Title

Sexual Exposures Associated With Mpox Infection: California, November 2022 to June 2023.

Journal

The Journal of Infectious Diseases, 229(Supplement_2)

Authors

Snyder, Robert

Saadeh, Kayla

Tang, Eric

et al.

Publication Date

2024-03-26

DOI

10.1093/infdis/jiad447

Peer reviewed

The Journal of Infectious Diseases
SUPPLEMENT ARTICLE

Sexual Exposures Associated With Mpox Infection: California, November 2022 to June 2023

Robert E. Snyder,[1] Kayla Saadeh,[1] Eric C. Tang,[1] Kelly A. Johnson,[1] Samuel N. Holland,[1,2] Joshua Quint,[1] Nicole O. Burghardt,[1] Shua J. Chai,[1,3] Roshani Fernando,[1] Kimberly Gonzalez Barrera,[1] Cindy Hernandez,[1] Korie McManus,[1,2] Kieran Lorenz,[1,2] Jarett Maycott,[1,2] John McGinley,[1,2] and Joseph A. Lewnard[2]

[1]Sexually Transmitted Diseases Control Branch, California Department of Public Health, Richmond and Sacramento, California, USA; [2]School of Public Health, University of California, Berkeley, California, USA; and [3]Career Epidemiology Field Officer Program, Division of State and Local Readiness, Office of Readiness and Response, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Background. Exposures associated with mpox infection remain imperfectly understood.

Methods. We conducted a case-control study enrolling participants who received molecular tests for mpox/orthopoxvirus in California from November 2022 through June 2023. We collected data on behaviors during a 21-day risk period before symptom onset or testing among mpox case patients and test-negative controls.

Results. Thirteen of 54 case patients (24.1%) and 5 of 117 controls (4.3%) reported sexual exposure to individuals they identified as potential mpox case patients ("index contacts"; odds ratio [OR], 7.7 [95% confidence interval (CI), 2.5–19.3] relative to individuals who did not report exposure to potential mpox case patients). Among these participants, 10 of 13 case patients (76.9%) and 2 of 5 controls (40.0%) reported that their index contacts were not experiencing symptoms visible to participants during sex (OR, 14.9 [95% CI, 3.6–101.8]). Only 3 of 54 case patients (5.6%) reported exposure to symptomatic index contacts. Case patients reported more anal/vaginal sex partners than did controls (adjusted OR, 2.2 [95% CI, 1.0–4.8] for 2–3 partners and 3.8 [1.7–8.8] for ≥4 partners). Male case patients with penile lesions more commonly reported insertive anal/vaginal sex than those without penile lesions (adjusted OR, 9.3 [95% CI, 1.6–54.8]). Case patients with anorectal lesions more commonly reported receptive anal sex than those without anorectal lesions (adjusted OR, 14.4 [95% CI, 1.0–207.3]).

Conclusions. Sexual exposure to contacts known or suspected to have experienced mpox was associated with increased risk of infection, often when index contacts lacked apparent symptoms. Exposure to more sex partners, including those whom participants did not identify as index contacts, was associated with increased risk of infection in a site-specific manner. While participants' assessment of symptoms in partners may be imperfect, these findings suggest that individuals without visibly prominent mpox symptoms transmit infection.

An ongoing, multicountry mpox outbreak has involved sustained human-to-human spread of human mpox virus (hMPXV) among men who have sex with men (MSM). Epidemiologic features of this outbreak contrast with prior sporadic outbreaks involving limited person-to-person spread from index contacts with a history of travel to endemic countries or contact with imported animals [1–3], although sexual contact has been identified as a risk factor for person-to-person spread of hMPXV in ≥1 prior outbreak in Nigeria [4, 5]. Guidance from the US Centers for Disease Control and Prevention (CDC) emphasizes close, skin-to-skin contact with rashes or scabs from infected people as a key exposure driving transmission in the current outbreak, stating that people with mpox can spread infection to others from the time symptoms start until a rash has fully healed and a fresh layer of skin has formed [6]. While acknowledging the possibility of presymptomatic transmission 1–4 days before symptom onset in index contacts, this guidance currently states that no evidence shows hMPXV transmission by index contacts who never develop symptoms.

Among people infected with hMPXV, detection of viral genetic material has been reported from a variety of specimens, including lesion-unaffected skin, saliva, urine, blood, semen, feces, and swab samples taken from the oropharynx, anus, rectum, and genitals [7–11]. In addition, replication-competent hMPXV has been isolated from anorectal swab samples obtained from case patients who remained asymptomatic throughout their infection [12]. While presymptomatic hMPXV transmission has been identified in anecdotal reports [13, 14], the contribution of visible lesions to transmission by infected individuals is uncertain. Understanding hMPXV transmission is of importance to public health efforts aimed at identifying individuals at risk for infection [15, 16] and

Correspondence: Joseph A. Lewnard, PhD, School of Public Health, University of California, 2121 Berkeley Way, Room 5410, Berkeley, CA 94720 (jLewnard@berkeley.edu); Robert E. Snyder, PhD, Sexually Transmitted Diseases Control Branch, California Department of Public Health, 850 Marina Bay Pkwy, Richmond, CA 94804 (Robert.Snyder@cdph.ca.gov).

The Journal of Infectious Diseases® 2024;229(S2):S188–96

https://doi.org/10.1093/infdis/jiad447

communicating effective risk-management strategies [17]; clarifying the role of sexual exposures to case patients with or without symptoms may also inform control in high-income settings where MSM-associated outbreaks have occurred and in settings where the disease is endemic. We undertook a test-negative design case-control study aiming to identify risk factors for infection among individuals who underwent mpox testing in California from November 2022 through June 2023.

