

Case-Control Study of Shigellosis in San Francisco: The Role of Sexual Transmission and HIV Infection

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(See the editorial commentary by Daskalakis and Blaser on pages 335–7)

Background. *Shigella* species infect ~450,000 persons annually in the United States. Person-to-person transmission of *Shigella* species, which have a low infectious dose, occurs frequently, particularly in areas with poor sanitation and hygiene. Sexual transmission of *Shigella* species among men who have sex with men (MSM) has been inferred from outbreaks of shigellosis among that population, and limited studies have suggested the importance of human immunodeficiency virus (HIV) infection as a risk factor for shigellosis. No population-based study of sporadic shigellosis has evaluated the role of sexual practices (especially among MSM) and HIV infection along with other established risk factors for shigellosis.

Methods. We conducted a population-based case-control study of shigellosis in adults in San Francisco, California, during the period 1998–1999. Cases of *Shigella* infection were identified through laboratory-based active surveillance conducted by the California Emerging Infections Program. Seventy-six case patients were matched by sex with 146 control subjects. Exposure data were collected on established risk factors, sexual practices, and HIV infection status. Bivariable and multivariable analyses were conducted. Population-attributable fractions were calculated.

Results. From the multivariable analysis, for men, shigellosis was associated with MSM (odds ratio [OR], 8.24; 95% confidence interval [CI], 2.70–25.2), HIV infection (OR, 8.17; 95% CI, 2.71–24.6), direct oral-anal contact (OR, 7.50; 95% CI, 1.74–32.3), and foreign travel (OR, 20.0; 95% CI, 5.26–76.3), with population-attributable fractions of 0.72, 0.42, 0.31, and 0.18, respectively. For women, shigellosis was associated only with foreign travel (OR, 21.0; 95% CI, 2.52–899), with a population-attributable fraction of 0.37.

Conclusions. Among MSM, shigellosis is predominantly a sexually transmitted disease, with direct oral-anal contact conferring the highest risk and HIV infection likely contributing to increased host susceptibility.

Each year, an estimated 450,000 persons in the United States are infected with *Shigella* species, resulting in 6200 hospitalizations and 70 deaths [1]. Humans and other primates are the only natural reservoirs for *Shigella* species [2]. *Shigella* species are transmitted by the fecal-oral route, and most infections are transmitted from person to person, reflecting the low infectious dose [3]; as few as 10 viable organisms can result in clinical infection [4]. In areas in which infection is prev-

alent, risk for *Shigella* infection increases with poor hand hygiene, ingestion of contaminated food or water, inadequate sanitation and toileting, overcrowding, and sexual contact [5–13].

Among reported culture-confirmed infections in the United States during the period 1989–2002, 72% were due to *Shigella sonnei*, 18% were due to *Shigella flexneri*, 1.6% were due to *Shigella boydii*, and 0.7% were due to *Shigella dysenteriae* [3]. Most reported cases occurred in children <10 years of age, followed by women 20–39 years of age; the high rate of infection in the latter group was presumably related to caring for infected children. In the mid-1970s, shigellosis was recognized as a potentially sexually transmitted disease among men who have sex with men (MSM) [7, 14, 15]. In the late 1970s and early 1980s, the increased incidence of *S. flexneri* infection in men was attributed to the sexual

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practices of MSM, which frequently include anal contact [16].

A study conducted in the San Francisco Bay area in 1996 showed a correlation between an increased prevalence of HIV infection and increased incidence of shigellosis, suggesting that *Shigella* infection may be more severe among HIV-infected persons or that HIV infection may be an important risk factor for shigellosis in the MSM community [17]. Among persons infected with *Salmonella* or *Campylobacter* species, HIV-infected persons have more-severe infections [18].

How risk factors contribute to *Shigella* transmission dynamics can be conceptualized using the equation for the per capita infection rate among susceptible individuals: $I = cpP$, where c is the contact rate of susceptible individuals to a potentially infectious source, p is the probability that the agent is transmitted from this contact, and P is the probability that the source is infectious [19]. The transmission probability (p) is influenced by host susceptibility, source infectiousness, and factors that modify transmission risk independent of susceptibility or infectiousness (e.g., barrier methods). This simple model illustrates that all of these factors must come together in place and time for infections to be transmitted, propagated, and sustained.

