 1 test site (San Diego). Separate models for MSM and MSW were also created with the same set of variables to determine independent risk factors within these groups.

As disease control and surveillance activities, the components of this investigation were determined by CDC to be nonresearch public health activities that did not require approval from the CDC's Institutional Review Board.

RESULTS

After a peak rate of 445 cases of gonorrhea per 100,000 persons in California in 1985, the number of gonorrhea cases steadily decreased, to a nadir of 55.5 cases per 100,000 persons in 1997.

Rates fluctuated between 1997 and 1999 and increased steadily through 2003. In 2003, 25,754 cases were reported, corresponding to a rate of 71.7 cases per 100,000 persons [23]. According to GISP surveillance data, the rate of QRNG infection in the California STD clinics increased steadily from <1% in the first half of 2000 to 20.2% in last half of 2003 (figure 1). The 6 QRNG-infected GISP patients (all of whom were male) identified during July through September 2000 at the Orange County STD clinic reported multiple risks: all were born outside of the United States, 2 were Asian, 5 were heterosexual, and 3 reported commercial sex exposure. None reported antibiotic use. A common source exposure was not identified.

Expanded surveillance and case series. From January 2001 through June 2002, in southern California, isolates from a total of 1355 persons were tested, and 66 cases of QRNG infection (4.9%) were identified. QRNG prevalence varied by test site, as follows: San Diego, 33 (6.7%) of 491 cases; Orange County, 16 (4.8%) of 332; Long Beach, 12 (7.6%) of 159; and Kaiser Permanente Southern California regional laboratory, 5 (1.3%) of 373. Approximately one-half (52%) of the isolates were tested as part of ongoing GISP surveillance. Among these 703 GISP isolates, 39 (5.6%) were QRNG. Most cases of QRNG infection (80%) were identified after August 2001.

Sixty-two case patients with QRNG infection (94%) were male; the median age was 32.5 years (range, 18–62 years). Thirty-nine patients were non-Hispanic white, 13 were Hispanic, 5 were Asian/Pacific Islander, 6 were African American, and 3 had other or unknown race. Forty patients (61%) were born in the United States; the regions of origin for non–US-born patients included Central/South America, Asia, Europe, and Canada. Among the 62 men, 48 (77%) reported that they had sex with men only, 7 (11%) reported that they had sex with women only, 5 (8.1%) reported that they had both male and female sex partners, and 2 refused to disclose this information. All 4 female case patients reported that they had male sex partners.

Antibiotic use within the 3 months before diagnosis of gonorrhea was reported by 29% of patients with QRNG; 6 patients reported that they had taken fluoroquinolones. Travel outside of the continental United States within 3 months before gonorrhea diagnosis was reported by 40% of case patients. Eighty percent of subjects reported that they had multiple sex partners in the prior 6 months. Although commercial sex exposure was reported by only 4 case patients, 1 patient was an MSM sex worker identified in San Diego in September 2001 who reported that he had >40 partners in the previous 3 months. Among the 43 patients with data on HIV infection, 16 (37%) were HIV positive, all of whom were MSM.

Cross-sectional study. A total of 952 patients who attended 1 of the 4 California GISP STD clinic sites (Long Beach, Orange County, San Diego, and San Francisco) during the period of July 2001 through June 2002 had viable gonococcal isolates that were tested for fluoroquinolone resistance; 5 patients infected with nonviable isolates were excluded. Of these 952 patients, 70 (7.4%) were infected with QRNG, 45 (4.7%) were infected with isolates that had intermediate susceptibility to fluoroquinolones, and 837 (87.9%) were infected with susceptible isolates. Forty (89%) of the 45 intermediate isolates were from the San Francisco STD Clinic.

The southern California STD clinics (Long Beach, Orange County, and San Diego) had a combined QRNG prevalence of 8.9%, whereas QRNG constituted a smaller proportion (3.6%)

