ORIGINAL ARTICLE

Characteristics of confirmed mpox cases among clinical suspects: A prospective single-centre study in Belgium during the 2022 outbreak

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Abstract

Background: The presentation of mpox clade IIb during the 2022 outbreak overlaps with a range of other diseases. Understanding the factors associated with mpox is important for clinical decision making.

Methods: We described the characteristics of mpox patients who sought care at Belgian sexual health clinic. Furthermore we compared their characteristics to those of patients with a clinical suspicion of mpox but who tested negative on polymerase chain reaction.

Results: Between May 23 and September 20, 2022, 155 patients were diagnosed with mpox, and 51 patients with suspected symptoms tested negative. All mpox patients self-identified as men and 148/155 (95.5%) as gay or bisexual MSM. Systemic symptoms were present in 116/155 (74.8%) patients. All but 10 patients (145/155, 93.5%) presented with skin lesions. Other manifestations were lymphadenopathy (72/155, 46.5%), proctitis (50/155, 32.3%), urethritis (12/155, 7.7%), tonsillitis (2/155, 1.3%). Complications involved bacterial skin infection (13/155, 8.4%) and penile oedema with or without paraphimosis (4/155, 2.6%). In multivariable logistic regression models, the presence of lymphadenopathy (OR 3.79 95% CI 1.44–11.49), skin lesions (OR 4.35 95% CI 1.15–17.57) and proctitis (OR 9.41 95% CI 2.72–47.07) were associated with the diagnosis of mpox. There were no associations with age, HIV status, childhood smallpox vaccination, number of sexual partners and international travel.

Conclusions: The presence of proctitis, lymphadenopathies and skin lesions should increase clinical suspicion of mpox in patients with compatible symptoms.

Keywords: Mpox, Case series, Smallpox vaccination, HIV, Mpox PCR CT values, Belgium
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1. Background

The 2022 global outbreak of mpox (formerly monkeypox) is unprecedented in terms of the number of cases and extend of human-to-human transmission. As of 3 January 2023, over 83.000 mpox cases have been reported in 110 countries [1]. The strain responsible for this outbreak is a lineage of the subclade IIb *mpox virus*, which was previously confined to West Africa [2].

In Belgium, the first mpox case was detected on 10 May 2022. From then on, the number of cases increased rapidly and peaked in July 2022. By 3 January 2023, a total of 790 cases were reported country wide [3].

During the 2022 global outbreak, mpox disease presentation differed substantially from what was previously described in African endemic areas. Overall, the disease appeared to be milder, and its characteristic rash was more often localized to the presumed site of inoculation. Moreover, new disease manifestations emerged such as proctitis, penile oedema and paraphimosis [4–9]. It has been suggested that this difference in presentation may be related to the route of transmission, as

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most cases in the global outbreak were linked to sexual contact and disproportionally occurred among men who have sex with men (MSM) [10].

A thorough understanding of the risk factors and disease spectrum of mpox is important for early diagnosis of cases, and thus, epidemic management. Here, we describe the demographic, clinical and virological characteristics of suspected and confirmed mpox cases who sought care at the sexual health clinic of the Institute of Tropical Medicine (ITM) in Antwerp, Belgium.

2. Methods

Patients suspected of mpox (i.e. patients who fulfilled the case definition of a probable or suspected mpox case issued by WHO on 25 August 2022 [12]) who presented at ITM between 23 May and 20 September 2022 were asked to provide written informed consent for study participation. All patients were evaluated in a dedicated isolation room by a physician who collected data in a standardized electronic case report form on REDCap™ (Vanderbilt University, Nashville) on signs and symptoms, relevant medical and travel history, sexual risk behaviour, and contact with a confirmed or suspected mpox case.

Swabs from skin lesions and anorectal swabs were collected routinely. The collection of additional samples like urine, blood, saliva, and swabs from throat and urethra was done according to the physician's discretion, depending on the patient's symptoms and consent.

Mpox testing was done with a validated in-house polymerase chain reaction (PCR) as previously described [11]. Due to biosafety concerns, samples were not tested for other sexually transmitted infections (STIs), but patients were empirically treated with antibiotics in case of a suspicion of bacterial STIs.

TABLE 1. Demographics, medical history and exposure history of mpox positive and negative patients.

