Received: 8 February 2023 | Accepted: 8 April 2023

DOI: 10.1002/jmv.28769

RESEARCH ARTICLE

JOURNAL OF MEDICAL VIROLOGY WILEY

Presymptomatic viral shedding in high-risk mpox contacts: A prospective cohort study

Isabel Brosius[1] | Christophe Van Dijck[1,2] | Jasmine Coppens[1] | Leen Vandenhove[1] | Eugene Bangwen[1] | Fien Vanroye[1] | Jacob Verschueren[1] | The ITM MPOX Study Group | Sabine Zange[3] | Joachim Bugert[3] | Johan Michiels[4] | Emmanuel Bottieau[1] | Patrick Soentjens[1] | Johan van Griensven[1] | Chris Kenyon[1,5] | Kevin K. Ariën[4,6] | Marjan Van Esbroeck[1] | Koen Vercauteren[1] | Laurens Liesenborghs[1]

[1]Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium

[2]Laboratory of Medical Microbiology, University of Antwerp, Antwerp, Belgium

[3]Bundeswehr Institute of Microbiology, Munich, Germany

[4]Department of Biomedical Sciences, Institute of Tropical Medicine, Antwerp, Belgium

[5]Division of Infectious Diseases and HIV Medicine, University of Cape Town, Cape Town, South Africa

[6]Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium

Correspondence

Isabel Brosius, Department of Clinical Sciences, Institute of Tropical Medicine, Nationalestraat 155, 2000 Antwerp, Belgium.
Email: ibrosius@itg.be

Funding information

Departement of Economy, Science and Innovation of the Flemish government; Research Foundation–Flanders, Grant/Award Number: G096222N

Abstract

The risk of infection after exposure to clade IIb mpox virus (MPXV) is unknown, and potential presymptomatic shedding of MPXV remains to be demonstrated. High-risk contacts of mpox patients were followed-up in a prospective longitudinal cohort study. Individuals reporting sexual contact, >15 min skin-to-skin contact, or living in the same household with an mpox patient were recruited in a sexual health clinic in Antwerp, Belgium. Participants kept a symptom diary, performed daily self-sampling (anorectal, genital, and saliva), and presented for weekly clinic visits for physical examination and sampling (blood and oropharyngeal). Samples were tested for MPXV by PCR. Between June 24 and July 31, 2022, 25 contacts were included, of which 12/18 (66.0%) sexual and 1/7 (14.0%) nonsexual contacts showed evidence of infection by MPXV-PCR. Six cases had typical mpox symptoms. Viral DNA was detected as early as 4 days before symptom onset in 5 of them. In 3 of these cases, replication-competent virus was demonstrated in the presymptomatic phase. These findings confirm the existence of presymptomatic shedding of replication-competent MPXV and emphasize the high risk of transmission during sexual contact. Sexual contacts of mpox cases should abstain from sex during the incubation period, irrespective of symptoms.

KEYWORDS

monkeypox virus, mpox, presymptomatic, transmission, viral shedding

Isabel Brosius and Christophe Van Dijck contributed equally to this work.

1 | INTRODUCTION

Since May 2022, an outbreak of mpox (formerly monkeypox) has caused more than 80 000 laboratory-confirmed cases across the world, primarily among men who have sex with men (MSM).[1] This epidemic is caused predominantly by variant B.1 of the subclade IIb of monkeypox virus (MPXV), and, in contrast to previous outbreaks, is driven uniquely by human-to-human transmission, especially through sexual contact.[2] Highest MPXV DNA loads are demonstrated in skin lesion and anorectal samples.[3,4] In addition, the clinical presentation in this global outbreak differs from what was commonly reported before 2022. Lesions often predominate or first appear at the presumed site of inoculation and frequently involve mucosal membranes, resulting in proctitis, urogenital symptoms, or tonsillitis.[2,5]

Based on data from previous outbreaks, most guidelines, including those issued by WHO, ECDC, and US CDC, considered mpox patients infectious from the start of symptoms until the complete healing of skin lesions.[6,7] For that reason, public health messaging has mainly focused on awareness of symptoms, early diagnosis, and isolation of symptomatic cases.