For example, if a man has sex with a man, there are several factors to consider. First, did this man engage in behavior that put him in direct or indirect contact with fecal material (e.g., anal fisting, oral-anal contact)? Second, does he have a condition (e.g., HIV infection) that might increase susceptibility to *Shigella* infection or disease? Third, was his partner shedding *Shigella* species in his feces? The likelihood that his partner was shedding *Shigella* species may be reflected by the prevalence of

shigellosis in the local MSM community and the prevalence of conditions that may increase or prolong shedding. For example, although not established, if HIV infection increased or prolonged fecal shedding, then a higher prevalence of HIV infection in the MSM community could increase the prevalence of *Shigella* infection.

To date, no population-based analytic epidemiological study of sporadic shigellosis has been reported that evaluated the role of HIV infection and sexual behavior in the transmission of *Shigella* species. To assess the role of sexual behavior and HIV infection in the transmission of *Shigella* species in adults in San Francisco during a nonoutbreak period, we conducted a population-based case-control study. We used the conceptual approach described above to guide our analysis and interpretations.

METHODS

Overview. The California Emerging Infections Program (CEIP) is funded under a cooperative agreement with the Centers for Disease Control and Prevention and is a collaborative program among the California Department of Health Services, the University of California Berkeley School of Public Health, and the local public health departments of Alameda, Contra Costa, and San Francisco Counties and of the City of Berkeley. CEIP participates in the Foodborne Diseases Active Surveillance Network, which conducts population-based active surveillance for culture-confirmed cases of *Shigella* infection among the residents of the CEIP catchment area. Clinical laboratories serving these residents are contacted at least monthly to ascertain all culture-confirmed cases and to collect patient demographic information, including sex, age, and ethnicity.

Study design. This was a population-based case-control study. Case patients and control subjects were enrolled and interviewed by telephone, using a standardized enrollment protocol and a detailed survey. This study was approved by the State of California Institutional Review Board.

Subjects. Potential eligible case patients had culture-confirmed *Shigella* infection from any anatomic site during the time span 1 January 1998 through 31 December 1999 and were identified through CEIP surveillance. Inclusion criteria for case patients and control subjects were as follows: age ≥ 18 years, the ability to speak English, being a resident of San Francisco County, the presence of a telephone in the subject's primary residence, and consent to be included in the study. Case patients had to be interviewed within 21 days of the culture date and have a reference date. This reference date for case patients with diarrhea was the date of diarrhea onset; for case patients without diarrhea, the reference date was the date on which fever started. Control subjects were interviewed within 7 days of the matched case patient's interview. Control subjects were selected using sequential telephone digit dialing anchored on the telephone number of the matched case patient. An attempt was

Table 1. Characteristics of shigellosis case patients and matched control subjects.

Characteristic	Case patients (n = 76)	Control subjects (n = 147)	All (n = 223)
Sex			
F	18 (23.7)	36 (24.5)	54 (24.2)
M	58 (76.3)	111 (75.5)	169 (75.8)
MSM (% of men)	48/58 (82.8)	30/111 (27.0)	78/169 (46.2)
Age, years			
18–24	5 (6.6)	13/144 ^a (9.0)	18 (8.2)
25–44	58 (76.3)	84/144 ^a (58.3)	142 (64.5)
45–64	13 (17.1)	33/144 ^a (22.9)	46 (20.9)
≥ 65	0	14/144 ^a (9.7)	14 (6.4)
Ethnicity			
White	52 (68.4)	98 (66.7)	150 (67.3)
Latino/Hispanic	17 (22.4)	17 (11.6)	34 (15.2)
Black	2 (2.6)	14 (9.5)	16 (7.2)
Asian/Pacific Islander	2 (2.6)	10 (6.8)	12 (5.4)
Other	3 (3.9)	8 (5.4)	11 (4.9)

NOTE. Data are no. (%) of patients, unless otherwise indicated. MSM, men who have sex with men.