	Mpox positive (N = 155)	Mpox negative (N = 51)	Univariable OR (95% CI)	Multivariable OR (95% CI)
Gender – n (%)			Not calculated	Not calculated
Cis-man	155(100)	49 (96.1)	–	–
Cis-woman	0 (0)	1 (2.0)	–	–
Trans-woman	0 (0)	1 (2.0)	–	–
Age in years - median (IQR)	39.0 (33.0–46.0)	37.0 (31.0–44.0)	1.02 (0.98–1.05)	1.00 (0.95–1.06)
Self-identified sexual orientation – n (%)				
Homosexual	144(92.9)	43 (84.3)	Reference	Reference
Bisexual	4(2.6)	4 (7.8)	0.30 (0.07–1.31)	0.14 (0.02–1.09)
Heterosexual	7(4.5)	4 (7.8)	0.52 (0.15–2.07)	0.26 (0.05–1.41)
HIV status – n/N (%)				
Negative	93 (60.0)	33 (64.7)	Reference	Reference
Negative, not using PrEP	22/93 (23.7)	9/33 (27.3)	–	–
Negative, using PrEP	63/93 (67.7)	21/33 (63.3)	–	–
Negative, use of PrEP unknown	8/93 (8.6)	3/33 (9.0)	–	–
Positive	53 (34.2)	13 (25.5)	1.46 (0.72–3.10)	1.26 (0.50–3.40)
Unknown	10 (6.5)	5 (9.8)	Not calculated	Not calculated
History of smallpox vaccination – n/N (%)				
Unvaccinated	102 (65.8)	32 (62.7)	Reference	Reference
Childhood vaccination (self-reported or scar)	25 (16.1)	8 (15.7)	0.98 (0.42–2.51)	0.75 (0.18–3.57)
Post-exposure vaccination	2 (1.3)	3 (5.9)	0.21 (0.03–1.31)	0.19 (0.02–1.32)
Pre-exposure vaccination	1 (0.6)	1 (2.0)	0.31 (0.01–8.08)	0.13 (0.00–3.75)
Unknown	25 (16.1)	7 (13.7)	Not calculated	Not calculated
Contact with a suspected or confirmed mpox case during the 3 weeks prior to symptom onset – n/N (%)				
No reported contact	118 (76.1)	27 (52.9)	Reference	Reference
Reported sexual contact	30 (19.4)	15 (29.4)	**0.46 (0.22–0.98)**	**0.35 (0.13–0.90)**
Reported other[a] contact	7 (4.5)	9 (17.6)	**0.18 (0.06–0.52)**	0.46 (0.11–2.07)
Sexual behaviour in the 3 weeks prior to symptom onset				
Not sexually active – (%)	10 (6.5)	9 (17.6)	Reference	Reference
Sexually active – n (%)	145 (93.5)	42 (82.4)	**3.11 (1.16–8.21)**	3.17 (0.75–12.83)
Number of sexual partners - median (IQR)	2 (1.0–5.0)[b]	2.0 (1.0–3.0)[c]	1.03 (0.98–1.12)	1.01 (0.96–1.09)
Type of sexual practice – n/N (%)			Not calculated	Not calculated
Anal-insertive	92/145 (63.4)	25/42 (59.5)	–	–
Anal-receptive	95/145 (65.5)	22/42 (52.4)	–	–
Oral	69/145 (47.6)	24/42 (57.1)	–	–
Vaginal	8/145 (5.5)	3/42 (7.1)	–	–
Unknown	7/145 (4.8)	0 (0)	–	–
International travel 3 weeks prior to symptom onset – n/N (%)				
No	87 (56.1)	32 (62.7)	Reference	Reference
Yes	63 (40.6)	19 (37.3)	1.22 (0.64–2.37)	0.88 (0.38–2.07)
Unknown	5 (3.2)	0 (0)	Not calculated	Not calculated
Most common travel destinations			Not calculated	Not calculated
Spain	26/63 (41.3)	6/19 (31.6)	–	–
The Netherlands	9/63 (14.3)	2/19 (10.5)	–	–
Germany	6/63 (9.5)	1/19 (5.3)	–	–
France	5/63 (7.9)	3/19 (15.8)	–	–

Abbreviations: PrEP, preexposure prophylaxis.
[a]Household contact, skin-to-skin, non-touch <1.5 m.
[b]Data were missing for 7 patients.
[c]Data were missing for 4 patients.