METHODS

Design

Clinical providers and laboratories in California report all hMPXV or orthopoxvirus tests to the California Department of Public Health (CDPH). We defined case patients as individuals with positive results from any hMPXV/orthopoxvirus test reported to CDPH during the study period. Controls were individuals who tested negative for hMPXV/orthopoxvirus without an accompanying positive or indeterminate test result. We called case patients and controls by telephone, making up to 5 calls or voicemail message attempts per prospective enrollee. Eligible participants were ≥18 years old, were tested 14–30 days before the interview, and spoke sufficient English or Spanish to provide informed consent to participate by telephone. At the request of the Los Angeles County Department of Public Health, Los Angeles County residents (except those residing in Pasadena or Long Beach) were not invited to participate. Case patients in Los Angeles closely resembled those in the rest of the state in terms of gender (96% men, 2% women, and 2% transgender, nonbinary, or other across both jurisdictions), race/ethnicity (45%–48% Hispanic/Latino, 25%–31% white, 13%–17% black, and 4%–6% Asian across both jurisdictions), and age distribution [18, 19]. The study protocol received a nonresearch determination from the Committee for the Protection of Human Subjects of the California Health and Human Services Agency.

Exposures

We used a standardized, computer-guided interview form (Qualtrics) to collect data from participants. Interview items addressed participants' demographic and clinical characteristics (including age, sex [male or female] and gender identity [eg, man, woman, transgender, and nonbinary], race/ethnicity, and symptoms), sexual behaviors with all partners during the 21 days preceding dates of symptom onset or testing (whichever was earliest; "risk period"), and whether participants were aware of any interaction with a potential mpox case patient (defined as a "potential index contact") during this risk period. Questions on sexual encounters with individuals not identified as potential index contacts were introduced in December after enrollment had begun. Using first name, last name, and date of birth, we cross-referenced participants against the CDPH Office of AIDS human immunodeficiency virus (HIV) case registry to validate participant-reported HIV infection status; with the CDPH sexually transmitted infection case registry to validate participant-reported chlamydia, gonorrhea, and syphilis infection history; and with the California Immunization Registry to validate participant-reported JYNNEOS vaccination status.

We requested that participants recall any interactions with (1) individuals who had symptoms of mpox during their interaction or (2) individuals who participants learned may have had mpox after their interaction occurred. Participants who answered "yes" to either type of exposure were asked to specify whether they were aware that their contacts were diagnosed with mpox by a healthcare provider ("diagnosed index contacts") or if they were unaware whether their contacts received any such diagnosis ("suspected index contacts"). To ensure capture of any relevant symptoms in index contacts, questions about index contact exposures followed an earlier questionnaire block addressing participants' own experience with symptoms listed on the CDC case report form [20]. For participants who reported exposure to a diagnosed or suspected index contact, we asked whether this exposure involved long-lasting face-to-face contact (≥3 hours), touching one another's skin, touching shared fomites (eg, food/dishes/utensils, towels/bedding/clothing; or drugs/drug equipment), providing care to the index contact while they were sick, or sexual contact (eg, intimate touching, use of shared sex toys, oral sex, or anal/vaginal intercourse).

Statistical Analysis

We first aimed to determine the association of hMPXV infection status with exposure to a potential diagnosed or suspected index contact within the risk period. We computed odds ratios (ORs) and accompanying 95% confidence intervals (CIs) comparing recall of the following exposures between case patients and controls: any exposure, nonsexual exposure, or sexual exposure to potential index contacts; sexual exposure to potential index contacts whom participants recalled as experiencing symptoms; and sexual exposure to potential index contacts whom participants did not recall as experiencing symptoms. We analyzed each of these exposures separately for diagnosed and suspected index contacts. All analyses defined no known contact (sexual or nonsexual) with a potential index contact as the reference exposure. We stratified analyses by participants who reported intimate touching, oral sex, anal/vaginal sex, or use of sex toys with multiple partners during the risk period and those who did not report multiple sexual partners. We also stratified analyses by participants' HIV infection status, as HIV infection could modify the likelihood of hMPXV infection, given exposure.

Because few participants reported exposure to potential index contacts, we also aimed to identify whether sexual partnerships not known to involve index contacts were associated with

infection. To mitigate potential confounding driven by differences in risk behavior between case patients and controls or the willingness of case patients and controls to report sexual exposures, we restricted these analyses to case patients and controls who provided information on ≥1 sexual partnership during the risk period. We computed ORs measuring the association of case or control status with the number of partners with whom participants reported intimate touching, oral sex (giving or receiving), anal or vaginal sex (insertive or receptive), and anal or vaginal sex without condoms. We computed adjusted ORs for each exposure, using conditional logistic regression models matching participants on sex and whether they reported contact with any potential index contact. Analyses addressing each sexual exposure adjusted for the number of partners with whom participants reported engaging in all other sexual acts listed above.

To assess the biological plausibility that reported exposures accounted for hMPXV infection among case patients, we further estimated associations of specific reported sex acts with sites of lesion occurrence among case patients who reported lesions. We compared odds of intimate touching of the penis, receptive oral sex involving the penis, and insertive anal or vaginal sex (with or without condoms) among male case patients reporting penile lesions or no penile lesions during their illness. In addition, we compared odds of intimate touching of the anus/rectum, receptive oral sex on the anus/rectum, and receptive anal sex (with or without condoms) among case patients (male or female) reporting anorectal lesions or no anorectal lesions during their illness. For intimate touching and oral sex exposures, we repeated analyses among participants who did not report condomless anal or vaginal sex acts. Because we enrolled few female case patients, we did not undertake similar analyses comparing case patients with or without vaginal lesions. We used logistic regression to adjust for other sex acts reported by participants. We conducted statistical analyses using R software (version 4.3.0; R Foundation for Statistical Computing).