^a Denominator is 144, rather than 147, because data were not available for all subjects.

Table 2. Distribution of *Shigella* species and clinical symptoms.

Characteristic	Proportion (%) of patients
<i>Shigella</i> species infection	
<i>Shigella dysenteriae</i>	1/76 (1.3)
<i>Shigella flexneri</i>	40/76 (52.6)
<i>Shigella sonnei</i>	35/76 (46.1)
Symptoms	
Abdominal pain	69/76 (90.8)
Rectal urgency	64/76 (84.2)
Chills	62/75 (82.7)
Lightheadedness	50/76 (65.8)
Night sweats	46/73 (63.0)
Mucus in stool	43/70 (61.4)
Nausea	43/76 (56.6)
Tenesmus	42/76 (55.3)
Blood in stool	40/74 (54.1)
Vomiting	28/76 (36.8)

made to enroll 2 control subjects for each case patient. Control subjects could not have had *Shigella* species isolated in the 30 days preceding the case patient's specimen date. Control subjects were questioned about the 7 days prior to the case patient's reference date.

Measurements. Case patients were questioned about the onset of diarrhea and fever, the symptoms of their infection, whether they were treated with antibiotics for their infection, and whether they were admitted to a hospital for treatment of their infection. Case patients and control subjects were asked about their demographic data and medical history, including HIV infection status and other underlying conditions that could affect their immune status. Questions were also asked about the use of antibiotics and other medications, consumption of foods and water, foreign travel, detailed sexual practices, and other person-to-person contacts in the week before the onset of the case patient's diarrhea. Case patients and control subjects were asked about the sex of their sex partners during the last 2 years. Questions about sexual practices included frequency, number of partners, and sexual practices that involve indirect and direct oral-anal contact in the week before onset of the case patient's diarrhea. Indirect anal contact meant a case patient's penis, finger, or instrument was inserted into a partner's anus. Direct anal contact meant case patient had direct oral contact with a partner's anus.

Data analysis. The primary risk variables were having direct or indirect anal contact (mostly occurring by sexual acts), being MSM, and having HIV infection. The primary confounding variables were those traditionally associated with *Shigella* infection (e.g., foreign travel). Bivariable and multivariable analyses were conducted.

Case patients were matched to control subjects on the basis

of sex and telephone exchange. Matching on the basis of telephone exchange was done for convenience and not to control for a potential confounder. To improve the precision of estimation, we conducted a frequency-matched analysis (ignoring matching by telephone exchange). This was possible because pairwise matching on a single dichotomous variable (sex) is equivalent to frequency matching on that variable. Because the risks of given exposures (e.g., oral-anal contact) differed by sex (primarily because of MSM), in the multivariable analyses, men and women were modeled separately. Also, MSM were modeled separately to see if strong predictors in sex-specific models held up within MSM. Potential confounders were included in the models if they improved fit.

The population-attributable fraction (PAF) is the theoretical proportion of shigellosis cases that would have been prevented had a specific exposure never occurred, assuming that the exposure is causal. We calculated the PAF for various exposures from the results of the multivariable logistic regression models using PAF methods for case-control studies [20]. All analyses were conducted in R, an open-source programming language and environment for statistical computing and graphics [21].

RESULTS

From 1 January 1998 through 31 December 1999, 238 cases of shigellosis were identified by CEIP active surveillance, and 174 (73.1%) were in persons ≥ 18 years of age. Of the 110 case patients (63.2%) who were interviewed, 34 were not eligible because 21 days had elapsed after onset of symptoms or they were not English speaking, leaving 76 case patients who were enrolled into the study. We attempted to match 2 control subjects to each case patient; 147 control subjects were enrolled into the study.

