MAJOR ARTICLE

Azithromycin-Resistant Syphilis Infection: San Francisco, California, 2000–2004

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Background. The incidence of syphilis has been increasing in the United States since reaching a nadir in 2000. Several clinical trials have demonstrated that treatment with oral azithromycin may be useful for syphilis control. After reports of azithromycin treatment failures in San Francisco, we investigated the clinical and epidemiologic characteristics of patients with syphilis due to azithromycin-resistant *Treponema pallidum* infection.

Methods. We reviewed city-wide case reports and conducted molecular screening for patients seen at the San Francisco metropolitan STD clinic (San Francisco City Clinic) to identify patients who did not respond to azithromycin treatment for syphilis or who were infected with azithromycin-resistant *T. pallidum*. We conducted an epidemiologic investigation and retrospective case-control study to identify risk factors for acquiring syphilis due to azithromycin-resistant *T. pallidum*.

Results. From January 2000 through December 2004, molecular screening of 124 samples identified 46 azithromycin-resistant *T. pallidum* isolates and 72 wild-type *T. pallidum* isolates. Six instances of treatment failure were identified through record review. In total, we identified 52 case patients (one of whom had 2 episodes) and 72 control patients. All case patients were male and either gay or bisexual, and 31% (16 of 52) were infected with human immunodeficiency virus. Investigation of patient-partner links and a retrospective case-control study did not reveal a sexual network or demographic differences between cases and controls. However, 7 case patients had recently used azithromycin, compared with 1 control patient. Surveillance data demonstrated that azithromycin-resistant *T. pallidum* prevalence increased from 0% in 2000 to 56% in 2004 among syphilis cases observed at the San Francisco City Clinic.

Conclusions. Azithromycin-resistant *T. pallidum* is widespread in San Francisco. We recommend against using azithromycin for the management of syphilis in communities where macrolide-resistant *T. pallidum* is present and recommend active surveillance for resistance in sites where azithromycin is used.

Treatment of syphilis-infected patients and their sexual contacts remains an important public health challenge. After a steady decrease in the incidence of US cases during the 1990s, the Centers for Disease Control and Prevention initiated a plan in 1999 to eliminate syphilis from the United States [1]. Unfortunately, beginning in 2001, the incidence of primary and secondary (P&S) syphilis began increasing in the United States (from 2.2 cases per 100,000 population in 2001 to 2.5 cases per 100,000 population in 2003), mainly among men who have sex with men [2, 3]. San Francisco has experienced a striking increase in the number of P&S syphilis cases among men who have sex with men, from a nadir of 5 cases in 1998 to 320 cases in 2004, and now has the highest rate among US metropolitan centers (78.8 male cases per 100,000 male population) [2].

Standard therapy for treating syphilis is intramuscular injection of benzathine penicillin G, which continues to be the only treatment unequivocally recommended by the Centers for Disease Control and Prevention [4]. For penicillin-allergic patients or for those who cannot tolerate an intramuscular injection, treatment with oral doxycycline (100 mg twice daily for 14 days) has been an accepted alternative [4]. Other drugs have been studied as alternatives for syphilis treatment, including tetracycline, erythromycin, and ceftriaxone, but they require frequent dosing, prolonged treatment, or intramuscular injection [5, 6].

Received 5 May 2005; accepted 24 August 2005; electronically published 28 December 2005.

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Clinical Infectious Diseases 2006; 42:337–45

1058-4838/2006/4203-0006$15.00

Azithromycin is a macrolide antibiotic with Food and Drug Administration–approved indications for the treatment of multiple bacterial infections [7]. Macrolides are bacteriostatic drugs that bind to the 23S rRNA subunit of bacterial ribosomes and block protein synthesis. Oral azithromycin therapy has few significant adverse effects (primarily gastrointestinal upset) or interactions with other drugs, with the advantages of a long tissue half-life ($t_{1/2}$, 68 h) and excellent tissue penetration, including the CNS [8, 9].

In 1990, Stamm et al. [10] demonstrated that azithromycin inhibited in vitro protein synthesis in *Treponema pallidum,* and Lukehart et al. [11] demonstrated that azithromycin was as effective as parenteral benzathine penicillin G or oral erythromycin at treating syphilis in test rabbits. Subsequent human clinical trials demonstrated that azithromycin was effective at treating P&S syphilis [12–16] and incubating syphilis [17, 18]. Azithromycin was used extensively for syphilis control in the following 3 areas from 1994 through 2000: Rakai, Uganda [19], Vancouver, British Columbia [20], and Los Angeles, California [21]. In the Rakai study, azithromycin was shown to be equally as effective as penicillin for the treatment of P&S syphilis [19].