RESULTS

Enrollment

Between November 2022 and June 2023, we enrolled 54 mpox case patients and 117 controls (Table 1). In total, 49 case patients (90.7%) and 92 controls (78.6%) were assigned male sex at birth, and 48 case patients (88.9%) and 92 controls (78.6%) were cisgender men. We also enrolled 2 transgender men and 1 transgender woman as case patients. Among 49 male case patients, 39 (88.9%) reported male sex partners during the risk period, versus 32 of 92 male controls (34.8%) (64.0% of 50 male controls who provided information on ≥1 sex partner during the risk period). Racial and ethnic composition was similar among case patients and controls. Case patients were more likely than controls to have HIV infection, to have laboratory-confirmed history of chlamydia, gonorrhea, or syphilis, and to have received ≥1 JYNNEOS vaccine dose. Differences in vaccination among case patients and controls were attenuated within analyses subset to MSM and non-MSM strata (Supplementary Table 1).

Table 1. Characteristics of Enrolled Case Patients and Test-Negative Controls

Characteristic	Prevalence, No. (%)	
	Case Patients (n = 54)	Test-Negative Controls (n = 117)
Sex at birth		
Male	49 (90.7)	92 (78.6)
Female	5 (9.3)	25 (21.4)
Gender		
Cisgender men	48 (88.9)	92 (78.6)
Cisgender women	3 (5.6)	25 (21.4)
Transgender men	2 (3.7)	0
Transgender women	1 (1.9)	0
Sexual behavior during risk period (among participants assigned male sex at birth)		
Male sex partners	39/49 (79.6)	32/92 (34.8)
No male sex partners or no recent sex partners identified[a]	10/49 (20.4)	60/92 (65.2)
Race or ethnicity[b]		
White	24 (44.4)	67 (57.3)
Hispanic	23 (42.6)	48 (41.0)
Asian	5 (9.3)	10 (8.5)
Black or African American	5 (9.3)	6 (5.1)
Native Hawaiian or Pacific Islander	1 (1.9)	2 (1.7)
American Indian or Alaska Native	1 (1.9)	3 (2.6)
Self-reported history of chlamydia, gonorrhea, or syphilis		
No history of infection reported	18 (33.3)	75 (64.1)
Infection <3 wk previously	10 (18.5)	5 (4.3)
Infection ≥3 wk and <12 mo previously	8 (14.8)	13 (11.1)
Infection ≥1 y previously	18 (33.3)	24 (20.5)
Self-reported history of other STIs		
No history of infection reported	49 (90.7)	95 (81.2)
Infection <3 wk previously	0	7 (6.0)
Infection ≥3 wk and <12 mo previously	0	0
Infection ≥1 y previously	5 (9.3)	15 (12.8)
HIV infection[c]		
Living with HIV infection	19 (35.2)	18 (15.4)
Not living with HIV infection	35 (64.8)	99 (84.6)
History of JYNNEOS vaccination		
No vaccination	34 (63.0)	89 (76.1)
1 Vaccine dose	8 (14.8)	12 (10.3)
2 Vaccine doses	12 (22.2)	16 (13.7)

Abbreviations: HIV, human immunodeficiency virus; STIs, sexually transmitted infections.

[a]Calculated among male participants who provided information on ≥1 sex partner during the risk period; 39 of 44 case patients (88.9%) and 32 of 50 controls (64.0%) had male sex partners.

[b]We indicate all races or ethnicities listed by participants; totals do not sum to 100% because individuals could report identifying with multiple racial or ethnic categories.

[c]We verified HIV infection status against California Department of Public Health Office of AIDS HIV case registry data.

Exposure to Potential Index Mpox Contacts

Seventeen case patients (30.8%) and 7 controls (6.0%) reported exposure to a potential index contact during the risk period (OR, 7.2 [95% CI, 2.5–13.5] for case patients vs controls; Table 2). Eight case patients and 4 controls identified their potential index contact as a diagnosed index contact (OR, 5.9 [95% CI, 1.7–19.9] for case patients vs controls). Most case patients (13 of 17 [76.5%]) and controls (5 of 7 [71.4%]) indicated that their exposures to potential index contacts were sexual (OR, 7.7 [95% CI, 2.5–19.3] among case patients vs controls). We also observed higher odds of nonsexual exposure to potential index contacts among case patients than among controls (OR, 5.9 [95% CI, 1.1–47.3]).

Among 13 case patients and 5 controls reporting sexual exposure to potential index contacts, 10 case patients and 2 controls could not recall their contact experiencing visibly apparent symptoms during encounters (OR, 14.9 [3.6–101.8] for case patients vs controls; Table 2). This association was apparent for exposures to diagnosed as well as suspected index contacts. We obtained similar findings in stratified analyses for participants who reported or did not report multiple partnerships during the study period (Supplementary Tables 2 and 3). Within the full sample, only 3 case patients (5.6%) and 3 controls (2.6%) reported sexual exposure to potential index contacts whom participants could recall as experiencing mpox symptoms at the time of the encounter (OR, 3.0 [0.5–15.9]; Table 2).

Seven of 19 case patients with HIV infection (36.8%) reported exposure to a potential index contact, and 6 (31.6%) reported sexual exposure (Table 3). No controls with HIV infection reported exposure to potential index contacts, precluding numerical analyses within this subgroup. Among HIV-uninfected participants, case patients had higher odds than controls of reporting any exposure to a potential index contact (OR, 5.3 [95% CI, 1.7–10.7] for case patients vs controls) and sexual exposure to a potential index contact (5.2 [1.5–14.4]).