Data were analysed with R (version 4.1.2). We calculated proportions for categorical variables and medians with interquartile ranges for continuous variables.

In a logistic regression model, we compared confirmed mpox cases (i.e. those with positive PCR on any sample) with negative cases. Furthermore, we used logistic and linear regression models to assess associations of certain variables with disease severity and PCR cycle threshold (CT) values on anal swabs as outcome variables. We defined severe disease as the presence of >100 skin lesions, complications (bacterial superinfection, penile oedema with/without paraphimosis), proctitis requiring opioid analgesics, a WHO performance status of 2 or higher, or hospitalization.

This study was approved by ITM's Institutional Review Board (1641/22, d.d. 31/10/2022) and by the University of Antwerp Ethics Committee (4981, d.d. 28/11/2022).

3. Results

Between 23 May and 20 September 2022, 232 patients consulted ITM with a suspicion of mpox. In 173 (74.6%) cases, the

TABLE 2. Clinical characteristics and laboratory results of patients with mpox (N = 155).

	Mpox positive (N = 155)		Mpox negative (N = 51)		Univariable OR	Multivariable OR
Duration of symptoms at clinic visit in days – median (IQR)	7.0	(4.75–10.0)	6.5	(2.75–13.3)	**0.97 (0.95–0.98)**	**0.97 (0.95–0.98)**
Systemic symptoms -						
No – n (%)	39	(25.2)	25	(49.0)	Reference	Reference
Yes – n (%)	116	(74.8)	26	(51.0)	**2.86 (1.48–5.55)**	1.54 (0.65–3.58)
Fever or shivers – n/N (%)	94/116	(81.0)	17/26	(65.4)	-	-
Fatigue – n/N (%)	62/116	(53.4)	20/26	(76.9)	-	-
Myalgia – n/N (%)	49/116	(42.2)	11/26	(42.3)	-	-
Headache – n/N (%)	35/116	(30.2)	9/26	(34.6)	-	-
Backpain – n/N (%)	13/116	(11.2)	1/26	(3.8)	-	-
Arthralgia – n/N (%)	10/116	(8.6)	1/26	(3.8)	-	–
Lymphadenopathy - n (%)						
No	83	(53.5)	44	(86.3)	Reference	Reference
Yes	72	(46.5)	7	(13.7)	**5.45 (2.45–13.92)**	**3.79 (1.44–11.49)**
Skin lesions						
Absent – n (%)	10	(6.5)	8	(15.7)	Reference	Reference
Present – n (%)	145	(93.5)	43	(84.3)	2.70 (0.97–7.27)	**4.35 (1.15–17.57)**
Number of skin lesions – n/N (%)					Not calculated	Not calculated
1-4	52/145	(35.9)	19/43	(44.2)	-	-
5-25	78/145	(53.8)	19/43	(44.2)	-	-
26-100	14/145	(9.7)	2/43	(4.7)	–	–
> 100	1/145	(0.7)	0	(0)	–	–
Unknown	0	(0)	3/43	(7.0)	–	–
Location of skin lesions – n/N (%)					Not calculated	Not calculated
Genital	81/145	(55.9)	15/43	(34.9)	-	-
Penis	57/145	(39.3)	9/43	(20.9)	-	-
Pubis	28/145	(19.3)	3/43	(7.0)	-	-
Scrotum	35/145	(24.1)	5/43	(11.6)	-	-
Perianal or butt cheeks	58/145	(40.0)	11/43	(25.6)	-	-
Perianal	47/145	(32.4)	8/43	(18.6)	-	-
Butt cheeks	19/145	(13.1)	5/43	(11.6)	-	-
Lips or oral cavity	22/145	(15.2)	3/43	(7.0)	-	-
Oral cavity	11/145	(7.6)	2/43	(4.7)	-	-
Lips	11/145	(7.6)	2/43	(4.7)	-	-
Face	39/145	(26.9)	6/43	(14.0)	–	–
Head	4/145	(2.8)	0/43	(0)	–	–
Trunk	49/145	(33.8)	8/43	(18.6)	–	–
Extremities	63/145	(43.4)	15/43	(34.9)	–	–
Palms/soles	26/145	(17.9)	5/43	(11.6)	–	–
Number of affected anatomical sites– median (IQR)[a]	2.0	(1.0–3.0)	1.0	(1.0–2.0)	-	-
Local manifestations -n (%)						
Proctitis	50	(32.3)	3	(5.9)	**7.62 (2.62–32.40)**	**9.41 (2.72–47.07)**
Urethritis	12	(7.7)	3	(5.9)	1.34 (0.41–6.07)	1.69 (0.37–9.84)
Tonsillitis	2	(1.3)	1	(2.0)	0.65 (0.06–14.24)	0.42 (0.02–12.74)
Throat pain	18	(11.6)	6	(11.8)	0.99 (0.39–2.85)	1.40 (0.42–5.39)
Cough	5	(3.2)	0	(0)	Not calculated	Not calculated
Complications – n (%)						
Bacterial skin infection	13	(8.4)	2	(3.9)	2.24 (0.59–14.67)	3.09 (0.63–23.74)
Penile oedema with or without paraphimosis	4	(2.6)	1	(2.0)	1.32 (0.19–26.23)	0.92 (0.10–20.72)
WHO performance status at visit clinic -n (%)						
0 or 1	145	(93.5)	48	(94.1)	Reference	Reference
2 or 3	10	(6.5)	3	(5.9)	1.10 (0.32–5.07)	1.54 (0.35–8.60)
4	0	(0)	0	(0)	–	–
Hospitalized -n (%)	2	(1.3)	0	(0)	Not calculated	Not calculated
Severe disease[b] - n (%)	35	(22.6)	6	(11.8)	Not calculated	Not calculated