In addition to treatment of infected patients, another goal of syphilis-control programs is to treat sex partners of case patients to limit the spread of disease within sexual networks [1]. Azithromycin has been used successfully as patient-delivered partner therapy to treat sexual contacts of patients with chlamydial infection [22–25] and, therefore, was considered to be a safe, convenient, field- or partner-delivered therapy for syphilis control [6, 13, 15, 18]. In response to the rapidly increasing syphilis epidemic in San Francisco, the San Francisco Department of Public Health began using azithromycin as an alternative for prophylactic treatment of incubating syphilis in July 1999 and for treatment of P&S syphilis in April 2000. At the time of this investigation, the most commonly prescribed azithromycin regimens in the United States were a 1-g oral dose for incubating syphilis [17] and a 2-g oral dose for P&S syphilis [15].

Despite the recent use of azithromycin in syphilis management, macrolide-resistant *T. pallidum* had previously been identified. Clinical cases of syphilis that did not respond to treatment with the macrolide erythromycin were initially reported in the 1980s [26–28]. The first molecular confirmation of macrolide resistance in *T. pallidum* came from the Street 14 case, in which a *T. pallidum* isolate was obtained in the 1970s from a penicillin-allergic patient with secondary syphilis who did not respond to 45 days of erythromycin treatment [28]. Eight different mutations of bacterial 23S rRNA genes have been described that confer macrolide resistance by altering the site at which the drug interacts with the ribosome [29]. In 2000, the Street 14 strain was shown to contain an A-to-G base mutation in both 23S rRNA genes at cognate position A2058 [30]—the most common mutation identified in macrolide-resistant pathogens (A2058G) [29]. Most recently, we published a brief report on the molecular biology of 12 *T. pallidum* isolates containing the A2058G mutation from San Francisco and another 20 from Seattle, Baltimore, and Dublin (Ireland) from 1998–2003 [31]. A *T. pallidum* isolate with this mutation was shown to be resistant to erythromycin and azithromycin treatment in vivo using test rabbits.

This report describes the clinical characteristics of patients infected with azithromycin-resistant *T. pallidum* in San Francisco during January 2000–December 2004 and the ensuing epidemiologic investigation and retrospective case-control study.

PATIENTS AND METHODS

Informed consent was obtained from all patients before obtaining samples. The investigation met clinical study guidelines of the US Department of Health and Human Services (Centers for Disease Control and Prevention Institutional Review Board Protocol 4067 and Human Subjects Review 2003-00353) and those established by the study site (University of California, San Francisco, Institutional Review Board Protocol H9978-15437) and laboratory (University of Washington, Seattle, Institutional Review Board Protocol 98-7740).

Molecular analysis. *T. pallidum* isolates were obtained from patients visiting the San Francisco metropolitan STD clinic (San Francisco City Clinic [SFCC]) and analyzed as described elsewhere [31]. Briefly, samples obtained from suspect lesions were sent to the University of Washington, Seattle, for analysis with a mutation screening assay. Restriction-enzyme analysis of PCR amplicons allowed identification of mutant isolates, which were subsequently verified by a nested PCR procedure to confirm the presence of the mutation in *T. pallidum* DNA [31].

Case definition. During January 2000–December 2004, cases of azithromycin-resistant syphilis were defined as confirmed for patients infected with a 23S rRNA mutant *T. pallidum* isolate, as probable for patients with persistent P&S syphilis despite treatment with 2 g of azithromycin in the preceding 30 days, and as suspect for patients with a newly diagnosed case who had received 1 g of azithromycin in the preceding 60 days for prophylaxis after sexual contact with a *T. pallidum*–infected partner. Control patients were those infected with a 23S rRNA wild-type *T. pallidum* isolate.

Case finding and surveillance. Patients were identified from reports of suspected azithromycin treatment failure identified during routine public health investigations. In addition, the San Francisco City and County sexually transmitted diseases registry was reviewed to identify all patients treated for syphilis with azithromycin from January 2000 through December 2004. Treatment of patients with azithromycin was performed at the discretion of the health care professionals, and no systematic method had been used for deciding whether to use penicillin, doxycyline, or azithromycin therapy. Lastly, the 23S rRNA mu-

tation screening assay was used to screen *T. pallidum* samples. Collection of *T. pallidum* samples was attempted for all patients seen at SFCC with primary or secondary syphilis and lesions amenable to sampling (ulcers, condyloma lata, or mucous patches), but all attempts were dependent on one of the authors being present for sample collection. Because of staffing limitations, no specimens were obtained during May 2002–April 2003. Because processing of samples was time intensive (ranging from weeks to months), clinical decisions were made before results of the molecular analysis were known.