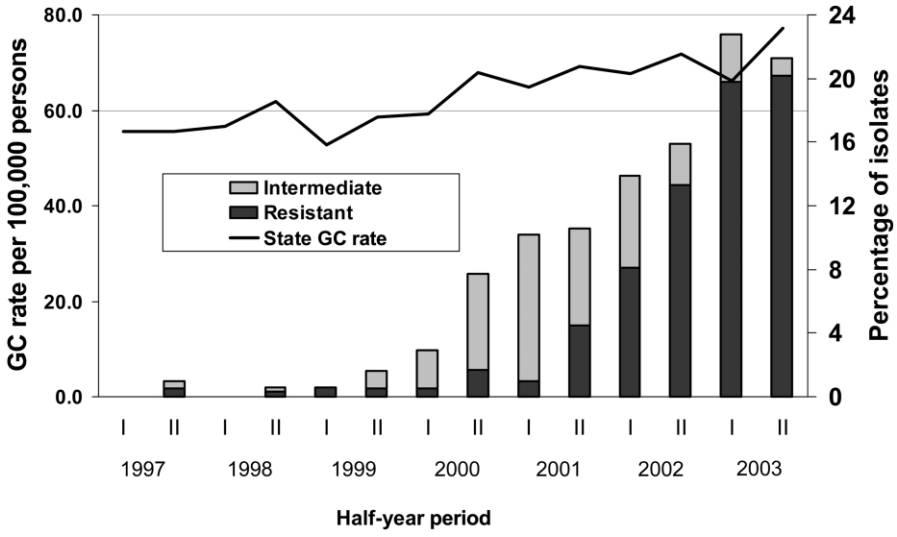

Figure 1. Percentage of *Neisseria gonorrhoeae* isolates that had intermediate resistance or were resistant to ciprofloxacin identified in California Gonococcal Isolate Surveillance Project, as well as statewide gonorrhea (GC) incidence, in half-year increments, 1997–2003.

Table 1. Prevalence of fluoroquinolone-resistant *Neisseria gonorrhoeae* (QRNG) strains, stratified by clinic location and patient characteristics, cross-sectional survey, July 2001 through June 2002.

Characteristic	Gonococcal Isolate Surveillance Project clinic location				
	Orange County	Long Beach	San Diego	San Francisco	All clinics combined
All patients	230 (7.0)	110 (10.9)	331 (9.7)	281 (3.6)	952 (7.4)
Age, years					
12–24	87 (6)	27 (7)	79 (5)	36 (0)	229 (4.8)
25–34	82 (9)	46 (9)	152 (9)	93 (0)	373 (6.7)
35–65	61 (7)	37 (16)	100 (14)	152 (7)	350 (9.7)
Race/ethnicity					
White	70 (11)	30 (17)	181 (14)	142 (2)	423 (9.9)
Hispanic	108 (4)	25 (12)	47 (2)	25 (12)	205 (5.4)
Black	25 (4)	51 (8)	79 (4)	91 (2)	246 (4.1)
Asian/Pacific Islander	15 (20)	3 (0)	6 (17)	17 (12)	41 (15)
Other/unknown	12 (0)	1 (0)	18 (6)	6 (0)	37 (2.7)
Sexual orientation group					
WSM	20 (5)	2 (50)	24 (0)	1 (0)	47 (4.3)
MSM	138 (7)	50 (18)	220 (14)	198 (2)	606 (8.6)
MSW	69 (7)	58 (3)	87 (2)	79 (8)	293 (5.1)
Multiple partners[a]					
Yes	159 (7)	74 (12)	240 (10)	230 (4)	703 (7.4)
No	63 (5)	34 (9)	91 (9)	42 (2)	230 (6.5)
Unknown	8 (25)	2 (0)	0	9 (11)	19 (16)
Commercial sex[b]					
Yes	17 (6)	3 (33)	28 (14)	20 (20)	68 (15)
No	202 (7)	95 (11)	299 (9)	163 (2)	759 (7.4)
Unknown	11 (0)	12 (8)	4 (0)	98 (3)	125 (3.2)
HIV status					
Positive	19 (21)	16 (18)	60 (22)	80 (5)	175 (13.7)
Negative	0	71 (11)	220 (7)	158 (2)	449 (6.0)
Unknown	211 (6)	23 (4)	51 (6)	43 (7)	328 (5.8)
Travel history[c]					
Yes	0	1 (100)	17 (35)	2 (0)	20 (35)
No	0	3 (100)	98 (14)	63 (2)	164 (11.0)
Unknown	230 (7)	106 (8)	216 (6)	216 (4)	768 (5.9)
Antibiotic use[c]					
Yes	6 (17)	3 (67)	18 (33)	5 (20)	32 (31)
No	199 (6)	105 (10)	304 (9)	242 (4)	850 (6.6)
Unknown	25 (16)	2 (0)	9 (0)	34 (0)	70 (5.7)
Injection drug use[b]					
Yes	9 (11)	6 (33)	18 (22)	14 (0)	47 (15)
No	211 (7)	97 (10)	309 (9)	170 (4)	787 (7.5)
Unknown	10 (0)	7 (0)	4 (0)	97 (4)	118 (3.4)
Symptoms[d]					
Yes	157 (6)	101 (9)	252 (9)	273 (4)	783 (6.5)
No	71 (9)	9 (33)	79 (11)	8 (0)	167 (10.8)
Unknown	2 (50)	0	0	0	2 (50)