Note: Denominator is the total number of participants unless otherwise specified.
Abbreviations: WHO: World Health organization.
[a]Eight anatomical sites: genital region, perianal or butt cheeks, lips or oral cavity, face, head, trunk, extremities and palms or soles.
[b]Severe disease: either being hospitalized, being unable to carry out daily activities (who performance status >1), having over 100 skin lesions, severe proctitis requiring opioid analgesics, or complications (severe penile oedema, paraphimosis, severe penile oedema, bacterial superinfection).

TABLE 3. Characteristics of ten patients who did not have skin lesions.

Age	Duration of symptoms before attending the clinic (days)	Lesions[a]	Systemic symptoms[a]	Other symptoms[a]	Contact with mpox case[b]	Additional relevant information
36	5	No	Fever	Tonsillitis, lymphadenopathy	Yes	–
46	5	No	–	Proctitis, urethritis	No	–
38	12	No	Fever	Proctitis	No	–
41	3	No	–	Proctitis	No	–
31	13	No	Fever, headache, back pain	Proctitis, lymphadenopathy	Yes	–
59	9	No	Fever, back pain	–	Yes	–
72	24	No	Fever, shivers, tiredness	Proctitis, diarrhoea, abdominal cramps, lymphadenopathy	No	Co-infection Shigella
30	3	No	Tiredness, myalgia	–	Yes	–
60	1	No	Cough, shivers, tiredness	–	Yes	–
26	18	Yes[c]	Fever, shivers, tiredness	Proctitis, throat ache, lymphadenopathy	No	–

[a]Present at the time of visit clinic or patient reported that these symptoms had been present before visit clinic. .
[b]Contact with a confirmed or suspected case in the 3 weeks before onset of symptoms.
[c]Patient noticed a lesion at his oral mucosa 5 days before visit clinic that was no longer visible during clinical examination.

diagnosis was confirmed and 155 of them (89.6%) provided informed consent. The remaining 59 cases were mpox-negative, of whom 51 (86.4%) consented.

3.1. Characteristics of mpox patients

All 155 mpox-confirmed patients self-identified as male and 148 (95.5%) as gay or bisexual MSM (Table 1).

All but ten (145/155, 93.5%) presented with skin lesions (Table 2), of which the majority (129/145, 89.0%) had 25 or fewer lesions. The most frequently affected body site was the anogenital area (111/145, 76.6%). The ten cases without skin lesions either presented with symptoms caused by mucosal involvement (proctitis, n = 5; proctitis and urethritis, n = 1; tonsillitis, n = 1) or systemic symptoms only (n = 3; Table 3).