Table 2. Recall of Exposure to Mpox Index Contacts Among Participants

Exposure[a]	Prevalence of Exposure, No. (%)		
	Case Patients (n = 54)	Test-Negative Controls (n = 117)	OR (95% CI)[b]
Exposure to an index contact			
Any index contact	17 (31.5)	7 (6.0)	7.2 (2.5–13.5)
Diagnosed index contact	8 (14.9)	4 (3.4)	5.9 (1.7–19.9)
Suspected index contact	9 (16.7)	3 (2.6)	8.9 (2.4–37.0)
Nonsexual exposure to an index contact			
Any index contact	4 (7.4)	2 (1.7)	5.9 (1.1–47.3)
Diagnosed index contact	2 (3.7)	2 (1.7)	3.0 (.3–27.3)
Suspected index contact	2 (3.7)	0	…
Sexual exposure to an index contact			
Any index contact	13 (24.1)	5 (4.3)	7.7 (2.5–19.3)
Diagnosed index contact	6 (11.1)	2 (1.7)	8.9 (2.0–66.3)
Suspected index contact	7 (13.0)	3 (2.6)	6.9 (1.8–30.6)
Sexual exposure to an index contact with apparent symptoms at the time of the encounter			
Any index contact	3 (5.6)	3 (2.6)	3.0 (.5–15.9)
Diagnosed index contact	1 (1.9)	1 (0.9)	3.0 (.1–111.3)
Suspected index contact	2 (3.7)	2 (1.7)	3.0 (.3–27.3)
Sexual exposure to an index contact without apparent symptoms at the time of the encounter			
Any index contact	10 (18.5)	2 (1.7)	14.9 (3.6–101.8)
Diagnosed index contact	5 (9.3)	1 (0.9)	14.9 (2.5–531.8)
Suspected index contact	5 (9.3)	1 (0.9)	14.9 (2.5–531.8)

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]We define "exposure to an index contact" as any recollection of a partner experiencing mpox symptoms during an interaction, or recollection of interaction with a partner who participants subsequently learned may have had mpox. Participants were asked to specify whether they were aware of index contacts having received an mpox diagnosis from a healthcare provider, regardless of their answer to the previous questions.

[b]All analyses define individuals without any recall of exposure to an index contact as the referent group (37 of 54 case patients [68.5%]; 110 of 117 controls [94.0%]).

All Sexual Exposures Among Case Patients and Controls

Information on sexual acts undertaken with ≥1 partner during the risk period were available from 37 case patients and 65 controls (Table 4). Comparing case patients with controls, the adjusted ORs for reporting anal/vaginal sex with 2–3 or ≥4 partners (vs 0–1 partners) were 2.2 (95% CI, 1.0–4.8) and 3.8 (1.7–8.8), respectively. For anal/vaginal sex without condoms, the corresponding adjusted ORs were 2.3 (95% CI, 1.2–4.4) and 3.6 (1.5–8.8), respectively. In addition, case patients, compared with controls, had 3.0-fold (95% CI, 1.0–9.0) and 2.9-fold (.9–9.4) higher adjusted odds of reporting intimate touching with 2–3 or ≥4 partners (vs 0–1 partners).

Male case patients with penile lesions had 9.3-fold (95% CI, 1.6–54.8) higher adjusted odds of reporting insertive anal/vaginal sex acts with any partner during the risk period, compared with male case patients who did not experience penile lesions (Table 5). Likewise, case patients with anorectal lesions, compared with those without such lesions, had 14.4-fold (95% CI, 1.0–207.3) higher adjusted odds of reporting receptive anal sex with any partner during the risk period. We did not identify strong evidence that intimate touching or oral sex involving the penis or anus/rectum were associated with occurrence of lesions at either site among case patients. In addition, insertive anal/vaginal sex and receptive anal sex acts with condoms were not independently associated with penile or anorectal lesion occurrence, respectively (adjusted OR, 1.6 [95% CI, .1–25.5] and 0.9 [.2–5.2], respectively), although few participants reported condom use during anal or vaginal sex.

Table 3. Recall of Exposure to Mpox Index Contacts Among Participants With or Without HIV Infection

Exposure[a]	Prevalence of Exposure, No./Total No. (%)		OR (95% CI)[b]
	Case Patients	Test-Negative Controls	
Recalled exposure to an index contact			
Participants living with HIV	7/19 (36.8)	0/18	…
Participants not living with HIV	10/35 (28.6)	7/99 (7.1)	5.3 (1.7–10.7)
Nonsexual exposure to an index contact			
Participants living with HIV	1/19 (5.3)	0/18	…
Participants not living with HIV	3/35 (8.6)	2/99 (2.0)	5.5 (.9–44.4)
Sexual exposure to an index contact			
Participants living with HIV	6/19 (31.6)	0/18	…
Participants not living with HIV	7/35 (20.0)	5/99 (5.1)	5.2 (1.5–14.4)

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio.

[a]We define "exposure to an index contact" as any recollection of a partner experiencing mpox symptoms during an interaction, or recollection of interaction with a partner who participants subsequently learned may have had mpox. Participants were asked to specify whether they were aware of index contacts having received an mpox diagnosis from a healthcare provider, regardless of their answer to the previous questions.

[b]All analyses defined individuals without any recall of exposure to an index contact as the referent group (12 case patients and 18 controls living with HIV; 25 case patients and 92 controls not living with HIV).