NOTE. Data are no. of patients tested (% infected with QRNG). Data on 6 persons were excluded (4 men were missing information on sexual orientation, and 2 subjects were male-to-female transgender persons). MSM, men who have sex with men; MSW, men who have sex with women only; WSM, women who have sex with men.

[a] More than 1 partner in the previous 6 months.

[b] Exposure in previous 6–12 months.

[c] Exposure in previous month.

[d] Symptoms at site of infection (e.g., urethral discharge or dysuria in a patient with urethral infection). Patients with no symptoms and those who presented with symptoms at an anatomic site determined not to be infected were considered to not have symptoms.

Table 2. Risk factors for acquisition of fluoroquinolone-resistant *Neisseria gonorrhoeae* infection, California, July 2001 through June 2002.

Characteristic	No. of patients (n = 952)	Crude PR (95% CI)	P
GISP site			
Orange County	230	2.0 (0.9–4.2)	.11
Long Beach	110	3.1 (1.4–6.9)	.007
San Diego	331	2.7 (1.4–5.4)	.004
San Francisco	281	1.0	
Age, years			
12–24	229	1.0	
25–34	373	1.4 (0.7–2.8)	.38
35–65	350	2.0 (1.1–3.9)	.04
Race/ethnicity			
White	423	1.0	
Asian/Pacific Islander	41	1.5 (0.7–3.3)	.42
All others	488	0.5 (0.3–0.8)	.002
Sexual orientation group			
MSW	293	1.0	
MSM	606	1.7 (1.0–2.9)	.08
WSM	47	0.8 (0.2–3.5)	1.0
Multiple partners[a]			
Yes	703	1.1 (0.7–2.0)	.77
No	230	1.0	
Commercial sex[b]			
Yes	68	2.0 (1.0–3.7)	.06
No	759	1.0	
HIV infection status			
Positive	175	2.3 (1.4–3.8)	.003
Negative	449	1.0	
Travel history[c]			
Yes	17	2.5 (1.0–5.5)	.08
No	98	1.0	
Antibiotic use			
Yes	32	4.7 (2.7–8.4)	<.001
No	850	1.0	
Injection drug use[b]			
Yes	47	2.0 (1.0–4.1)	.09
No	787	1.0	
Symptoms[d]			
Yes	783	0.6 (0.4–1.0)	.07
No	167	1.0	

NOTE. Standard asymptotic statistical tests were used to calculate 95% CIs. Fisher's exact tests were used to calculate P values. Patients with missing data were excluded from this analysis. GISP, California Gonococcal Isolate Surveillance; MSM, men who have sex with men; MSW, men who have sex with women only; PR, prevalence ratio; WSM, women who have sex with men.

[a] More than 1 partner in the previous 6 months.

[b] Exposure in previous 6–12 months.

[c] Exposure in previous month. For travel history, only data for San Diego were included.

[d] At site of infection (e.g., urethral discharge or dysuria in a patient with urethral infection). Patients with no symptoms and those presenting with symptoms at an anatomic site determined not to be infected were considered to not have symptoms.

of San Francisco isolates. Most (94.5%) isolates were from male patients; of the 47 isolates from female patients, 2 (4.3%) were QRNG. The majority of isolates (64%) were from MSM, who had a prevalence of QRNG infection of 8.6% (table 1). Heterosexual men had a prevalence of QRNG infection of 5.1%. Although reported travel history outside the continental United States and antibiotic use in the previous month were relatively uncommon, the prevalence of QRNG infection was high for patients who reported these activities (35% and 31%, respectively). Travel destinations included Europe, Central and South America, and Canada. Of the 32 patients who reported recent antibiotic use, only 4 reported fluoroquinolone use.