Overall, 50/155 (32.3%) patients had proctitis, 12/155 (7.7%) urethritis and 2/155 (1.3%) tonsillitis. Since patients were not tested for other STIs, it is uncertain whether all these symptoms could be attributed entirely to mpox. Systemic symptoms were reported by 116/155 (74.8%) patients and 72/155 (46.5%) had localized or generalized lymphadenopathy.

One third (53/145, 36.6%) of mpox patients were HIV-positive. The CD4 count was higher than 500 cells/μL in 38/43 (88.4%) HIV-positive patients with known CD4 count.

Most mpox patients were mildly ill. Yet, 35/155 (22.6%) patients had severe disease, defined by the presence of >100 skin lesions (n = 1), complications (bacterial superinfection, n = 13; penile oedema with/without paraphimosis, n = 4), proctitis requiring opioid analgesics (n = 9), a WHO performance status of 2 or higher (n = 10), or hospitalization (n = 2). Two patients were hospitalized because of severe vomiting and diarrhoea with concomitant Shigellosis (n = 1) and profuse diarrhoea with dehydration in an immunosuppressed patient (n = 1). No deaths occurred.

Almost all (145/155, 93.5%) patients had at least one and 105/145 (72.4%) had two or more sexual partners in the three weeks prior to symptom onset. Only 37/155 (23.9%) patients reported having had contact with a suspected or confirmed mpox case. This contact was sexual in 30/37 (81.1%) cases.

Twenty-five out of 155 (16.1%) mpox patients reported childhood smallpox vaccination. Three patients had received pre- (n = 1) or post-exposure vaccination (n = 2). These three cases had developed symptoms 4, 9 and 10 days after vaccination, respectively. Vaccination status was unknown in 24 (15.5%) cases.

The diagnosis of mpox was mostly based on a PCR on anal swabs (125/130, 96.2%) or skin swabs (131/137, 95.6%). Pharyngeal swabs, serum, saliva, and urethral swabs were PCR-positive in 15/25 (68.0%), 14/21 (66.7%), 2/5 (40.0%) and 1/1 (100%), respectively.

TABLE 4. Association of mpox PCR Ct value on anorectal swabs with clinical and behavioral characteristics.

	Mpox PCR Ct value on anorectal swabs	
Predictor	**Univariable β (95% CI)**	**Multivariable β (95% CI)**
Age (years)	1.00 (0.99–1.00)	1.00 (0.99–1.01)
Receptive anal intercourse in the previous 3 weeks		
No	*Reference*	*Reference*
Yes	**0.74 (0.66–0.83)**	**0.79 (0.69–0.91)**
Childhood smallpox vaccination (self-reported or scar)		
No	*Reference*	*Reference*
Yes	1.04 (0.87–1.23)	0.97 (0.78–1.20)
Proctitis		
No	*Reference*	*Reference*
Yes	**0.69 (0.60–0.79)**	**0.74 (0.64–0.86)**
HIV status		
Negative	*Reference*	*Reference*
Positive	0.89 (0.78–1.02)	0.90 (0.77–1.04)
Time since onset of symptoms (days)	1.00 (1.00–1.01)	1.00 (1.00–1.01)

TABLE 5. Association of age, childhood vaccination and HIV status with disease severity among confirmed monkeypox cases.

	Disease severity			
	Non-severe (n = 120)	Severe (n = 35)	UnivariableOR (95% CI)	Multivariable OR (95% CI)
Age (median, IQR)	38.5 [33.0–45.3]	40.0 [34.5–46.5]	0.98 (0.94–1.02)	0.92 (0.92–1.02)
Childhood smallpox vaccination (self-reported or scar)				
Unvaccinated, n (%)	82 (68.3%)	23 (65.7%)	Reference	Reference
Vaccinated, n (%)	18 (15.0%)	7 (20.0%)	0.72 (0.28–2.04)	1.36 (0.35–5.89)
Unknown, n (%)	20 (16.7%)	5 (14.3%)	0.72 (0.28–2.04)	1.63 (0.51–6.13)
HIV status				
Negative, n (%)	75 (62.5%)	17 (48.6%)	Reference	Reference
Positive, n (%)	39 (32.5%)	14 (40.0%)	0.63 (0.28–1.43)	0.66 (0.28–1.54)
Unknown, n (%)	6 (5.0%)	4 (11.4%)	0.34 (0.09–1.45)	0.33 (0.08–1.43)

[a]Severe disease was defined as >100 skin lesions, proctitis requiring opioid analgesics, complications (penile oedema with/without paraphimosis, bacterial skin infection), WHO performance status of 2 or higher, or need for hospitalization.