Epidemiologic investigation and case-control analysis. All patients were examined by clinicians for diagnosis, treatment, and counseling. SFCC staff in charge of syphilis control administered our standard syphilis case interview, which has questions about sex partners and behaviors associated with meeting partners (e.g., drug use and venues) during the critical exposure period. All case patient and control patient medical records and staff interview forms were reviewed, and follow-up interviews were conducted when necessary for disease control. The public-health records of all identified sex partners were reviewed for clinical diagnosis, treatment, follow-up, and identification of any additional sex partners. This process was continued for each related sexual contact until no additional contacts could be identified. As with all syphilis cases in San Francisco, a minimum of 3 attempts were made to contact patients and partners for clinical follow-up, and resolution of symptoms and serologic improvement was confirmed for all contactable persons. Data from all sources were combined to maximize the available information for performing a retrospective unmatched case-control analysis to identify common demographic or behavioral characteristics or meeting venues that might define a sexual network. Statistical analyses were performed using Epi Info, version 6 [32]. Statistical results are reported as prevalence percentages and *P* values, with use of the 2-tailed Fisher's exact test for univariate data or the χ^2 test for trend to compare $\geqslant$2 categorical variables [32].

RESULTS

During January 2000–December 2004, a total of 1308 individuals received a diagnosis of primary or secondary syphilis in San Francisco, of whom 533 (40.7%) received the diagnosis at SFCC. Of these 533 persons, 154 (28.9%) had samples obtained for molecular analysis, 118 (76.6%) of which contained amplifiable *T. pallidum* DNA. Of these 118 samples, 46 contained mutant 23S rRNA genes (from the group of confirmed case patient), and 72 had wild-type 23S rRNA genes (from the group of control patients). Six suspect or probable case patients (2, 3, 5, 7, 37, and 45) were identified solely through clinical treatment failure, because no isolates were available for molecular analysis (table 1), but they were not included in the case-control analysis (table 2). One case patient (4) was initially identified as a probable case patient after not responding to treatment, but he was subsequently confirmed by the molecular assay 9 (table 1). A subanalysis comparing the 118 individuals who were included in the case-control study with the 415 persons who received a diagnosis of primary or secondary syphilis at SFCC but were not included revealed no significant differences in age, race or ethnicity, sex, sexual orientation, or median number of sexual partners in the 90 days preceding infection (data not shown). However, patients included in the study were significantly less likely to report being HIV infected (33.9% [40 of 118]) than were those not included in the study (52.1%) ($P < .01$).

Seven case patients did not respond to initial treatment with azithromycin and were retreated with benzathine penicillin G or doxycycline. Six of these patients (2–5, 37, and 45) clinically improved after retreatment (table 1). However, patient 7 was retreated with penicillin but lost to follow-up. The other 45 case patients received either parenteral penicillin or oral doxycycline therapy at their initial clinical visit. Seven (13.5%) of 52 case patients (11, 12, 15, 16, 41, 43, and 46) reported taking 1 g of oral azithromycin for nonsyphilis-related reasons (e.g., chlamydial infection) in the 30 days preceding the onset of syphilis symptoms or diagnosis, compared with 1 (1.4%) of 72 control patients ($P < .01$). No patients taking azithromycin (1-g or 2-g doses) reported vomiting or diarrhea.

Case patients provided contact information for 89 (18.4%) of 484 sex partners. These partners either demonstrated no subsequent serologic evidence of syphilis infection or were treated with penicillin or doxycycline. Among the case patients, several (29–38, 30–7, and 41–5) reported sexual contact with other case patients during their infectious period. A single patient (18 and 34 in table 1 denote the same patient) was reinfected with azithromycin-resistant *T. pallidum* or, less likely, did not respond to intervening penicillin therapy.

The epidemic curve for the appearance of syphilis due to azithromycin-resistant *T. pallidum* in San Francisco is depicted in figure 1 and demonstrates that the majority of case patients were identified from the second quarter of 2003 onward, with prevalence rates of 4% (1 of 25 case patients) during 2000–2002, 41% (13 of 32) during 2003, and 56% (37 of 66) during 2004 (with the caveat that no samples were collected during May 2002–April 2003 because of staffing limitations). During January 2000–December 2004, staff at SFCC treated a total of 202 persons with a 2-g oral dose of azithromycin for P&S syphilis, and 616 patients and contacts were given a 1-g dose of azithromycin for incubating syphilis, for a total of 818 potentially treated persons. Although case patients in this investigation received directly observed oral azithromycin therapy, we could not confirm that all contacts given 1 g of azithromycin by SFCC staff during 2000–2004 took the medication, because

Table 1. Clinical information for patients with azithromycin treatment failures and azithromycin-resistant syphilis infection—San Francisco, 2000–2004.