However, it was recently demonstrated that asymptomatic MPXV infections could play an important role in transmission.[8–11] Furthermore, recent epidemiological data suggest that pre-symptomatic transmission also occurs and could be responsible for about half of all infections.[12] Presymptomatic transmission can take place when viral shedding precedes clinical symptoms and often has a major impact on epidemic dynamics, as observed during the COVID-19 outbreak.[13] Nevertheless, presymptomatic shedding of MPXV, the body sites from which it may occur and its timing in relation to the onset of symptoms remain elusive.[14]

To study the risk of infection after exposure to MPXV and the natural history of the early phase of MPXV infection, we performed a detailed follow-up of high-risk contacts of clade IIb MPXV infected patients. Here, we describe their clinical and virological characteristics from exposure until potential diagnosis.

2 | METHODS

2.1 | Study design and participants

In this study, we prospectively followed-up individuals who had high-risk contact with a confirmed mpox patient. Participants were recruited in two ways: either by referral through their index cases, or when they presented for postexposure vaccination (PEV). High-risk contact was defined as either sexual contact (exposure of mucosal membranes through receptive or insertive penetrative or oral sex, irrespective of exposure time), prolonged (>15 min) skin-to-skin contact with an mpox patient with skin lesions, or living in the same household as an mpox patient. Adult individuals were included in this study if their contact occurred in the 21 days before recruitment and if they provided written informed consent for study participation.

Study participants attended a predefined schedule of clinic visits, including one baseline visit and weekly follow-up visits (Figure 1A). At baseline, we recorded medical history including smallpox vaccination status, and date and type of contact with the index case. At every visit, symptoms were recorded through a standardized questionnaire, clinical signs of mpox were assessed by a thorough physical examination, and the following samples were collected: blood, saliva, oropharyngeal swabs, genital swabs (skin swab from the coronal sulcus for men or vaginal swab for women), anorectal swabs, and swabs from skin lesions if applicable. Between study visits, participants were asked to keep a symptom diary and to perform daily self-sampling of anorectal swabs, genital swabs, and saliva at home.[15–17] Study follow-up was ceased maximum 21 ± 2 days after inclusion or as soon as any sample was MPXV-PCR positive with C_t-value <34 in a participant with typical mpox symptoms which were defined as characteristic mpox skin lesions, proctitis, urethritis, or tonsillitis. Confirmed mpox cases were further managed and followed up in routine clinical care.

2.2 | Sampling and sample handling

Blood (BD Vacutainer®; BD Benelux NV), saliva (15 mL Safe-Lock Tubes; Eppendorf Belgium NV-SA) and all study swabs (Eswab; Copan Diagnostics) were collected during clinic visits by a trained physician or nurse and were processed immediately. Home-based samples were collected with the same type of swabs and tubes prelabelled for this purpose. Home-based samples were packaged in appropriate packaging material for storage in the participant's refrigerator and were brought to the clinic at the next study visit.

2.3 | Laboratory procedures

The MPXV-PCR used in this study was an in-house PCR targeting the MPXV-TNF receptor gene carried out on the Applied Biosystems QuantStudio PCR system, as described previously.[8,18] Viral culture was performed as described previously, on a subset of MPXV-PCR positive samples with cycle threshold (C_t) value <30, from participants with presymptomatic viral shedding.[8]

Orthopoxvirus serology was performed at the end of follow-up for all participants and at baseline for participants with positive end-of-follow-up serology (IgG titer ≥1:20). An in-house assay detecting anti-orthopoxvirus IgG at the Bundeswehr Institute of Microbiology was used.[19]

2.4 | Cut-offs and definitions

Considering the reports of false positive MPXV-PCR results in patients with a low clinical suspicion of MPX,[20] we defined two C_t-value cutoffs: one highly specific (C_t 34) and another highly sensitive (C_t 37). The latter cutoff was based on a specificity analysis of the saliva samples from 52 healthy volunteers, analyzed in triplicate. Nineteen out of 156 (12.2%)