Groups with increased prevalence of QRNG varied among the different GISP sites. Unlike the southern California clinic sites, the prevalence of QRNG was low among white patients in San Francisco. At both San Diego and Long Beach, the prevalence was higher among MSM than among MSW (P = .003 and P = .02, respectively), whereas MSM and MSW had a similar prevalence in Orange County. In San Francisco, MSW had higher prevalence than MSM (P = .03). Most clinic sites had higher QRNG prevalence among HIV-infected patients, patients who reported antibiotic use in the prior month, patients who reported commercial sex exposure in the prior 6–12 months, patients who reported injection drug use in the prior 6–12 months, and patients who lacked symptoms at the site of infection, although the number of patients with any of these risk factors was small in any individual clinic.

Factors that were positively associated with QRNG in univariate analysis included attendance at the Long Beach or San Diego STD clinic (compared with San Francisco), age of ⩾35 years, HIV infection, and antibiotic use within the prior month (table 2). Compared with white patients, persons of other race/ethnicity (primarily black and Hispanic patients) had a significantly lower prevalence of QRNG infection. Additional factors that were associated with QRNG but that did not reach statistical significance included MSM sexual orientation, commercial sex exposure, travel outside of the continental United States or to Hawaii, injection drug use, and lack of symptoms. When this analysis was repeated excluding from the denominator persons with gonococcal isolates with intermediate susceptibility to fluoroquinolones, there were only minor differences in the calculated PRs and no important differences in statistical associations.

Findings from the multivariate modeling are shown in table 3. Because of the highly significant interaction term between sexual orientation and clinic, MSM OR estimates for each clinic with the reference category being MSW from the same clinic are presented separately. Antibiotic use within the prior month was strongly associated with QRNG, as was MSM status (compared with MSW status) at the San Diego clinic. The association

Table 3. Independent risk factors for acquisition of fluoroquinolone-resistant *Neisseria gonorrhoeae* based on multivariate logistic regression, California, July 2001 through June 2002 (n = 952).

Factor	Adjusted OR (95% CI)	*P*
Race/ethnicity		
White	Reference	
Asian	2.0 (0.7–5.9)	.2
Other/unknown	0.5 (0.3–1.0)	.05
Antibiotic use	5.3 (2.2–12.8)	.0002
MSM status, by site[a]		
Long Beach	4.1 (0.8–20.8)	.08
Orange County	0.7 (0.2–2.4)	.6
San Diego	4.6 (1.0–20.3)	.05
San Francisco	0.2 (0.04–0.6)	.01
GISP site[b]		
San Francisco	Reference	
Long Beach	0.5 (0.1–2.3)	.3
Orange County	0.8 (0.2–2.8)	.7
San Diego	0.2 (0.1–1.3)	.09

NOTE. GISP, California Gonococcal Isolate Surveillance; MSM, men who have sex with men.

[a] Reference group for each category is non-MSM at the same test site.

[b] Comparisons between GISP sites are among non-MSM.

of QRNG with MSM at the Long Beach clinic was strong and nearly reached statistical significance. In contrast, MSM at the San Francisco clinic were at significantly decreased risk for acquisition of QRNG infection. There was also an increased risk of QRNG infection among persons of Asian race/ethnicity and a decreased risk among persons of other race/ethnicity, compared with white patients.

Multivariate modeling of risk factors for QRNG among only MSM demonstrated that the 3 southern California test sites (Long Beach, Orange County, and San Diego), antibiotic use, and HIV-positive status were significantly associated with QRNG. A multivariate model that included only MSW demonstrated that older age (35–65 years) and Asian race/ethnicity approached significance in their association with QRNG.

GISP surveillance. GISP surveillance data demonstrated that the proportion of QRNG-infected patients in California STD clinics within sexual orientation groups (MSM and MSW) varied by location over time (figure 2). Although sporadic cases were detected from 1994 to 2000, QRNG rates remained at <3% for all groups. In the second half of 2001, MSM in southern California experienced an increase in QRNG infection and had the highest rate (23.7%) in 2003. In 2002, MSM in San Francisco and MSW in southern California experienced increases over the prior years. In 2003, the prevalence of QRNG infection was 20.8% among MSM in San Francisco and 16.1% among MSW in southern California. MSW in San Francisco had steady rates of >5% in 2001 and 2002, and the rate then increased to 16.5% in 2003.