	Syphilis case			23S rRNA mutation	Past Azm therapy	Sexual orientation	HIV infection	No. of sexual partners			Initial test, result				Treatment failure			
Patient	Year (quarter) of diagnosis	Definition[a]	Stage					Named	Anonymous	Initial symptom(s)	DF	RPR titer	VDRL titer	1st Rx	Interval	Test result	2nd Rx	Time of follow-up, test result
1	2001 (1)	Confirmed	Primary	Yes	…	Bisexual	+	0	2	Penile ulcer	–	…	1:2	PCN	…	…	…	3 months, NR VDRL titer
2	2002 (3)	Probable	Primary	NT	…	Gay	+	1	2	Penile ulcer	…	1:128	…	Azm 2 g	39 days	Ulcer DF+, VDRL 1:256	PCN	7 months, RPR titer 1:8
3	2002 (4)	Suspected	Primary	NT	…	Gay	–	3	0	None (treated contact)	…	NR	NR	Azm 1 g	11 days	Ulcer DF+, VDRL NR	PCN	2 months, NR VDRL titer
4	2003 (2)	Confirmed	Primary	Yes	…	Gay	+	2	98	Tongue ulcer, 0.5 cm	…	NR	1:1	Azm 2 g	18 days	Ulcer 1.5 cm, VDRL 1:8	Dox	3 months, VDRL titer 1:2
5	2003 (2)	Suspected	Secondary	NT	…	Gay	+	0	25	None (treated contact)	…	NR	NR	Azm 1 g	42 days	Rash, VDRL 1:64	PCN	3 months, WR VDRL titer
6	2003 (2)	Confirmed	Secondary	Yes	…	Gay	+	Refused	-	None (treated contact)	…	…	1:128	PCN	…	…	…	6 weeks, VDRL titer 1:64
7	2003 (2)	Suspected	Primary	NT	…	Gay	–	3	0	None (treated contact)	…	NR	…	Azm 1 g	43 days	Penile ulcer, RPR 1:16	PCN	Lost to follow-up
8	2003 (2)	Confirmed	Primary	Yes	…	Gay	+	0	5	Penile ulcer	+	…	1:1	PCN	…	…	…	3 months, NR VDRL titer
9	2003 (2)	Confirmed	Primary	Yes	…	Gay	–	1	3	Penile ulcer	+	…	1:1	PCN	…	…	…	Lost to follow-up
10	2003 (3)	Confirmed	Secondary	Yes	…	Gay	–	15	0	Rectal condyloma	…	…	1:64	PCN	…	…	…	3 months, VDRL titer 1:4
11	2003 (3)	Confirmed	Primary	Yes	5 days	Gay	+	0	3	Penile ulcer	+	…	NR	PCN	…	…	…	3 months, NR VDRL titer
12	2003 (3)	Confirmed	Primary	Yes	18 days	Gay	–	1	4	Penile ulcer	+	…	…	PCN	…	…	…	6 months, NR VDRL titer
13	2003 (4)	Confirmed	Primary	Yes	…	Gay	+	0	4	Penile ulcer	–	Stat+	WR	Dox	…	…	…	Lost to follow-up
14	2003 (4)	Confirmed	Primary	Yes	…	Bisexual	–	0	12	Penile ulcer	+	…	1:2	PCN	…	…	…	2 months, NR VDRL titer
15	2003 (4)	Confirmed	Primary	Yes	14 days	Gay	–	Refused	-	Rectal ulcer	+	…	1:1	PCN	…	…	…	1 month, NR VDRL titer
16	2003 (4)	Confirmed	Primary	Yes	30 days	Gay	–	1	4	Penile ulcer	+	Stat+	…	Dox	…	…	…	2 months, NR VDRL titer
17	2004 (1)	Confirmed	Primary	Yes	…	Gay	–	4	26	Penile ulcer	+	…	NR	Dox	…	…	…	3 months, NR VDRL titer
18[e]	2004 (1)	Confirmed	Primary	Yes	…	Gay	–	2	8	Penile ulcer	+	…	NR	PCN	…	…	…	6 months, VDRL titer 1:8
19	2004 (1)	Confirmed	Primary	Yes	…	Gay	–	5	2	Penile ulcer	+	NR	NR	PCN	…	…	…	4 months, NR VDRL titer
20	2004 (1)	Confirmed	Primary	Yes	…	Gay	–	3	1	Penile ulcer	+	…	NR	PCN	…	…	…	3 months, NR VDRL titer
21	2004 (1)	Confirmed	Secondary	Yes	…	Gay	–	0	2	Rectal condyloma	+	…	1:64	PCN	…	…	…	Lost to follow-up
22	2004 (1)	Confirmed	Primary	Yes	…	Gay	–	2	0	Penile ulcer	+	NR	NR	PCN	…	…	…	Lost to follow-up
23	2004 (1)	Confirmed	Primary	Yes	…	Gay	–	0	3	Penile ulcer	+	Stat+	1:1	PCN	…	…	…	Lost to follow-up
24	2004 (2)	Confirmed	Primary	Yes	…	Gay	–	0	2	Penile ulcer	–	Stat+	1:32	PCN	…	…	…	Lost to follow-up
25	2004 (2)	Confirmed	Primary	Yes	…	Gay	–	4	0	Penile ulcer	+	Stat+	1:4	PCN	…	…	…	Lost to follow-up
26	2004 (2)	Confirmed	Primary	Yes	…	Gay	–	Refused	-	Penile ulcer	+	…	1:32	Dox	…	…	…	8 months, NR VDRL titer
27	2004 (2)	Confirmed	Primary	Yes	…	Gay	–	0	2	Penile ulcer	+	Stat+	…	PCN	…	…	…	8 months, NR VDRL titer