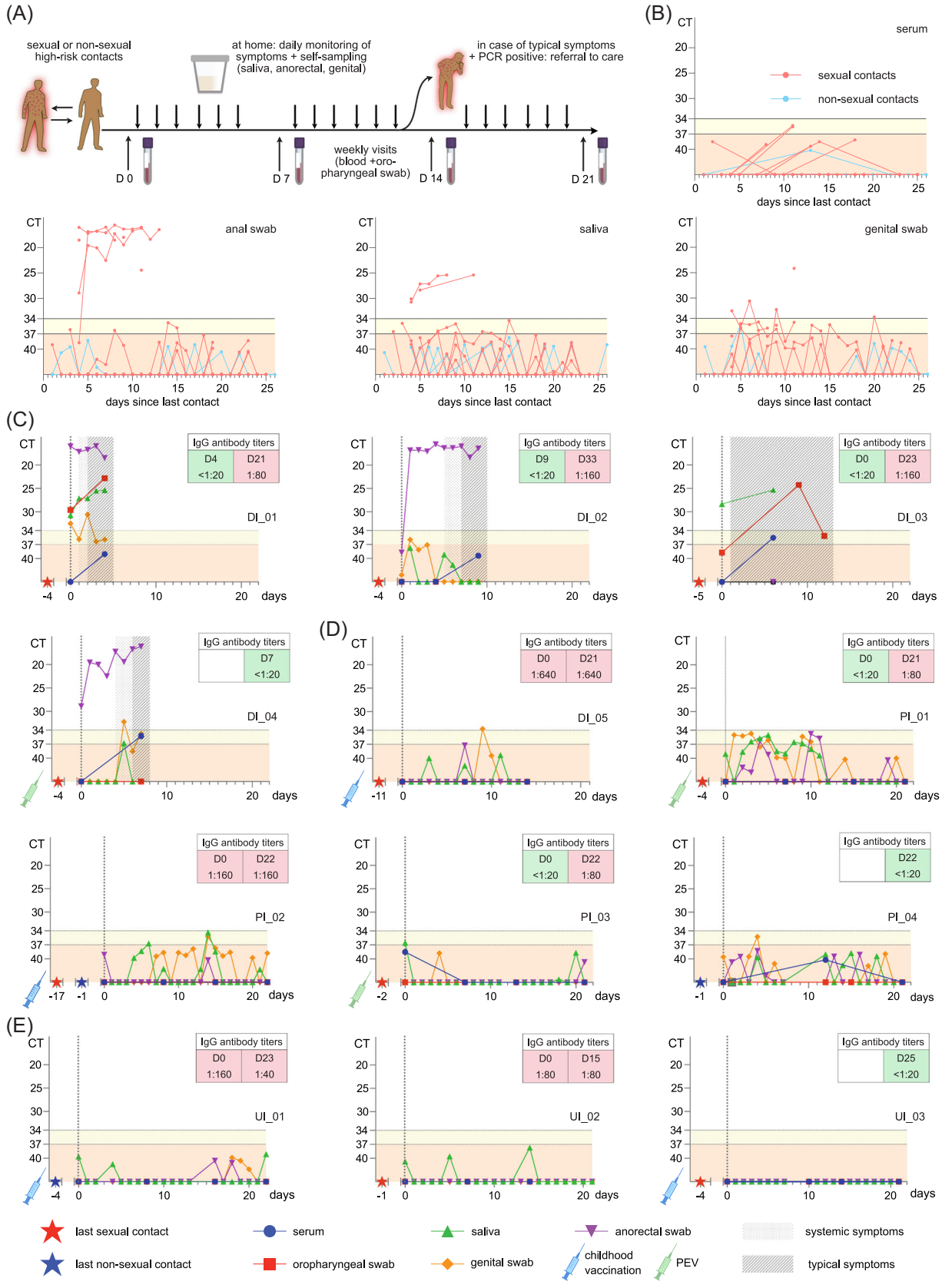

FIGURE 1 (See caption on next page)

analyses were MPXV-PCR positive, with a median C_t-value of 39.5 (range 39.3–42.6) (Supprting Information: Supplementary Table 1 and Supplementary Figure 1). A cutoff C_t-value of 37 was chosen to provide an additional margin of 2 C_t-values to preserve adequate specificity. Samples with C_t-values between 34 and 37 underwent confirmation testing by repeating the MPXV-PCR and a PCR melting curve analysis. Unconfirmed results were reported as negative.

Based on the two MPXV-PCR C_t-value cutoffs, the infection status of individual participants was defined as one of three outcomes: definitely infected, possibly infected, or uninfected (Box 1).

BOX 1: Outcome definitions

- Definitely infected = at least one sample with a MPXV-PCR C_t-value <34.
- Possibly infected = at least one sample with a MPXV-PCR C_t-value ≥34 to <37.
- Uninfected = all MPXV-PCR C_t-values ≥37.

C_t, cycle threshold; MPXV, monkeypox virus.