The demographic characteristics of case patients and matched control subjects are summarized in table 1. Seventy-six percent of case patients were men, case patients were younger than control subjects (mean age, 37.4 years vs. 40.7 years; $P < .01$), and case patients had a higher percentage of Latino and/or Hispanic subjects (22.4% vs. 11.6%) but a lower percentage of black (2.6% vs. 9.5%) and Asian and/or Pacific Islander (2.6% vs. 6.8%) subjects. There were 40 cases (52.6%) of *S. flexneri* infection, 35 cases (46.1%) of *S. sonnei* infection, and 1 case (1.3%) of *S. dysenteriae* infection (table 2). The clinical symptoms are summarized in table 2. With respect to *Shigella* species, *S. flexneri* infection was associated with MSM and MSM-related factors, and *S. sonnei* infection was associated with foreign travel (table 3).

The frequency-matched (on sex) bivariable analyses assessing exposures in the week before symptoms (for case patients) and case reference date (for control subjects) are summarized in table 4. Shigellosis was not associated with sexual activity in the prior week; however, shigellosis was associated with MSM

Table 3. Factors associated with *Shigella* infection, comparing infection due to *Shigella flexneri* with infection due to *Shigella sonnei*.

Variable	<i>S. flexneri</i>	<i>S. sonnei</i>	<i>P</i>
Male sex	36/40 (90.0)	22/35 (62.9)	.0063
MSM	36/36 (100)	12/22 (54.5)	<.0001
History of STD	27/40 (67.5)	14/35 (40.0)	.0213
HIV positive	22/40 (55.0)	6/35 (17.1)	.0008
Any sexual activity	26/40 (65.0)	18/34 (52.9)	.3463
Sexual anal contact			
No sexual activity and no anal contact	13/40 (32.5)	24/35 (68.6)	...
Sexual activity but no anal contact	5/40 (12.5)	4/35 (11.4)	...
Indirect anal contact ^a	10/40 (25.0)	4/35 (11.4)	...
Direct anal contact ^b	12/40 (30.0)	3/35 (8.6)	.0105
Foreign travel	1/40 (2.5)	16/35 (45.7)	<.0001
Diarrheal contact ^c	4/38 (10.5)	4/33 (12.1)	1.0000
Drinking unfiltered water ^d	1/40 (2.5)	4/29 (13.8)	.1537

NOTE. Data are no. of individuals with the specified characteristic/no. of individuals for whom information was available (%). MSM, men who have sex with men; STD, sexually transmitted disease.

^a Penis, finger, or instrument was inserted by case patient into potential source anus.

^b Oral contact of case patient with potential source anus.

^c Spent time with person(s) with diarrheal illness (not sexual contact).

^d Drank unboiled, untreated, and unfiltered water from ponds, streams, or lakes.

(OR, 13.0; $P < .001$), HIV infection (OR, 13.9; $P < .001$), indirect anal contact (OR, 2.93; $P = .02$), direct anal contact (OR, 10.2; $P < .001$), foreign travel (OR, 6.19; $P < .001$), and drinking untreated water from a pond, stream, or lake (OR, 11.1; $P = .03$) in the week before the case patient reference date. In a dose-response fashion, frequency and type of oral-anal contact were associated with shigellosis (table 4).

The multivariable unconditional logistic regression analysis is summarized in table 5. Among men (model A), foreign travel (OR, 20.0; $P = .0001$), MSM (OR, 8.24; $P = .0002$), HIV positivity (OR, 8.17; $P = .0002$), and direct anal contact (OR, 7.50; $P < .01$) were associated with shigellosis. Among women (model B), only foreign travel was associated with shigellosis (OR, 21.0; $P = .0002$). Among MSM (model C), HIV infection (OR, 8.59; $P < .001$) and direct anal contact (OR, 9.56; $P = .01$) were associated with shigellosis.

The PAFs were calculated separately for men (model A), women (model B), and MSM (model C) for the study period. For men, the PAFs were 0.18 for foreign travel, 0.73 for MSM, 0.42 for HIV infection, and 0.31 for indirect and direct oral-anal contact combined. For women, the PAF for foreign travel was 0.37. For MSM, the PAFs were 0.07 for foreign travel, 0.52 for HIV infection, and 0.39 for indirect and direct oral-anal contact combined.