In stratified analyses, the odds of reporting intimate touching or oral sex exposures on the penis among HIV-negative case patients were 18.0-fold (95% CI, 1.3–702.9) and 14.8-fold (1.5–245.5) higher, respectively, among case patients with penile lesions than among those without such lesions (Table 6). Among HIV-negative case patients who did not report penile lesions, none reported insertive anal/vaginal sex acts. The odds of reporting intimate touching and receptive oral sex on the anus/rectum were 6.4-fold (95% CI, .7–207.5) and 14.5-fold (1.5–473.1) higher, respectively, among HIV-negative case patients with anorectal lesions than among those without such lesions. All HIV-negative case patients who experienced anorectal lesions reported receptive anal sex, and 6 out of 7 reported condomless receptive anal sex (OR, 19.5 [95% CI, 2.0–650.4]).

DISCUSSION

Our analyses provide evidence suggesting that individuals without visibly prominent symptoms of mpox may transmit hMPXV infection. First, few case patients enrolled in our study recalled sexual exposure to potential index contacts experiencing symptoms that were apparent to participants at the time of the encounter. A greater proportion recalled exposure to potential index contacts who were not experiencing apparent symptoms, and these exposures were associated with increased odds of infection. Second, anal or vaginal intercourse with more partners was independently associated with increased risk of infection after adjustment for participants' known exposure to potential index contacts, supporting the hypothesis that exposures to partners not identified as potential index contacts accounted for a substantial share of hMPXV acquisition. Third, recent insertive and receptive sex acts were associated with lesion occurrence at penile and anorectal anatomic sites, respectively. Collectively, the low proportion of case patients recalling exposure to symptomatic individuals, the association of infection risk with sexual encounters involving individuals who did not experience mpox symptoms, and the specificity of this association by site of sexual exposure and lesion occurrence suggest that hMPXV is often acquired through sexual contact with individuals not experiencing prominent mpox symptoms.

Whereas current US public health guidance emphasizes contact with rashes or scabs as the primary route of hMPXV transmission [6], our analyses complement other reported evidence demonstrating transmission by individuals without symptoms [21]. Contact-tracing studies in the United Kingdom [13] and the Netherlands [14] that established links between confirmed case patients identified presymptomatic transmission in 28%–80% of all confirmed case pairs. In Nigeria, 87% of exposures associated with sexual contact occurred while index contacts were not experiencing rash or other skin symptoms [4, 22]. However, these studies may misrepresent the frequency of transmission by persons without symptoms owing to the potential for asymptomatic cases to go undiagnosed or for partnerships involving such individuals to go unascertained. This risk may be especially pronounced in the context of anonymous encounters.

Within our study, anonymous sex may have hindered participants' ability to identify instances where they were exposed to presymptomatic individuals with whom they had no further contact, including after these individuals experienced symptoms. Thus, our finding that 10 of 54 case patients reported contact with potential index contacts while they were not experiencing symptoms may underestimate the proportion of transmission associated with exposure to presymptomatic index contacts. However, anonymous sex is unlikely to account for the low proportion of case patients who recalled exposure to partners while these partners were experiencing apparent symptoms (3 of 54 case patients). This observation suggests that exposure to symptomatic individuals may account for a smaller-than-expected proportion of mpox cases.

Three studies in which MSM were prospectively tested for hMPXV DNA via anorectal swab samples found that a majority of detections were associated with infections that did not ultimately result in symptoms or care seeking [12, 23, 24]; in one study, these asymptomatic infections were confirmed to result in seroconversion and replication-competent viral shedding [12]. Many patients report significant pain and discomfort

Table 4. Sexual Exposures Among Participants Providing Information on ≥1 Sexual Encounter During the Risk Period

Exposure	Prevalence of Exposure, No./Total No (%)		OR (95% CI)	
	Case Patients (n = 37)	Test-Negative Controls (n = 65)	Unadjusted	Adjusted[a]
Intimate touching				
Any exposure	37 (100.0)	62 (95.4)	…	…
0–1 Partner	4 (10.8)	27 (41.5)	Reference	Reference
2–3 Partners	16 (43.2)	21 (32.3)	3.4 (1.3–9.0)	3.0 (1.0–9.0)
≥4 Partners	17 (45.9)	17 (26.2)	3.9 (1.5–10.3)	2.9 (.9–9.4)
Oral sex				
Any exposure	33 (89.2)	58 (89.2)	…	…
0–1 Partner	14 (37.8)	38 (58.5)	Reference	Reference
2–3 Partners	13 (35.1)	20 (30.8)	1.5 (.8–2.7)	0.9 (.4–1.8)
≥4 Partners	10 (27.0)	7 (10.8)	2.2 (1.2–4.0)	0.7 (.3–1.8)
Anal/vaginal sex				
Any exposure	36 (97.3)	58 (89.2)	…	…
0–1 Partner	9 (24.3)	40 (61.5)	Reference	Reference
2–3 Partners	16 (43.2)	19 (29.2)	2.5 (1.2–5.0)	2.2 (1.0–4.8)
≥4 Partners	12 (32.4)	6 (9.2)	3.6 (1.8–7.1)	3.8 (1.7–8.8)
Anal/vaginal sex without condoms				
Any exposure	31 (83.8)	54 (83.1)	…	…
0–1 Partner	16 (43.2)	49 (75.4)	Reference	Reference
2–3 Partners	13 (35.1)	12 (18.5)	2.1 (1.2–3.7)	2.3 (1.2–4.4)
≥4 Partners	8 (21.6)	4 (6.2)	2.7 (1.5–4.9)	3.6 (1.5–8.8)
Anal/vaginal sex with condoms				
Any exposure	14 (37.8)	15 (23.1)	…	…
0–1 Partner	31 (83.8)	59 (90.8)	Reference	Reference
2–3 Partners	5 (13.5)	4 (6.2)	1.6 (.8–3.1)	1.6 (.8–3.1)
≥4 Partners	1 (2.7)	2 (3.1)	1.0 (.2–4.9)	1.2 (.2–10.0)