28	2004 (2)	Confirmed	Primary	Yes	…	Gay	−	0	40	Penile ulcer	+	NR	NR	PCN	…	…	…	3 months, NR VDRL titer
29[b]	2004 (3)	Confirmed	Secondary	Yes	…	Gay	+	3	0	Rectal condyloma	+	…	1:64	PCN	…	…	…	10 weeks, VDRL 1:8
30[c]	2004 (3)	Confirmed	Primary	Yes	…	Gay	+	0	5	Penile ulcer	+	…	NR	PCN	…	…	…	6 weeks, NR VDRL titer
31	2004 (3)	Confirmed	Primary	Yes	…	Gay	+	1	19	Rectal ulcer	+	…	1:2	PCN	…	…	…	Lost to follow-up
32	2004 (3)	Confirmed	Primary	Yes	…	Gay	−	Refused	-	Penile ulcer	+	Stat+	1:32	PCN	…	…	…	3 months, VDRL 1:2
33	2004 (3)	Confirmed	Primary	Yes	…	Gay	−	0	7	Penile ulcer	+	…	1:2	PCN	…	…	…	Lost to follow-up
34[e]	2004 (3)	Confirmed	Primary	Yes	…	Gay	−	1	2	Penile ulcer	+	…	1:8	PCN	…	…	…	4 months, NR VDRL titer
35	2004 (3)	Confirmed	Primary	Yes	…	Gay	+	1	1	Penile ulcer	+	1:4	1:2	PCN	…	…	…	Lost to follow-up
36	2004 (3)	Confirmed	Primary	Yes	…	Gay	−	2	1	Penile ulcer	+	…	WR	Dox	…	…	…	Pending 6-month visit
37[c]	2004 (3)	Suspected	Secondary	NT	…	Gay	+	1	0	None (treated contact)	…	NR	NR	Azm 1 g	31 days	VDRL 1:2, TP-PA+	PCN	2 months, NR VDRL titer
38[b]	2004 (3)	Confirmed	Primary	Yes	…	Bisexual	−	1	0	Penile ulcer	+	Stat+	1:32	PCN	…	…	…	Pending 6-month visit
39	2004 (3)	Confirmed	Primary	Yes	…	Gay	+	5	5	Penile ulcer	+	…	NR	PCN	…	…	…	1 month, NR VDRL titer
40	2004 (3)	Confirmed	Primary	Yes	…	Bisexual	−	0	3	Penile ulcer	+	Stat+	1:64	PCN	…	…	…	Pending 6-month visit
41[d]	2004 (3)	Confirmed	Primary	Yes	7 days	Gay	−	2	0	Penile ulcer	+	NR	WR	PCN	…	…	…	4 months, NR VDRL titer
42	2004 (3)	Confirmed	Primary	Yes	…	Gay	−	0	6	Penile ulcer	+	…	1:8	Dox	…	…	…	Pending 6-month visit
43	2004 (4)	Confirmed	Primary	Yes	28 days	Gay	−	1	3	Penile ulcer	+	NR	NR	PCN	…	…	…	3 months, NR VDRL titer
44	2004 (4)	Confirmed	Primary	Yes	…	Gay	−	1	4	Penile ulcer	+	WR	1:2	PCN	…	…	…	3 weeks, VDRL WR
45[d]	2004 (4)	Suspected	Secondary	NT	…	Gay	−	1	3	None (treated contact)	…	NR	NR	Azm 1 g	28 days	VDRL 1:4, TP-PA+	PCN	3 months, NR VDRL titer
46	2004 (4)	Confirmed	Primary	Yes	7 days	Gay	+	0	25	Penile ulcer	+	Stat+	1:8	PCN	…	…	…	Pending 3 month visit
47	2004 (4)	Confirmed	Primary	Yes	…	Gay	−	1	1	Penile ulcer	+	1:4	1:8	PCN	…	…	…	Pending 3 month visit
48	2004 (4)	Confirmed	Primary	Yes	…	Gay	−	0	10	Penile ulcer	+	…	1:1	PCN	…	…	…	Pending 3 month visit
49	2004 (4)	Confirmed	Secondary	Yes	…	Gay	−	3	28	Rectal condyloma	+	…	1:16	PCN	…	…	…	Pending 3 month visit
50	2004 (4)	Confirmed	Primary	Yes	…	Gay	−	0	20	Penile ulcer	+	…	WR	PCN	…	…	…	Pending 3 month visit
51	2004 (4)	Confirmed	Primary	Yes	…	Gay	−	17	2	Penile ulcer	+	…	WR	PCN	…	…	…	6 weeks, NR VDRL titer
52	2004 (4)	Confirmed	Primary	Yes	…	Bisexual	+	1	2	Penile ulcer	+	…	NR	PCN	…	…	…	Pending 1 month visit