DISCUSSION

California surveillance data indicate both increasing levels of QRNG and increasing rates of gonorrhea from 1999 through 2003. The cluster of QRNG cases in southern California in 2000 appeared to involve sporadic imported cases with no common source exposure. Serotype and auxotype determination confirmed that these 6 cases were microbiologically unrelated (Joan Knapp, personal communication). After August 2001, an increasing proportion of QRNG isolates were from MSM. The MSM sex worker with QRNG infection identified in San Diego in September 2001 may have played a role in the large number of cases among MSM subsequently identified in San Diego. By 2002, QRNG infection appeared to be widespread among MSM in southern California. These conclusions were supported by strain typing and molecular analysis of California QRNG isolates from 2000–2002, in which investigators found that, although there were >20 different type designations, more than one-half of the isolates belonged to the same outbreak strain, three-quarters of which were recovered from MSM, including the sex worker in San Diego [24]. On the basis of GISP surveillance through 2003, QRNG continued to increase among both MSM and heterosexuals in California.

Our finding that MSM in some southern California STD clinics were at increased risk of acquiring QRNG infection is consistent with published reports from other parts of the United States [25, 26] and the United Kingdom [27–29]. Of note, 2001 data from Hawaii demonstrated that heterosexuals were at increased risk of acquiring QRNG infection, compared with MSM [30]. These geographic and temporal differences are likely related to the role that different sexual networks play in the spread of STDs at different times and in different places.

Overuse of antibiotics has been implicated in increasing rates of antimicrobial resistance [31]. In our population, recent antibiotic use was associated with QRNG; however, only a minority of patients reported fluoroquinolone use. Similar associations with tetracycline, penicillin, and fluoroquinolone resistance have been identified in the United States and The Philippines [32–34]; however, other risk analyses have not demonstrated this association [30, 35–39]. The process of developing resistance is multifactorial, and antimicrobials used to treat infections other than STDs may well have a larger role in causing resistance in *N. gonorrhoeae* than does use of antimicrobials for gonococcal infection. Thus, the overuse of antibiotics continues to be a concern in the development of antimicrobial-resistant organisms.

Changes over time in the epidemiology of antimicrobial-resistant *N. gonorrhoeae* are not uncommon. When the prevalence of QRNG began to increase in Hawaii in 1999, most

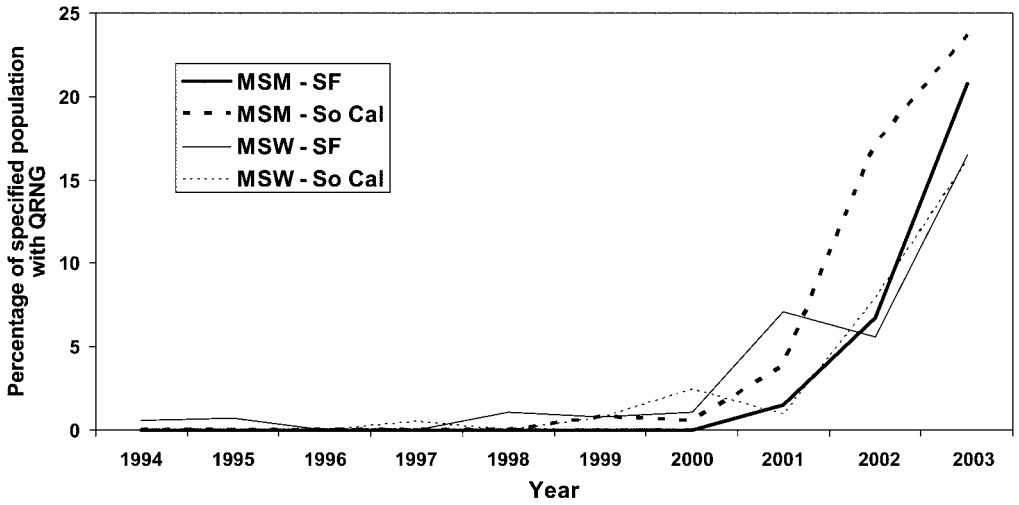

Figure 2. Proportion of patients infected with fluoroquinolone-resistant *Neisseria gonorrhoeae* (QRNG) among patients identified by California Gonococcal Isolate Surveillance (GISP) in California clinics, by sexual orientation and location, 1994–2003. MSM, men who have sex with men; MSW, men who have sex with women only; So Cal, southern California GISP sites (Long Beach, Orange County, and San Diego); SF, San Francisco.

case patients reported foreign travel [9]. As the epidemic evolved, travel history was no longer a significant risk factor, probably reflecting endemic transmission of QRNG in the population [30, 40, 41]. A similar evolution occurred in London, England, between 1997 and 2000 [42]. These epidemiologic changes necessitate continuous monitoring to ensure appropriate interventions and treatment recommendations.