2.5 | Statistical analyses

Baseline characteristics and outcome variables were described as counts and proportions for categorical variables and means or medians with interquartile range for continuous variables. A two-sided Fisher's exact test was used to compare proportions and a two-sided Mann–Whitney *U* test to compare continuous variables. A $p \le 0.05$ was considered significant. Analyses were done with SPSS version 28.0.1.1 (IBM SPSS Statistics) and Prism version 9.4.1 (GraphPad Software; LLC). Figure panels and artwork were created with Affinity Designer version 2.0.0 (Serif Software).

3 | RESULTS

Recruitment started June 24, 2022 and ended July 31, 2022, due to the waning mpox epidemic. During this period, 25 high-risk contacts of 23 confirmed mpox cases were included. All participants except 1 (96.0%) self-identified as MSM; the median age was 43 years (IQR: 36–51, Table 1). Eighteen (72.0%) participants reported having had sexual contact with an index case. Seven (28.0%) were nonsexual high-risk contacts: 5 were household contacts, and 2 had prolonged skin-to-skin contact with an mpox confirmed case. The median time between the last exposure and inclusion was 4 (IQR: 3–7) days. Five participants received PEV, and 6 reported being vaccinated against smallpox during childhood. Overall, participants were followed-up for a median of 16 (IQR: 8–22) days, that is, until Day 23 (IQR: 14–26) after their last high-risk contact.

A total of 1108 samples were collected and analyzed by MPXV-PCR (Supporting Information: Supplementary Table 1), including 323 saliva, 323 anorectal, 312 genital, 70 oropharyngeal, 66 serum, and 14 skin samples. A total of 184 (16.6%) samples were MPXV-PCR positive, of which 142/184 (77.1%) showed C_t-values of 34 and higher. Overall, anorectal samples more often had a C_t-value <34 (7.7% of samples), compared to saliva (2.5%) and genital swabs (1.3%). In contrast, saliva and genital swabs were more often borderline (C_T 34–37) positive (3.1% and 4.1% of samples, respectively) compared to anorectal swabs (1.2%) (Figure 1B and Supppprting Information: Supplementary Figure 1).

Using the aforementioned outcome definitions (Box 1), we found that a high proportion ($n = 12/18$, 66.7%) of sexual contacts were definitely ($n = 8/18$, 44.4%) or possibly infected ($n = 4/18$, 22.2%) (Table 1). In contrast, among the nonsexual contacts (household or prolonged skin-to-skin contact), only 1 out of 17 (14.2%) was possibly infected, and none were definitely infected ($p = 0.03$ for comparing infection status between sexual and nonsexual contacts, Fisher's exact test). In definitely infected contacts, MPXV-PCR was positive (C_t-value <34) in anorectal, saliva, and genital samples in 75% ($n = 6/8$), 37.5% ($n = 3/8$), and 25% ($n = 2/8$) of cases, respectively. In 4 participants, MPXV was found in only 1 anatomical site (2 anorectal, 1 oral, and 1 genital).

Serum samples for serology, taken more than 21 days after exposure, were available from 11/14 (78.6%) unvaccinated participants ($n = 4$ definitely infected, $n = 2$ possibly infected, and $n = 5$ uninfected), and demonstrated seroconversion in all 4 definitely infected participants. The 2 possibly infected participants either had orthopoxvirus IgG at baseline or remained seronegative (Supporting Information: Supplementary Table 1).

Among the 8 definitely infected cases, 6 (75.0%) developed typical mpox symptoms, 1 (12.5%) had only fever and another (12.5%) only fatigue (Table 2). Typical symptoms included skin lesions ($n = 4$), proctitis ($n = 2$), and tonsillitis ($n = 1$), and were preceded by a prodromal phase in all cases. Only 4 out of 6 participants with MPXV-PCR positive anorectal swabs (C_t-value <34) had either proctitis or anal skin lesions, 2 of whom did not report receptive anal intercourse (1 did report receptive rimming). From 3 participants with MPXV-PCR

FIGURE 1 Serology and MPXV-PCR results for selected cases. (A) Schematic overview of the study design. (B) Overview of MPXV-PCR results of all sexual and nonsexual contacts, in relation to the day of last exposure (Day 0). Dots indicate PCR cycle threshold (C_t) values of individual samples; lines indicate individual participants. C_t-values <34 (white area), 34–37 (yellow area), and ≥37 (red area) are considered positive, weakly positive and negative, respectively. (C–E) Serology and MPXV-PCR results in a selection of the most illustrative cases, in relation to the day of inclusion (Day 0); (C) selected symptomatic cases with presymptomatic shedding, (D) selected asymptomatic or atypical cases, (E) selected uninfected participants. Different geometric symbols represent individual C_t value results of different sample types. Stars indicate the day of last sexual or nonsexual exposure and the syringes indicate vaccination status, shaded areas indicate the presence of systemic and typical monkeypox symptoms. Individual participant identification consists of category: DI = definitely infected, PI = possibly infected, or UI = uninfected and participant number. D denotes day. MPXV, monkeypox virus.