DISCUSSION

This is the first population-based study of sporadic shigellosis in adults that evaluated the role of sexual acts (including oral-anal contact), the sex of sex partners, and HIV infection along

with other established risk factors for infection. In men and women, foreign travel outside the United State in the prior week was the strongest single factor associated with shigellosis (for both men and women, the OR was ≥ 20 ; $P < .001$). Among men, being MSM, having HIV infection, and having direct oral-anal contact were independently associated with shigellosis (ORs were ~ 8 for each risk factor; $P < .001$). Among MSM only, HIV infection and direct oral-anal contact remained independently associated with shigellosis (ORs were ~ 9 for both risk factors; $P \leq .01$).

Our epidemiological study corroborates previous research [7, 14–16] that suggests that shigellosis is a sexually transmitted disease among MSM and that sexual practices among MSM that include anal contact are risky. We also found that sexual practices among MSM involving direct oral-anal contact are particularly risky for shigellosis. Although these findings may have been generally assumed by some, they have not been well documented in a population-based study of sporadic shigellosis. Foreign travel, on the other hand, has been well documented as a risk factor for shigellosis [23, 24].

Is HIV infection a contributing factor in shigellosis? This could be true in 2 ways: HIV infection may increase the shedding of *Shigella* species or may increase the susceptibility of the host. At an individual level, if an HIV-infected person is more susceptible to *Shigella* infection, then contact with a person who is infected is more likely to result in infection. At a group level, if HIV-infected persons with shigellosis are more likely to shed *Shigella* species and if HIV-infected persons are more likely to have sexual contact with other HIV-infected persons

Table 4. Bivariable frequency-matched ORs for the occurrence of shigellosis according to selected sexual exposures and nonsexual risk factors.

Variable	Case patients	Control subjects	OR (95% CI)	P
MSM	48/76 (63.2)	30/147 (20.4)	13.0 (5.82–28.8)	<.001
History of STD	41/76 (53.9)	48/144 (33.3)	2.41 (1.35–4.30)	.003
HIV positive	28/76 (36.8)	7/147 (4.8)	13.9 (5.51–34.9)	<.001
AIDS diagnosis	11/74 (14.9)	5/144 (3.5)	5.08 (1.67–15.5)	.004
Any sexual activity	44/75 (58.7)	67/138 (48.6)	1.50 (0.85–2.66)	.160
Sexual anal contact				
No sexual activity and no anal contact	38/76 (50.0)	90/147 (61.2)	1.00 (Reference)	...
Sexual activity but no anal contact	9/76 (11.8)	40/147 (27.2)	0.60 (0.25–1.41)	.241
Indirect anal contact ^a	14/76 (18.4)	13/147 (8.8)	2.93 (1.19–7.23)	.020
Direct anal contact ^b	15/76 (19.7)	4/147 (2.7)	10.2 (3.04–34.2)	<.001
Anal contact, no. of times ^c				
0	47/76 (61.8)	130/147 (88.4)	1.00 (Reference)	...
1–2 times	19/76 (25.0)	13/147 (8.8)	4.74 (2.09–10.7)	<.001
≥3 times	10/76 (13.2)	4/147 (2.7)	8.10 (2.36–27.8)	<.001
Foreign travel	18/76 (23.7)	7/146 (4.8)	6.19 (2.45–15.6)	<.001
Diarrheal contact ^d	8/72 (11.1)	5/139 (3.6)	3.38 (1.06–10.8)	.039
Unfiltered water ^e	5/70 (7.1)	1/146 (0.7)	11.1 (1.27–96.9)	.030

NOTE. Data are no. of individuals with the specified characteristic/no. of individuals for whom information was available (%). MSM, men who have sex with men; STD, sexually transmitted disease.

^a Penis, finger, or instrument was inserted by case patient into potential source anus.

^b Oral contact of case patient with potential source anus.

^c Variable constructed combining indirect and direct anal contact.

^d Spent time with person(s) with diarrheal illness (not sexual contact).