NOTE. Azm, oral azithromycin; DF, darkfield microscopy; Dox, doxycycline (100 mg orally twice daily for 2 weeks); NR, nonreactive; NT, not tested; PCN, benzathine penicillin G (2.4 mU intramuscularly); RPR, rapid plasma reagin; Rx, treatment; Stat+, Stat RPR reactive; TP-PA, *Treponema pallidum* particle agglutination; VDRL, Venereal Diseases Reagent Laboratory; WR, weakly reactive.

[a] "Confirmed" denotes infection with a 23S rRNA mutant *T. pallidum* isolate, "probable" denotes persistent primary and secondary syphilis despite treatment with 2 g azithromycin in the preceding 30 days, and "suspect" denotes a newly diagnosed case in patient who had received 1 g azithromycin in the preceding 60 days for prophylaxis after sexual contact with a syphilis-infected partner.

[b] Linked by direct sexual contact.

[c] Linked by direct sexual contact.

[d] Linked by direct sexual contact.

[e] Same patient.

Table 2. Predictors of syphilis due to azithromycin-resistant *Treponema pallidum* versus that due to nonresistant *T. pallidum*, San Francisco, 2000–2004.

Characteristic	Confirmed case patients (n = 46)	Control patients (n = 72)	P[a]
Age, years	37.5 (32–44)	37 (30.5–43)	.76
Race			
White	32 (70)	36 (50)	
Hispanic	8 (17)	20 (28)	.11
Black	1 (2)	8 (11)	
Asian	5 (11)	6 (8)	
Male	46 (100)	72 (100)	Undefined
Sexual orientation			
Gay	42 (91)	63 (88)	
Bisexual	4 (9)	3 (4)	.09
Heterosexual	0 (0)	6 (8)	
No. of partners in past 90 days	4.5 (3–10)	5 (3–10)	.83
No. of anonymous partners in past 90 days	3 (2–7)	3 (1–9)	.81
HIV positive	13 (28)	24 (34)	.53
Homeless	0 (0)	2 (3)	Undefined
Any illicit drug use	23 (50)	30 (45)	.28
Injection-drug use	2 (4)	4 (6)	.72
Sex worker	4 (9)	2 (3)	.22
Sex worker contact	1 (2)	1 (2)	.78
Repeat syphilis case	3 (7)	2 (3)	.38
Primary syphilis	41 (89)	63 (88)	.79
Secondary syphilis	5 (11)	9 (12)	
Venue for meeting partners			
Bookstore	4 (9)	11 (15)	.30
Sex club	5 (11)	8 (11)	.97
Bath house	4 (9)	11 (15)	.30
Bars and clubs	9 (20)	16 (22)	.73
Internet	23 (50)	26 (36)	.14

NOTE. Data are no. (%) of patients or median value (interquartile range).

[a] By the 2-tailed Fisher's exact test (for univariate data) and the χ^2 test for trend (for categorical variables).

much of it was provided to patients to deliver to their sex partners for syphilis control.

Table 2 shows characteristics of confirmed case patients and control patients. Confirmed case patients had a median age of 36.5 years (range, 23–59 years); were predominantly white (69%), male (100%), and men who have sex with men (100%); and reported a median of 4 partners in the past 90 days (range, 1–100 partners). A total of 28% (13 of 46 confirmed case patients) reported being HIV positive. Analysis of factors including age, race or ethnicity, HIV serostatus, use of illicit drugs, commercial sex work, sex-worker contacts, or venues used to meet sex partners during the critical exposure period did not reveal any statistically significant associations (table 2). Repeating this analysis with the addition of the 6 case patients with suspected or probable syphilis also failed to show any statistically significant associations (data not shown).