3.2. Characteristics of mpox-negative patients

Reasons for testing in the 51 mpox negative patients were: an epidemiological link and skin lesions or proctitis/urethritis (23/51, 45.1%), an unexplained acute skin rash in sexually active MSM (21/51, 41.2%), an unexplained acute skin rash in a person with multiple and/or casual sexual partners (2/51, 3.9%), systemic symptoms in combination with an epidemiological link (1/51, 2.0%), unexplained acute skin rash for which common causes of acute rash or lesions did not explain the clinical picture (4/51, 7.8%).

3.3. Risk factors and symptoms associated with a diagnosis of mpox

Two different multivariable logistic regression models were used to explore associations between a diagnosis of mpox and certain risk factors (Table 1) and clinical characteristics (Table 2).

In the multivariable model examining risk factors, no significant associations were found between the diagnosis of mpox and age, sexual orientation, HIV status, history of smallpox vaccination, sexual activity 3 weeks prior to symptom onset, the number of sexual partners, and recent international travel. There was a negative association between an mpox diagnosis and a reported sexual mpox contact in the previous three weeks (OR 0.46, 95% CI 0.22 to 0.98) in the tested population.

Clinical characteristics that were significantly associated with the diagnosis of mpox in a different multivariable logistic regression model were: lymphadenopathy (OR 3.79, 95% CI 1.44 to 11.49), proctitis (OR 9.41, 95% CI 2.72 to 47.07) and skin lesions (OR 4.35, 95% CI 1.15 to 17.57). The duration of symptoms before attending the clinic was negatively associated with an mpox diagnosis (OR 0.97, 95% CI 0.95 to 0.98). There was no association with the presence of tonsillitis, urethritis, throat pain, bacterial skin infection, penile oedema, systemic symptoms or WHO performance status.

3.4. HIV, smallpox vaccination and disease severity

Disease severity was not significantly associated with a history of HIV, childhood smallpox vaccination and age among mpox cases (OR 0.66 [95% CI 0.28–1.54], 1.36 [95% CI 0.35–5.89] and 0.92 [95% CI 0.92–1.02] respectively in multivariable logistic regression analysis, Table 5).

3.5. Receptive anal intercourse, proctitis and anorectal mpox viral load

Proctitis was more common in patients who reported anal-receptive intercourse (41/95, 43.2%) compared to those who did not (9/60, 15.0%, OR 4.30, 95% CI 1.97 to 10.25, univariable logistic regression). Anorectal swabs were more often PCR-positive in those who reported anal-receptive intercourse (82/88, 93.1%) versus those who did not (43/52, 82.7%, OR 2.86, P5% CI 0.97 to 9.04, not significant, univariable logistic regression). Moreover, anal-receptive sex was associated with lower anorectal mpox PCR CT values (median 23.1, IQR 19.4 to 32.1) compared to no anal-receptive sex (median 36.5, IQR 28.7 to 40.3, estimate 0.79, 95% CI 0.69 to 0.91, multivariable linear regression adjusted for age, time since symptom onset, vaccination status, HIV status and the presence of proctitis, Table 4). There was no significant association between insertive anal sex and urethritis or penile lesions (OR 0.86, 95% CI 0.39 to 1.81, univariable logistic regression).