^e Drank unboiled, untreated, and unfiltered water from ponds, streams, or lakes.

(assortative mixing by HIV status), then the HIV infection group membership can be a causal risk factor. In fact, this phenomenon of sexual “serological sorting” has been well described: MSM who know their HIV status are more likely to seek serologically concordant sex partners [25]. Finally, it is possible that knowledge of the discordant HIV status of sex partners may promote the substitution of behaviors that increase the risk of transmitting HIV with behaviors that increase the risk of transmitting enteric pathogens.

Some case reports and case series suggest more-severe shigellosis among HIV-infected patients [26–31]. One case-control study from Zambia, conducted during an epidemic of dysentery (most of it due to *S. dysenteriae*), found an association between dysentery and HIV infection (crude OR, 9.2; 95% CI, 5.0–16.9) [32]. Case patients and control subjects were similar in age, sex, and distance from the clinic. No other factors were associated with dysentery, although the study did not collect behavioral data or control for potential confounders. This study suggested that HIV infection may contribute to disease transmission and/or disease expression. Our study found a similar association (adjusted OR, 8.50; 95% CI, 2.79–25.9), suggesting that HIV infection does play an important causal role. Although we do not know the mechanism, our study is more consistent with increased susceptibility to infection as an explanation.

Among men, the PAFs for being MSM, having HIV infection,

and having direct and indirect oral-anal contact were 0.72, 0.42, and 0.31, respectively. Therefore, up to that fraction of cases might have been prevented if a causal and modifiable risk factor had been removed. For example, if HIV infection were causal through increased susceptibility, then up to 42% of shigellosis in men in San Francisco might have been prevented if there had been no HIV infection. Although being MSM is not a modifiable factor, it can be causal at the population level as a sexual network group with a higher prevalence of *Shigella* infection. Again, prevalence of infection operates through the relationship $I = cpP$. Reducing any component (c , p , or P) results in lowering the infection rate among susceptible individuals (I). Therefore, if the prevalence of *Shigella* infection in MSM had been reduced to near zero in San Francisco, then up to 72% of *Shigella* infections in men might have been prevented. Naturally, because HIV-infected men may be more susceptible to infection, this would also benefit them, because >90% of the HIV-infected men with shigellosis were MSM.

The strengths of this study include the following: the case patients and control subjects were population-based, we studied sporadic shigellosis (in the absence of an outbreak), and we collected data on oral-anal sexual exposures, HIV status, and established risk factors for *Shigella* infection. To control for factors associated with being MSM, we also evaluated risk factors among MSM only. Our results represent the baseline ep-

Table 5. Multivariable unconditional logistic regression models of shigellosis according to associated risk factors.

Model, variable	Case patients	Control subjects	OR (95% CI)	P
A: men only				
Foreign travel	11/58 (19.0)	7/110 (6.4)	20.0 (5.26–76.3)	<.0001
MSM	48/58 (82.8)	30/110 (27.3)	8.24 (2.70–25.2)	.0002
HIV positive	28/58 (48.3)	7/110 (6.4)	8.17 (2.71–24.6)	.0002
Sexual anal contact				
No anal intercourse	29/58 (50.0)	93/110 (84.5)	1.00 (reference)	...
Indirect anal contact ^a	14/58 (24.1)	13/110 (11.8)	1.57 (0.49–5.04)	.4489
Direct anal contact ^b	15/58 (25.9)	4/110 (3.6)	7.50 (1.74–32.3)	.0068
B: women only ^c				
Foreign travel	7/18 (39.9)	0/36	21.0 (2.52–899)	.0002
C: MSM only				
Foreign travel	4/48 (8.3)	2/30 (6.7)	4.84 (0.74–31.8)	.1007
HIV positive	28/48 (58.3)	5/30 (16.7)	8.59 (2.56–28.9)	.0005
Sexual anal contact				
No anal intercourse	19/48 (39.6)	20/30 (66.7)	1.00 (reference)	...
Indirect anal contact	14/48 (29.2)	8/30 (26.7)	1.69 (0.50–5.76)	.3995
Direct anal contact	15/48 (31.3)	2/30 (6.7)	9.56 (1.69–54.0)	.0106

NOTE. Data are no. of individuals with the specified characteristic/no. of individuals for whom information was available (%). MSM, men who have sex with men.