DISCUSSION

This report summarizes the results of a clinical, molecular, and epidemiologic investigation of cases of syphilis due to azithromycin-resistant *T. pallidum* infection in San Francisco during January 2000–December 2004. Seven clinical treatment failures were observed during this period, and 46 case patients were identified by using a molecular screening assay for macrolide-resistant *T. pallidum*, revealing a total of 52 cases (1 patient experienced clinical treatment failure and was also shown to be infected with a *T. palladium* isolate containing a 23rRNA mutation). Three case patients were sexually linked to 3 other case patients, suggesting person-to-person transmission of syphilis caused by azithromycin-resistant *T. pallidum*. However, the epidemiologic investigation was limited by the low percentage (18.4%) of named partners and was unable to identify

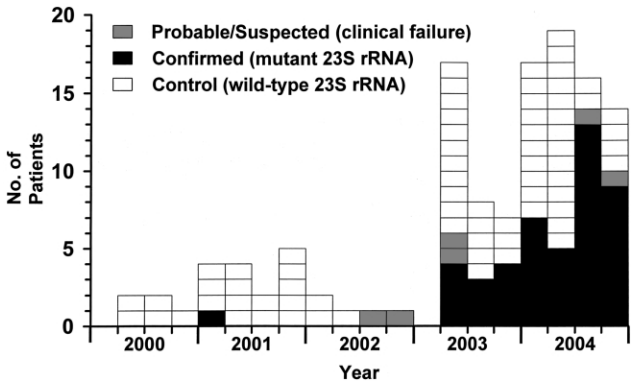

Figure: 1. Patients with confirmed, probable, and suspected cases of syphilis due to azithromycin-resistant *Treponema pallidum* in San Francisco during 2000–2004. Persons with probable and suspect cases were identified on the basis of reports of treatment failure, persons with confirmed cases had pathogens with the 23S rRNA mutation, and control subjects had pathogens with wild-type 23S rRNA.

a closed sexual network within which the azithromycin-resistant strain might be circulating. A case-control analysis failed to identify any unique patient characteristics associated with infection due to macrolide-resistant *T. pallidum*. Because of the increasing prevalence of azithromycin resistance, we made a city-wide recommendation to discontinue the use of azithromycin for treatment of P&S syphilis in 2003 and to discontinue its use for prophylactic treatment of incubating syphilis in 2004.

Recently, we described the molecular biology and geographic distribution of macrolide-resistant isolates in a retrospective study from Seattle, San Francisco, Baltimore, and Dublin [31]. The prevalence of mutant isolates varied widely, from 11% (2 of 19 isolates) in Baltimore (1998–2000) to 37% (11 of 30) in San Francisco (2003) and 88% (15 of 17) in Dublin (2002). In the current study, we demonstrate that age, race or ethnicity, number of sexual partners, and venues for meeting partners did not define a closed sexual network in which the resistant strain was circulating. Because several men who have sex with men also reported sex with women, it is possible the resistant strain might spread into heterosexual populations. The similar clinical presentation of case patients and control patients and their comparable response to definitive treatment with penicillin or doxycycline indicates that the mutant phenotype is likely similar to that of the wild-type strain.

The observation that 7 case patients had taken azithromycin in the 30 days preceding onset of their symptoms or diagnosis is noteworthy. The most likely explanation is that patients became infected with an existing strain of *T. pallidum* that was already macrolide resistant. Probable examples of direct transmission of a macrolide-resistant strain involve case patients 29 and 38 (table 1), who were sex partners with confirmed cases, and the 2 case patients (37 and 45) who experienced azithromycin treatment failure following sexual contact with confirmed case patients (30 and 41, respectively). Given the large number of anonymous sex partners reported by the case patients, there is a strong likelihood that many transmission links exist that we could not uncover. If spread of a preexisting resistant strain has occurred, then avoiding the use of macrolides might eliminate the strain by reducing macrolide selective pressure. Such an effect was observed among erythromycin-resistant group A streptococci in Finland after reduction of macrolide use [33, 34]. In the common bacterium *Escherichia coli,* the presence of a 23S rRNA mutation is associated with a selective disadvantage in the absence of macrolide pressure [29], and the mutant *T. pallidum* strain might therefore be expected to disappear if macrolide use decreases. Unfortunately, it is also possible that widespread use of macrolides for treatment of chlamydial infection and non–STD-related illnesses would continue to place substantial antibiotic pressure on *T. pallidum.* We note that the 3 large clinical reports on the use of azithromycin for treatment of syphilis [19–21] all preceded the identification of widespread distribution of macrolide-resistant *T. pallidum* [31]. In Vancouver, although an initial decrease in the number of syphilis cases was observed during the 6 months following the azithromycin intervention, an overall increase in cases was observed by the end of 2001 [35]. This was attributed to a rebound effect of repeat infections within the recently treated core group, but it is also possible that emergence of macrolide-resistant *T. pallidum* contributed to the rapid rebound.