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]We estimated adjusted associations in logistic regression models, accounting for participant sex, recall of exposure to a potential index contact, and other reported sexual acts performed; analyses were adjusted for the number of partners with whom participants report engaging in all listed behaviors and matched on participants' history of sexual contact with a potential index contact and sex (male or female).

associated with mpox lesions [25–27], which may reduce their likelihood of pursuing sexual contact while symptomatic. Although US public health guidance indicates that no case patients of transmission have been definitively linked to exposure to infected persons who never developed signs or symptoms of illness, guidelines allowing only for lesion-based diagnostic testing impede detection of asymptomatic case patients [6]. This may lead to missed opportunities for identifying individuals at risk of spreading hMPXV, as well as inaccurate estimates of the incidence and prevalence of hMPXV infection [7–11].

In our study, all participants with HIV infection who reported exposure to a potential index contact were infected with mpox, precluding direct comparisons of the association of infection risk with participants' recall of exposure to index contacts according to HIV infection status. Attenuated effect size estimates for this association among HIV-negative participants suggests that HIV infection may be associated with the risk of acquiring infection given exposure to an mpox case patient. Lesion sites were also less strongly associated with sexual exposure sites among case patients with HIV infection, consistent with the hypothesis that HIV enhances the clinical severity of mpox (as noted in prior studies undertaken within sub-Saharan Africa [22] as well as the current outbreak among MSM [28]). While the prevalence of HIV infection was greater among case patients than among controls in our analysis, our study was underpowered for generating adjusted estimates of the effect of HIV infection on the risk of hMPXV infection.

Case patients reported engaging in intimate touching, oral sex, and anal/vaginal sex with more partners than did controls, suggesting that contact with more partners is associated with increased risk of infection. Although we did not identify a strong association between case status and anal/vaginal sexual acts involving condoms, this finding may not indicate protective effect modification by condom use owing to the limited number of participants reporting condom use. Similarly, the lack of an association between oral sex acts and case status may owe to correlation between the number of partnerships involving both intimate touching and oral sex. In a prior mpox outbreak within a heterosexual network in Nigeria, infection was likewise associated with condomless vaginal sex [4, 5]. Consistent with our findings, the presence or absence of genital

Table 5. Rash Location and Site-Specific Sexual Exposures Among Case Patients

Exposure by Anatomic Site and Patient Group	Patients, No. (%)		OR (95% CI)	
	Rash at Indicated Site	No Rash	Unadjusted	Adjusted[a]
Penis				
Case patients assigned male sex at birth	n = 22	n = 12	…	…
Intimate touching of penis by partners	20 (90.9)	9 (75.0)	3.3 (.5–23.6)	4.0 (.1–140.1)
Received oral sex on penis	19 (86.4)	8 (66.7)	3.2 (.6–17.5)	0.5 (.0–12.0)
Insertive anal/vaginal sex (any)	18 (81.8)	4 (33.3)	9.0 (1.8–45.4)	9.3 (1.6–54.8)
Insertive anal/vaginal sex—with condom	1 (4.5)	3 (25.0)	1.7 (.2–18.8)	1.6 (.1–25.5)
Insertive anal/vaginal sex—without condom	17 (77.3)	4 (33.3)	6.8 (1.4–32.4)	6.4 (1.1–37.8)
Case patients assigned male sex at birth who did not report condomless insertive anal/vaginal sex	n = 5	n = 8	…	…
Intimate touching of penis by partners	4 (80.0)	5 (62.5)	2.4 (.2–33.0)	3.0 (.1–107.1)
Received oral sex on penis	3 (60.0)	4 (50.0)	1.5 (.2–14.4)	0.8 (.0–17.6)
Rectum/anus				
All case patients	n = 14	n = 23	…	…
Intimate touching of rectum/anus by partners	13 (92.9)	14 (60.9)	8.4 (.9–75.6)	1.7 (.1–32.7)
Received oral sex on anus	9 (64.3)	10 (43.5)	2.3 (.6–9.2)	0.8 (.1–4.4)
Receptive anal sex (any)	13 (92.9)	10 (43.5)	16.9 (1.9–150.8)	14.4 (1.0–207.3)
Receptive anal sex—with condom	2 (14.3)	2 (8.7)	1.4 (.3–6.6)	0.9 (.2–5.2)
Receptive anal sex—without condom	12 (85.7)	8 (34.8)	11.2 (2.0–63.2)	10.2 (1.2–86.6)
Case patients who did not report condomless receptive anal sex	n = 2	n = 15	…	…
Intimate touching of rectum/anus by partner	1 (50.0)	7 (46.7)	1.1 (.1–21.8)	1.1 (.1–22.8)
Received oral sex on anus	1 (50.0)	3 (20.0)	4.0 (.2–84.1)	4.0 (.2–83.7)

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]We estimated adjusted associations in logistic regression models accounting for all other reported sexual acts listed within the tables.

and anorectal lesions in the Nigerian outbreak aligned with participants' reported history of sexual exposures.

Our analysis has several limitations. Low case counts and testing effort during the study period limited our sample size and opportunities to adjust for covariates, including JYNNEOS vaccination status and HIV-related clinical variables, such as viral suppression. While conducting enrollment by telephone enabled interviewers to build trust with participants, some individuals may have declined to participate owing to inconvenience or concerns around disclosing personal sexual histories. These factors may introduce nonresponse bias and limit external generalizability of our findings. Whereas the population at risk for mpox includes individuals of diverse sexual orientations and gender identities, our sample was insufficient for subgroup analyses within all relevant strata of interest (eg, transgender participants). Finally, recall of exposures over the 21-day period before participants' dates of testing or symptom onset may be imperfect, including for questions concerning symptoms in potential index contacts. This may have led to underestimation of the proportion of index contacts who experienced symptoms at the time of sexual encounters with participants. Recall bias is also a concern if case patients may have been more likely to recall potential exposures than controls or if the test-negative control population overrepresented individuals who sought testing proactively after low-risk exposures [29]. We did not ask participants whether index contacts could recall recent illnesses from which they had recovered, and some may have been in the recovery phase with lesions that were less noticeable.