TABLE 1 Participant characteristics and clinical outcome by type of high-risk contact.

	Type of high-risk contact		
	Sexual (*n* = 18)	Nonsexual (*n* = 7)	Overall (*n* = 25)
Baseline characteristics			
Age (years)—median [Q1, Q3]	42.0 [33.8–50.5]	43.0 [41.5–48.5]	43.0 [36.0–51.0]
Male gender—*n* (%)	18 (100)	6 (85.7)	24 (96.0)
Smallpox vaccination			
Childhood vaccination—*n* (%)	5 (27.8)	1 (14.3)	6 (24.0)
Postexposure vaccination—*n* (%)	4 (22.2)	1 (14.3)	5 (20.0)
None—*n* (%)	7 (38.9)	5 (71.4)	12 (48.0)
Unknown—*n* (%)	2 (11.1)	0 (0)	2 (8.0)
HIV positive—*n* (%)	4 (22.2)	1 (14.3)	5 (20.0)
Immunosuppression—*n* (%)	1 (5.6)[a]	0 (0)	1 (4.0)
Other comorbidities	0 (0)	1 (14.3)[b]	1 (4.0)
Number of days between last exposure and enrollment—median [IQR]	4·00 [3.00–8.50]	3.00 [1.00–4.50]	4.00 [3.00–7.00]
Number of days of follow-up by PCR after enrollment—median [IQR]	12.5 [7.25–17.0]	22·0 [17.5–22.0]	16.0 [8.00–22.0]
Outcome			
Definitely infected—*n* (%)	8 (44.4)	0 (0)	8 (32.0)
Possibly infected—*n* (%)	4 (22.2)	1 (14.3)	5 (20.0)
Not infected—*n* (%)	6 (33.3)	6 (85.7)	12 (48.0)

[a]Common variable immunodeficiency.

[b]Crohn's disease, not using immunosuppressive medication.

positive oropharyngeal and saliva samples (C_t-value <34), 2 presented with tonsillitis without other oral lesions and 1 had no oropharyngeal signs or symptoms.

Among 5/6 (83.3%) definitely infected cases with typical presentation, viral DNA was detected 1 (*n* = 3) to 4 (*n* = 2) days before the onset of any symptoms. Figure 1C–E depicts the evolution of symptoms and PCR results for selected illustrative cases. The remaining cases are presented in Supporting Information: Supplementary Figure 2. Viral culture was attempted on 4 presymptomatically collected anorectal samples and 1 saliva sample. Three out of the 4 anorectal samples yielded replication-competent virus. The fourth anorectal sample had insufficient volume for culture and no virus was cultured out of the saliva sample.

Of the 5 possibly infected cases, none developed typical mpox symptoms. Two were asymptomatic, 1 had only night sweats, and 2 had other symptoms (headache, *n* = 1; sore throat without tonsillitis, *n* = 1). Overall, patients without typical symptoms (2 definitely infected, 5 possibly infected) had significantly lower viral loads compared to participants with typical symptoms (median of lowest recorded C_t-value 17.1 vs. 34.8, $p = 0.003$, Mann–Whitney test). Infected patients without typical symptoms tended to be more often vaccinated against smallpox, either during childhood (*n* = 2/7) or by PEV (*n* = 3/7) compared to participants with typical symptoms (1/6 received PEV), although the difference was not statistically significant ($p = 0.103$, Fisher's exact test).

4 | DISCUSSION

Our extensive follow-up of high-risk contacts provides unique and detailed insights into the early stages of mpox disease. First, we detected presymptomatic MPXV DNA and even replication-competent virus in 5 out of 6 participants with typical mpox symptoms, as early as 4 days before symptom onset. In reality, presymptomatic shedding might start even earlier, as 7 cases in our study were already PCR-positive at inclusion. The existence of presymptomatic transmission was suggested by an epidemiological study of surveillance and contact tracing data in the United Kingdom, which found that the median serial interval in 79 case-contact pairs was shorter than the median incubation period of 54 cases in the data set and that exposure of the contact took place during the presymptomatic phase of the index case in 10 out of 13 case-contact pairs.[12] We now provide biological evidence of presymptomatic shedding of viable MPXV, corroborating the epidemiological evidence of presymptomatic transmission. Moreover, we show that anorectal and, to a lesser extent, saliva and genital self-sampling are useful to detect early-stage infections, irrespective of symptoms or the nature of the sexual exposure.