An alternative hypothesis regarding treatment failures in persons who had recently used azithromycin is that infection of individuals with waning levels of macrolides might provide selective pressure on de novo mutations occurring in wild-type *T. pallidum.* If mutations arise frequently, macrolides will not be suitable for syphilis treatment even in populations that have not encountered the resistant strain. In the absence of a robust means for molecular typing of *T. pallidum* to measure the genetic relatedness of individual isolates, whether all of these cases spread from the introduction of a clonal strain into a sexual network or whether they arose de novo multiple times remains unknown.

An upper limit of 5% in the prevalence of antibiotic resistance is commonly cited as a cutoff for discontinuing use of a particular antibiotic [36]. However, in 2003, Blandford and Gift [37] presented an analysis of the cost-effectiveness of single-dose azithromycin versus that of parenteral penicillin, even with limited macrolide efficacy. In their analysis, azithromycin remained cost-effective in STD-control programs for field-delivered therapy at efficacy levels as low as 75%; however, from the health care system perspective, efficacy rates of $\geqslant$86% were needed to offset the additional costs of treating late-stage infections resulting from treatment failure. The estimated efficacy level of azithromycin in San Francisco (44%, given the resis-

tance prevalence of 56% observed during 2004) is below the lower bounds described by Blandford and Gift [37] and indicates that azithromycin should not be used for syphilis management in this setting.

This study has certain limitations. First, the collection of *T. pallidum* isolates was from a single clinic, which may limit the generalizability of our results. However, SFCC evaluates ~33% of all incident syphilis cases in the city, and thus, selection bias should be small. Second, other factors might cause azithromycin clinical failures, such as reinfection, subtherapeutic levels of drug caused by poor absorption, or *T. pallidum* strains with 1 of the 7 other described 23S rRNA genetic mutations [29]. However, our inability to identify other mutations would tend to underestimate the >50% prevalence of azithromycin-resistant strains that we report. Third, the large proportion of anonymous sexual contacts and the inability to directly link *T. pallidum* isolates by molecular typing continues to limit the ability of public health workers to understand the spread of syphilis through sexual networks. Fourth, the relative homogeneity of the populace infected with syphilis in San Francisco (primarily, men who have sex with men) makes it difficult to identify statistically significant cofactors, such as meeting venues, without very large samples.

In conclusion, we describe the introduction and spread of azithromycin-resistant *T. pallidum* infection in San Francisco during 2000–2004. Despite decreased local use of azithromycin for treating syphilis from October 2003 onward, the prevalence of infection with azithromycin-resistant *T. pallidum* increased to >50% in 2004, suggesting that the mutant strain is common. Therefore, we conclude that intramuscular injection of 2.4 mU of benzathine penicillin G remains the best treatment for P&S syphilis and recommend that penicillin-allergic patients be treated with oral doxycycline [4]. Efforts to reduce the use of azithromycin should be undertaken, and ongoing surveillance is needed to monitor the distribution of the resistant strain.

Acknowledgments

We thank the patients, clinicians, and staff of the San Francisco City Clinic (SFCC) for participation in the project; Sally Liska and Leah Rauch (San Francisco Department of Public Health [SFDPH]) for assistance with the laboratory analysis of *Treponema pallidum* isolates; Robert Kohn (SFDPH) for assistance with compiling azithromycin usage data at SFCC; Janet Blair (Office of Workforce and Career Development, Epidemic Intelligence Service State Branch, Centers for Disease Control and Prevention [CDC]) and Stuart Berman (National Center for HIV, STD, and TB Prevention, Division of STD Prevention, CDC) for critical comments on the project; and Gail Bolan (California Department of Health Services) and George Rutherford (Center for AIDS Prevention Studies) for acquiring initial funding for the molecular studies.

Financial support. City and County of San Francisco, California HealthCare Foundation, US Public Health Service (AI 34616 and AI 42143 to S.A.L.), and Pfizer (medical research grant).

Potential conflicts of interest. J.D.K. received grant support or speaker's fees from Pfizer and King Pharmaceuticals. All other authors: no conflicts.

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