Our findings have several practical implications. First, the association of increased risk with more partnerships implies that mpox incidence may be sensitive to changes in behavior. Reductions in new partnership formation among MSM during 2022 may have contributed to declining case numbers alongside vaccination, as supported by recent modeling studies [30, 31], although avoidance of sexual contact is not a viable or culturally appropriate long-term prevention strategy. Second, the association between lesion location and sexual practices may have relevance for interpreting clinical or surveillance data on case patients, helping to identify plausible routes of exposure and potentially identify partners for testing. Third, our findings add to growing evidence that clinical symptoms may not be requisite to hMPXV transmission. While limited by our reliance on participants' identification of potential index contacts and assessment of their symptoms, our results enhance earlier evidence of transmission by individuals without symptoms [4, 5, 13, 14]. Efforts are needed to better characterize the natural history of hMPXV infection, including the risk of transmission associated with differing clinical stages and clinical presentations, particularly in settings with high JYNNEOS vaccination coverage in at-risk populations [32]. Development of diagnostic protocols not reliant on lesion-based sampling may enhance our ability to identify individuals at risk of transmitting hMPXV.

Table 6. Rash Location and Site-Specific Sexual Exposures Among Case Patients With or Without HIV

Exposure by Anatomic Site and HIV Status	Patients, No. (%)		Unadjusted OR (95% CI)
	Rash at Indicated Site	No Rash	
Penis (male case patients only)			
Case patients living with HIV and assigned male sex at birth	n = 10	n = 6	…
Intimate touching of penis by partners	8 (80.0)	4 (66.7)	2.1 (.2–28.9)
Received oral sex on penis	8 (80.0)	4 (66.7)	2.1 (.2–28.9)
Insertive anal/vaginal sex (any)	8 (80.0)	3 (50.0)	4.7 (.5–65.0)
Insertive anal/vaginal sex—with condom	0	0	…
Insertive anal/vaginal sex—without condom	8 (80.0)	3 (50.0)	4.7 (.5–65.0)
Case patients not living with HIV and assigned male sex at birth	n = 13	n = 6	…
Intimate touching of penis by partners	12 (92.3)	3 (50.0)	18.0 (1.3–702.9)
Received oral sex on penis	11 (84.6)	2 (33.3)	14.8 (1.5–245.5)
Insertive anal/vaginal sex (any)	11 (84.6)	0	…
Insertive anal/vaginal sex—with condom	2 (15.4)	0	…
Insertive anal/vaginal sex—without condom	9 (69.2)	0	…
Rectum/anus			
Case patients living with HIV	n = 7	n = 11	…
Intimate touching of rectum/anus by partners	5 (71.4)	6 (54.5)	2.3 (.3–25.0)
Received oral sex on anus	2 (28.6)	5 (45.5)	0.4 (.0–3.4)
Receptive anal sex (any)	5 (71.4)	5 (45.5)	3.4 (.4– 37.8)
Receptive anal sex—with condom	1 (14.3)	1 (9.1)	1.7 (.0–76.7)
Receptive anal sex—without condom	4 (57.1)	4 (36.4)	2.5 (.3–21.8)
Case patients not living with HIV	n = 7	n = 16	…
Intimate touching of rectum/anus by partners	6 (85.7)	9 (56.2)	6.4 (.7–207.5)
Received oral sex on anus	6 (85.7)	6 (37.5)	14.5 (1.5–473.1)
Receptive anal sex (any)	7 (100.0)	9 (56.2)	…
Receptive anal sex—with condom	3 (42.9)	4 (25.0)	2.3 (.3–17.8)
Receptive anal sex—without condom	6 (85.7)	5 (31.2)	19.5 (2.0–650.4)

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the views or opinions of the California Department of Public Health, the California Health and Human Services Agency, or the US Centers for Disease Control and Prevention.

Data availability. Deidentified data that underlie the results reported in this article will be made available on reasonable request.

Financial support. The study was supported by the US Centers for Disease Control and Prevention cooperative agreement (grant PS19-1901 to the California Department of Public Health STD Control Branch) and the National Institute of Allergy and Infectious Diseases (grant R01-AI14812701 to J. A. L.).

Supplement sponsorship. This article appears as part of the supplement "Mpox: Challenges and Opportunities Following the Global 2022 Outbreak," sponsored by the Centers for Disease Control and Prevention (Atlanta, GA).

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Mitjà O, Ogoina D, Titanji BK, et al. Monkeypox. Lancet **2023**; 401:60–74.
2. Gessain A, Nakoune E, Yazdanpanah Y. Monkeypox. New Engl J Med **2022**; 387:1783–93.
3. Bolanda JD, Li Y, Reynolds MG, et al. Extended interhuman transmission of monkeypox in a hospital community in the Republic of the Congo, 2003. Am J Trop Med Hyg **2005**; 73:428–34.
4. Ogoina D, Yinka-Ogunleye A. Sexual history of human monkeypox patients seen at a tertiary hospital in Bayelsa, Nigeria. Int J STD AIDS **2022**; 33:928–32.