The documented high rates of QRNG infection led the California Department of Health Services and the CDC to issue new guidelines for treating gonorrhea acquired in California [40, 43]. First-line treatment is now limited to 1 class of drug, cephalosporins, although alternatives include spectinomycin and azithromycin at the 2-g dose. Sentinel surveillance has identified no important resistance to cephalosporins in the United States [44]. Treatment guidelines for California did not differentiate by sexual orientation for several reasons: (1) certain populations (e.g., women and young African American persons) were not adequately sampled, even with expanded surveillance; (2) recommendation simplicity increases provider compliance; and (3) our investigation provided evidence that risk factors change in a relatively short time as QRNG strains spread into different populations.

Health care providers in other parts of the country should ask patients with gonorrhea whether they or their sex partners could have acquired the infection in an area with high rates of QRNG (e.g., California, Hawaii, other Pacific Islands, Asia, United Kingdom, or other areas with emerging endemic QRNG). Recently, the CDC recommended cephalosporins as first-line treatment for MSM with gonorrhea [26]. These new recommendations highlight the importance of ascertaining the sex of sex partners. Clinicians should remain alert to treatment failures and counsel patients to return for additional treatment if symptoms persist or recur.

There were several limitations to these investigations. First, the prevalence of and risk factors for QRNG infection in STD clinic patients with gonorrhea may not be generalizable to all patients with gonorrhea. Compared with the demographic characteristics of patients with gonorrhea throughout the state, patients with gonococcal isolates that have undergone susceptibility testing were more likely to be male, older, and non-Hispanic white race [40, 45]. Furthermore, STD clinic populations in California overrepresent MSM patients [46]. Second, small numbers of QRNG cases limited our power to detect risk factors, especially by clinic. Third, medical record data often are incomplete. In particular, travel history was generally not recorded—and perhaps not even assessed—despite current recommendations. Travel is a risk factor only when it involves sexual exposure to a person with QRNG; thus, better data are needed for precise interpretation.

With rates of QRNG infection increasing across the United States, continued surveillance and assessment of risk factors is critical to ensure a timely and effective public health response. Public health laboratories need to be supported in maintaining the capacity to culture gonorrhea and to perform antimicrobial susceptibility testing. Rapid dissemination of new treatment recommendations to clinicians is essential. Although high-level resistance to ceftriaxone and treatment failure has not been identified among *N. gonorrhoeae* isolates in the United States [44], the emergence of multidrug-resistant *N. gonorrhoeae* has been reported [47]. Furthermore, reports from China indicate the sporadic occurrence of gonococcal isolates with decreased susceptibility to ceftriaxone [48, 49]. The eventual importation

and endemic spread of these strains necessitates continued research and development of new antimicrobials and research on drug efficacy for the treatment of gonorrhea.

Acknowledgments

We thank the following people for their assistance with this investigation: Stewart Coulter, Edwin Lopez, and Jessica Frasure, STD Control Branch, California Department of Health Services, Berkeley, CA; Paul Hannah, Orange County Public Health Laboratory, Santa Ana, CA; Dawn Kiefler and Gerry Washabaugh, San Diego County Health and Human Services Agency, San Diego, CA; Helene Calvet, Mimi Lachica, City of Long Beach Department of Health and Human Services, Long Beach, CA; Lynn Fischer, Virginia Zapitz, and Sally Liska, San Francisco Department of Public Health, San Francisco, CA; Peter Kerndt, Los Angeles County Department of Health Services, Los Angeles, CA; Franklyn Judson and Josephine M. Ehret, Denver Gonococcal Isolate Surveillance Project (GISP) Regional Laboratory, Denver Health, Colorado; King K. Holmes and Wil Whittington, Seattle GISP Regional Laboratory, University of Washington, Seattle; and David L. Trees, Susan M. Conner, Hillard S. Weinstock, Stuart M. Berman, and Alesia Harvey, Division of STD Prevention, National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA.

Financial support. Centers for Disease Control and Prevention (Comprehensive STD Prevention Systems and Infertility Prevention Project Grant H25/CCH904362) and California Department of Health Services.

Potential conflicts of interest. J.D.K. receives medical research funding from Pfizer and speaking fees from King Pharmaceuticals. All other authors: no conflicts.

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