Second, our findings indicate that the risk of infection after exposure to clade IIb MPXV through sexual contact may be higher than previously appreciated. In contrast, the risk for household and

TABLE 2 Clinical presentation and viral DNA detection by outcome.

	Definitely infected (*n* = 8)	Possibly infected (*n* = 5)	Uninfected (*n* = 12)	Overall (*n* = 25)
Asymptomatic—*n* (%)	0 (0)	2 (40.0)	7 (58.3)	9 (36.6)
Fever or night sweats only—*n* (%)	1 (12.5)	1 (20.0)	0 (0)	2 (8.0)
Other[a] symptoms only—*n* (%)	1 (12.5)	2 (40.0)	4 (33.3)	7 (28.0)
Typical[b] symptoms—*n* (%)	6 (75.0)	0 (0)	1 (8.3)[c]	7 (28.0)
Skin lesions—*n* (%)	4/6 (66.7)	NA	0/1 (0)	4/7 (57.1)
Proctitis—*n* (%)	2/6 (33.3)	NA	0/1 (0)	2/7 (28.6)
Urethritis—*n* (%)	0/6 (0)	NA	0/1 (0)	0/7 (0)
Tonsillitis—*n* (%)	1/6 (16.7)	NA	1/1 (100)[c]	3/7 (42.9)
Preceded by fever or other[a] symptoms—*n* (%)	6/6 (100)	NA	0/1 (0)	6/7 (85.7)
Preceded by presymptomatic MPXV DNA detection (C_t-value <37)—*n* (%)	5/6 (83.3)	NA	NA	5/6 (83.3)
Number of days between most recent contact and first positive MPXV DNA detection (C_t-value <37)—median (IQR)	5·00 [4.00–9.50]	5.0 [5.0–12.0]	NA	5.0 [4.0–11.0]
Number of days between most recent contact and first symptoms—median (IQR)	8.0 [4.5–10.0]	10.0 [6.5–13.5]	9.00 [6.00–9.00]	8.5 [5.0–10.0]

Abbreviations: C_t, PCR cycle threshold; IQR, interquartile range; MPXV, monkeypox virus; NA, not applicable.

[a]Other symptoms: headache, fatigue, mild sore throat without tonsillitis on clinical exam.

[b]Typical symptoms: classical monkeypox skin lesions, proctitis, urethritis, tonsillitis.

[c]Case UI_06 was diagnosed with a respiratory infection including tonsillitis due to COVID-19 during follow-up.

other nonsexual contacts appears to be low. Larger studies may allow to estimate the risk of infection more accurately.

Last, our data demonstrate that even though skin lesions and proctitis were commonly reported in mpox cases during the 2022 global outbreak,[2] such clinical presentations may be less common than generally assumed, as less than half of the infected cases in our study presented with typical mpox symptoms, and only one-third had skin lesions. Notably, the cases without typical symptoms in our study generally had low viral loads, and most were vaccinated either through PEV or during childhood. They might, therefore, have been able to suppress viral replication and the development of full-blown disease. However, it is noteworthy that we faced similar difficulties as others when interpreting weakly positive (C_t-values 34–37) MPXV-PCR results.[20] The use of serology to aid in the interpretation of infection status proved problematic because many cases had orthopoxvirus antibodies at baseline or developed them after postexposure smallpox vaccination. Others remained seronegative despite confirmed MPXV-PCR C_t-values <37. Possibly, antibody response is delayed or less pronounced in subclinical infections, although we cannot fully exclude low-grade contamination during the testing procedure. Overall, the exact clinical and epidemiological significance of cases with low levels of detectable viral DNA has yet to be determined.

In conclusion, our data emphasize the high risk of infection during sexual contact, even in the presymptomatic phase. High-risk contacts of an mpox case should be aware of the possibility of presymptomatic viral transmission, especially during sexual intercourse, and should be advised to abstain from sex for at least the duration of the incubation period, regardless of symptoms.