4. Discussion

In our centre during the Belgian mpox epidemic, most cases were MSM with multiple sexual partners in the previous weeks. Their demographic and clinical characteristics were similar to those reported elsewhere throughout the 2022 epidemic [4–7,9,13]. The majority had mild symptoms with low impact on activities of daily life. Still, some cases were temporarily

incapacitated and a few were hospitalized. Most patients had a limited number of lesions, often located in the anogenital or perioral region. Of note, ten patients had no skin lesions at the time of presentation and three of them had only systemic symptoms. These findings underline the importance of a high index of suspicion and a low threshold for testing in persons at risk of infection during an mpox epidemic. The presence of lymphadenopathy, proctitis or skin lesions in sexually active MSM should further raise suspicion. Surprisingly, we found a negative association between a reported contact with a confirmed or suspected mpox index case and an mpox diagnosis. This association can, however, likely be explained by referral bias: individuals with subtle or atypical clinical signs or symptoms who reported a contact with a presumed mpox case were more likely to be referred for testing than those who did not report such a contact, whereas those with obvious mpox symptoms were referred for testing irrespective of their contact history. In addition, we could not verify the level of suspicion or diagnosis of mpox in their index cases.

There is growing evidence that sexual contact is an important mode of transmission for clade IIb mpox and some authors argue that mpox is to be called a sexually transmitted infection [10]. One argument is the association between the affected body site and the site of exposure, in particular the anorectum (proctitis) in people who had receptive anal intercourse, which we also found in our data [6,13]. Interestingly, mpox viral DNA was found in the anorectum of almost all mpox patients, even in those who reported no receptive anal sex. This may indicate that viremia after inoculation elsewhere results in secondary dissemination to the anorectum as previously hypothesized [14]. Furthermore, our data demonstrate an association of receptive anal intercourse with higher anorectal viral loads. This suggests that the anorectum was the site of most intense viral replication – and presumably inoculation – in cases who had receptive anal intercourse, providing another argument that mpox is transmitted through anal sex.

Based on studies in the 1980's in mpox-endemic areas in Africa, the smallpox vaccine is thought to have about 85% cross-protective efficacy against mpox [15]. Nevertheless, this cross-protective effect probably wanes over time. Indeed, about one in five mpox cases in our study and up to 25% of mpox cases in other cohorts during the 2022 global outbreak were vaccinated against smallpox during childhood [4,6,7,9]. In addition, the lack of association between vaccination and an mpox diagnosis in our study suggests that the vaccine offers limited long-term protection. Data from our study could be complemented by data from similar studies in other settings to understand the utility of revaccinating individuals with a remote history of smallpox vaccination. If such individuals are incorrectly considered immune and therefore ineligible for booster vaccination, they may continue to sustain an outbreak.

A limitation of our study is the fact that data were collected at a single time point in a single outpatient centre. Therefore, the data may not be representative of the full disease course of all mpox patients in Belgium.

Nevertheless, this study contributes to a better understanding of clade IIb mpox. Our findings support the hypothesis that mpox is transmitted through anal intercourse. Since our data suggest that childhood smallpox vaccination does not protect against mpox infection and severe disease, we recommend that individuals reporting remote smallpox vaccination receive booster vaccination as a precautionary measure.

CRediT authorship contribution statement

Matilde Hens: Investigation, Software, Validation, Formal analysis, Data curation, Writing – original draft. **Isabel Brosius:** Conceptualization, Methodology, Funding acquisition, Validation, Writing – review & editing, Project administration. **Nicole Berens-Riha:** Conceptualization, Investigation, Writing – review & editing. **Jasmine Coppens:** Investigation, Writing – review & editing. **Liesbeth Van Gestel:** Investigation, Writing – review & editing. **Jojanneke Rutgers:** Investigation, Writing – review & editing. **Chris Kenyon:** Conceptualization, Investigation. **Patrick Soentjens:** Conceptualization, Investigation. **Saskia van Henten:** Investigation, Writing – review & editing. **Stefanie Bracke:** Investigation, Writing – review & editing. **Thibaut Vanbaelen:** Investigation, Writing – review & editing. **Leen Vandenhoven:** Investigation, Writing – review & editing. **Emmanuel Bottieau:** Conceptualization, Funding acquisition, Writing – review & editing. **Koen Vercauteren:** Investigation, Writing – review & editing. **Marjan Van Esbroeck:** Investigation, Writing – review & editing. **Laurens Liesenborghs:** Conceptualization, Methodology, Funding acquisition, Writing – review & editing, Supervision. **Christophe Van Dijck:** Conceptualization, Methodology, Software, Data curation, Formal analysis, Validation, Writing – review & editing, Supervision. **ITM mpox study group:** Investigation. **Christophe Van Dijck:** Investigation.

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