5. Ogoina D, James HI. Mpox among linked heterosexual casual partners in Bayelsa, Nigeria. New Engl J Med **2023**; 388:2101–4.
6. Centers for Disease Control and Prevention. Mpox in the US. https://www.cdc.gov/poxvirus/mpox/clinicians/prep-collection-specimens.html. Accessed 15 May 2023.
7. Hornuss D, Daehne T, Goetz V, et al. Transmission characteristics, replication patterns and clinical manifestations of human monkeypox virus—an in-depth analysis of four cases from Germany. Clin Microbiol Infect **2023**; 29:112.e5–e9.
8. Palich R, Burrel S, Monsel G, et al. Viral loads in clinical samples of men with monkeypox virus infection: a French case series. Lancet Infect Dis **2023**; 23:74–80.
9. Peiró-Mestres A, Fuertes I, Camprubí-Ferrer D, et al. Frequent detection of monkeypox virus DNA in saliva, semen, and other clinical samples from 12 patients, Barcelona, Spain, May to June 2022. Eurosurveillance **2022**; 27:2200503.
10. Coppens J, Vanroye F, Brosius I, et al. Alternative sampling specimens for the molecular detection of mpox (formerly monkeypox) virus. J Clin Virol **2023**; 159:105372.
11. Lim CK, McKenzie C, Deerain J, et al. Correlation between monkeypox viral load and infectious virus in clinical specimens. J Clin Virol **2023**; 161:105421.
12. De Baetselier I, Van Dijck C, Kenyon C, et al. Retrospective detection of asymptomatic monkeypox virus infections among male sexual health clinic attendees in Belgium. Nat Med **2022**; 28:2288–92.
13. Ward T, Christie R, Paton RS, Cumming F, Overton CE. Transmission dynamics of monkeypox in the United Kingdom: contact tracing study. BMJ **2022**; 379:e073153.
14. Miura F, Backer JA, van Rijckevorsel G, et al. Time scales of human mpox transmission in the Netherlands. J Infect Dis doi:10.1093/infdis/jiad091. Published 4 April 2023.
15. Van Dijck C, Hens N, Kenyon C, Tsoumanis A. The roles of unrecognized mpox cases, contact isolation and vaccination in determining epidemic size in Belgium: a modeling study. Clin Infect Dis **2023**; 76:e1421–3.
16. Cope AB, Kirkcaldy RD, Weidle PJ, et al. Evaluation of public health contact tracing for mpox among gay, bisexual, and other men who have sex with men—10 US jurisdictions, May 17–July 31, 2022. Am J Public Health **2023**; 113:815–8.
17. Smith LE, Potts HW, Brainard J, et al. Mpox knowledge, attitudes, beliefs, and intended behaviour in the general population and men who are gay, bisexual, and who have sex with men. medRxiv [Preprint: not peer reviewed]. 9 December 2022. Available from: https://www.medrxiv.org/content/10.1101/2022.12.07.22283201v1.
18. Los Angeles County Department of Public Health. Mpox. http://publichealth.lacounty.gov/media/monkeypox/data/index.htm. Accessed 5 June 2023.
19. California Department of Public Health. Mpox data. https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/Mpox-Data.aspx. Accessed 5 June 2023.
20. Centers for Disease Control and Prevention. 2022 US monkeypox outbreak short case report form. https://www.cdc.gov/poxvirus/mpox/pdf/scrf-short-form.pdf. Accessed 2 October 2023.
21. Freeman EE, Abbott S, Kurpiel B, Okwor T. The dynamics of monkeypox transmission. BMJ **2022**; 379:o2504.
22. Ogoina D, Iroezindu M, James HI, et al. Clinical course and outcome of human monkeypox in Nigeria. Clin Infect Dis **2020**; 71:e210–4.
23. Ferré VM, Bachelard A, Zaidi M, et al. Detection of monkeypox virus in anorectal swabs from asymptomatic men who have sex with men in a sexually transmitted infection screening program in Paris, France. Ann Intern Med **2022**; 175:1491–2.
24. Brosius I, Dijck CV, Coppens J, et al. Presymptomatic viral shedding in high-risk mpox contacts: a prospective cohort study. J Med Virol **2023**; 95:e28769.
25. Angelo KM, Smith T, Camprubí-Ferrer D, et al. Epidemiological and clinical characteristics of patients with monkeypox in the GeoSentinel network: a cross-sectional study. Lancet Infect Dis **2023**; 23:196–206.
26. Mailhe M, Beaumont A-L, Thy M, et al. Clinical characteristics of ambulatory and hospitalized patients with monkeypox virus infection: an observational cohort study. Clin Microbiol Infect **2023**; 29:233–9.
27. Matias WR, Koshy JM, Nagami EH, et al. Tecovirimat for the treatment of human monkeypox: an initial series from Massachusetts, United States. Open Forum Infect Dis **2022**; 9:ofac377.
28. Mitjà O, Alemany A, Marks M, et al. Mpox in people with advanced HIV infection: a global case series. Lancet **2023**; 401:939–49.
29. Lewnard JA, Patel MM, Jewell NP, et al. Theoretical framework for retrospective studies of the effectiveness of SARS-CoV-2 vaccines. Epidemiology **2021**; 32:508–17.
30. Endo A, Murayama H, Abbott S, et al. Heavy-tailed sexual contact networks and monkeypox epidemiology in the global outbreak, 2022. Science **2022**; 378:90–4.
31. Brand SPC, Cavallaro M, Cumming F, et al. The role of vaccination and public awareness in forecasts of mpox incidence in the United Kingdom. Nat Commun **2023**; 14:4100.
32. Owens LE. JYNNEOS vaccination coverage among persons at risk for mpox—United States, May 22, 2022–January 31, 2023. MMWR Morb Mortal Wkly Rep **2023**; 72:342–7.