AUTHOR CONTRIBUTIONS

Isabel Brosius, Laurens Liesenborghs, Marjan Van Esbroeck, Koen Vercauteren, Johan van Griensven, Patrick Soentjens, Emmanuel Bottieau, and Chris Kenyon conceptualized the study. Isabel Brosius, Laurens Liesenborghs, and Leen Vandenhove managed the participants clinically. Marjan Van Esbroeck, Koen Vercauteren, Fien Vanroye, Jacob Verschueren, Kevin K. Ariën, Eugene Bangwen, and Jasmine Coppens supervised and coordinated the laboratory analyses at the Institute of Tropical Medicine. Sabine Zange and Joachim Bugert supervised and coordinated the laboratory analyses at the Bundeswehr Institute of Microbiology. Jasmine Coppens and Eugene Bangwen performed the testing at the Institute of Tropical Medicine. Isabel Brosius, Laurens Liesenborghs, Jasmine Coppens, and Christophe Van Dijck analyzed the data. Laurens Liesenborghs, Patrick Soentjens, and Johan van Griensven secured funding. Isabel Brosius, Christophe Van Dijck, and Laurens Liesenborghs wrote the first draft of the manuscript, with revision by Koen Vercauteren and Marjan Van Esbroeck. Isabel Brosius and Christophe Van Dijck contributed equally. All authors reviewed and approved the final version of the manuscript.

ACKNOWLEDGMENTS

We thank our participants for their willing contribution, the study staff and all clinical and laboratory personnel that had part in sample

collection and processing; and participant and patient care. This work was funded by Agency of Care and Health and the Department of Economy, Science, and Innovation of the Flemish government and the Research Foundation–Flanders (grant G096222N to E. Bo. and L. L.). The funder had no role in the collection, analysis, and interpretation of data, nor in the writing of the report or the decision to submit the manuscript for publication. All authors vouch for the accuracy and completeness of the data.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Deidentified participant data collected for the study will be made available from the corresponding authors on reasonable request.

ETHICS STATEMENT

The study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki and registered on ClinicalTrials.gov (NCT05443867). The protocol was approved by the Institutional Review Board of the Institute of Tropical Medicine (ITM) (1604/22) and by the Ethics Committee of the Antwerp University Hospital (2022-3571). All participants provided written informed consent before enrollment. Anonymized raw data will be made available upon request according to ITM's data sharing policy.

ITM MPOX STUDY GROUP

Isabel Brosius, MD; Christophe Van Dijck, MD, PhD; Jasmine Coppens, PhD; Leen Vandenhove, MD; Eugene Bangwen, MSc; Bart Smekens, PhD; Johan van Griensven, MD, PhD; Chris Kenyon, MD, PhD; Emmanuel Bottieau MD, PhD; Patrick Soentjens, MD, PhD; PhD MD, Camille Couwenbergh, BSc; Natalie De Cock, BSc; Irith De Baetselier, PhD; Nicole Berens-Riha, MD; Matilde Hens, MD; Liesbeth Van Gestel, MD; Jojanneke Rutgers, MD; Christophe Burm, MSc; Fien Vanroye, MSc; Dorien Van den Bossche, MD; Eric Florence MD, PhD; Kadrie Ramadan, BSc; Karin Van Looveren, BSc; Jolien Baeyens, BSc; Johan Michiels, BSc; Hanne Rasson, BSc; Yolien Decaluwe, BSc; Cindy Van Hoyweghen, BSc; Marianne Mangelschots, BSc; Saskia van Henten, MD; Stefanie Bracke, MD; Thibaut Vanbaelen, MD; Jacob Verschueren, MSc; Kevin K. Ariën, PhD; Koen Vercauteren, MD, PhD; Marjan Van Esbroeck, MD; Sandra Coppens, Bsc; Tessa de Block, Bsc; Antonio Mauro Rezende, PhD; Leo Heyndrickx, Msc; Laurens Liesenborghs, MD, PhD.

VIRUS NOMENCLATURE

Family	Poxviridae
Subfamily	Choordopoxvirinae
Genus	Orthopoxvirus
Species	Mononkeypox virus
Clade	II
Subclade	IIb

ORCID

Isabel Brosius http://orcid.org/0000-0003-2227-8874
Eugene Bangwen http://orcid.org/0000-0003-2314-2258
Laurens Liesenborghs http://orcid.org/0000-0001-5616-8548

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: 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. doi:10.1002/jmv.28769