^a Penis, finger, or instrument was inserted by case patient into potential source anus.

^b Oral contact of case patient to potential source anus.

^c Contingency table analysis using 18 female case patients and 36 female control subjects. This is a small-sample adjusted OR using the method of Jewell [22].

idemiological characteristics of *Shigella* transmission in San Francisco. Although we applied a traditional case-control study design, we incorporated our understanding of *Shigella* transmission dynamics to guide the analysis and interpretation of the data. Other studies of *Shigella* outbreaks among MSM did not use population-based control subjects, did not collect detailed oral-anal contact histories, did not (or could not) collect data on or control for HIV-infection status, or did not consider how transmission risk factors can be interdependent and dynamic [7, 9, 14–17, 32–38].

There are limitations in conducting epidemiological risk factor studies of communicable infections when the risk factors are dynamic, interdependent, and dependent on location and calendar time. For example, a high frequency of risk behavior (e.g., direct oral-anal contact) is a risk factor only if a subject is selecting partners with a high prevalence of infection (i.e., if the *P* is high). In addition, of course, prevalence of infection differs by location and varies over time. In the terminology of Rothman and Greenland [39], for a risk factor to be a component cause, it must be part of a sufficient cause in which all of the components of the causal “pie” are present. Therefore, readers must be cautious in interpreting risk factor studies of communicable diseases. These risk factors can be naturally interdependent and, in this case, highly correlated, making traditional interpretation of regression coefficients more challenging.

Another limitation is that the association of HIV infection with shigellosis may in part be caused by a diagnostic bias among HIV-infected patients. HIV-infected patients are more likely to receive regular medical care, are more likely to seek medical evaluation for a diarrheal illness, and are more likely to be evaluated with stool cultures to rule out treatable conditions. However, even if such a diagnostic bias was operating, it would not likely account for the association we detected (ORs >8; *P* < .001) (table 5).

In this study, *S. flexneri* was the predominant strain occurring among MSM. This association has been previously noted [16]. Beginning in June 2000, 6 months after data collection for this study, San Francisco started experiencing a large, sustained outbreak of shigellosis among MSM in which *S. sonnei* was the predominant strain [9]. It is unlikely that the prevalence of HIV infection and fecal-oral risk behaviors changed significantly in San Francisco during this time interval. A more likely explanation is that the sufficient introduction of *S. sonnei* into this community changed the transmission dynamics of *Shigella* infection in this group, such that the prevalence of infectious cases exceeded some threshold, resulting in a sustained, explosive outbreak. This is plausible, because *S. sonnei* is less pathogenic and less virulent than *S. flexneri* [40] and could result in a higher number of asymptomatic and less severely ill (yet infectious) individuals circulating in the community, thereby

increasing transmission and driving the outbreak. Subsequently, similar outbreaks among MSM were reported in Canada, Australia, London, and Chicago [33, 34, 36, 38, 41].

Among MSM, shigellosis is predominantly a sexually transmitted disease, with direct oral-anal contact conferring the highest risk, and HIV infection likely contributes to transmission through increased host susceptibility. Given the continuing outbreaks of shigellosis among MSM [41], we believe that there is enough evidence and biological plausibility to recommend that MSM avoid direct oral-anal sexual contact, especially if sex partners are ill or if there are community outbreaks of enteric infection.

Scientific knowledge gaps in this area remain. Are HIV-infected persons more susceptible to *Shigella* infection or more likely to experience severe disease? Do HIV-infected persons with shigellosis shed more bacteria or shed bacteria for longer periods (with or without treatment)? Will barrier methods (e.g., dental dams) reduce the risk of transmission from direct oral-anal sexual contact? Answers to these and other questions will help medical and public health authorities to design better clinical and public health control interventions.

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