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Characteristics of women diagnosed with mpox infection compared to men: A case series from Brazil

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ABSTRACT

Background: Cisgender men were mostly affected during the 2022 mpox multinational outbreak, with few cases reported in women. This study compares the characteristics of individuals diagnosed with mpox infection according to gender in Rio de Janeiro.

Methods: We obtained surveillance data of mpox cases notified to Rio de Janeiro State Health Department (June 12 to December 15, 2022). We compared women (cisgender or transgender) to men (cisgender or transgender) using chi-squared, Fisher's exact, and Mood's median tests.

Results: A total of 1306 mpox cases were reported; 1188 (91.0%) men (99.8% cisgender, 0.2% transgender), 108 (8.3%) women (87.0% cisgender, 13.0% transgender), and 10 (0.8%) non-binary persons. Compared to men, women were more frequently older (40+years: 34.3% vs. 25.1%; $p < 0.001$), reported more frequent non-sexual contact with a potential mpox case (21.4% vs. 9.8%; $p = 0.004$), fewer sexual partnerships (10.9 vs. 54.8%; $p < 0.001$), less sexual contact with a potential mpox case (18.5% vs. 43.0%; $p < 0.001$), fewer genital lesions (31.8% vs. 57.9%; $p < 0.001$), fewer systemic mpox signs/symptoms (38.0% vs. 50.1%; $p = 0.015$) and had a lower HIV prevalence (8.3% vs. 46.3%; $p < 0.001$), with all cases among transgender women. Eight women were hospitalized; no deaths occurred. The highest number of cases among women were notified in epidemiological week 34, when the number of cases among men started to decrease.

Conclusions: Women diagnosed with mpox presented differences in epidemiological, behavioral, and clinical characteristics compared to men. Health services should provide a comprehensive assessment that accounts for gender diversity.

1. Background

The mpox virus was first identified in Denmark in 1959 and mpox disease has been endemic in West and Central African countries since the 1970s [1]. In 2022, a multi-country outbreak identified first in European countries subsequently spread to other regions, all considered non-endemic territories. By June 27, 2023, 88,060 cases had been identified, with the Americas featuring prominently in mpox transmission dynamics [2]. Brazil ranks second in the number of cases globally, surpassing 10,950 registered cases, most of them among gay, bisexual, and other cisgender men who have sex with men (MSM), in line with current epidemiological patterns described worldwide [3].

Previous data from endemic countries point to an increased risk of mpox severe disease among children, immunosuppressed patients and pregnant women. Women accounted for 36% of total cases in hospitalized patients in Congo between 2007 and 2011 [4]. Among cases

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reported in the United Kingdom before 2021, three out of seven patients were cisgender women, all related to secondary or tertiary transmission and presenting with disseminated rash, with one case of mpox-associated conjunctivitis [5]. This pattern differs from the current outbreak, in which women have been rarely diagnosed, representing no more than 2% of total cases regardless of gender identity and not always related to sexual contact [6–8].

In the United States (US), data from the US Centers for Disease Control (CDC) identified 769 cases of mpox among cisgender women during the 2022 multinational outbreak, of whom 3% were pregnant, and were mostly younger than cisgender men [9,10]. In addition, in a case series of mpox individuals receiving tecovirimat in the US, 12 (2.3%) were women [11]. In Europe, cisgender women were about 1% of mpox cases throughout the 2022 outbreak, with similar hospitalization rates as those of cisgender men (19 and 11 hospitalizations per 1000 cases, $p = 0.404$, respectively) [7]. While a Spanish study reporting 158 cases in women (2.1%) showed significant clinical differences related to sex-at-birth, a global case series from 15 countries reported 131 cases of mpox among cisgender and transgender women with no difference in clinical features compared to men [12,13]. Most mpox cases among women were reported in Europe and the US [14–21].

By June 2023, 8.9% of mpox diagnoses in Brazil were in female sex-at-birth (n = 982/10,931) [22]. At a major referral service for infectious diseases and LGBTQIA+ health care in Rio de Janeiro, only 8 out of 208 mpox cases were in cisgender women (3.8%), and no cases were in transgender women, from June to August 2022 [23]. Comparison of mpox cases diagnosed at this service in two periods (June to August 2022 *vs* September to December 2022) showed that more cases were diagnosed among cisgender and transgender women in the second period [15.6% (n = 24/154) vs 3.8% (n = 10/262); $p < 0.001$] when the incidence among men decreased [79% (n = 111/411) vs 93% (n = 215/232), $p < 0.001$] [24]. Twenty-two pregnant women were diagnosed with mpox by May 30, 2023 in Brazil, with two requiring hospitalization [25,26].

A study conducted in California (US) retrospectively screened 1848 samples from 1645 individuals who had been tested for bacterial sexually transmitted infections (STI) between April and August 2022 [27]. Among 0.7% (n = 11/1645) mpox PCR-positive, 45.5% (n = 5/11) were cisgender men, 36.4% (n = 4/11) cisgender women, and 18.2% (n = 2/11) transgender women and non-binary persons. None of the cisgender women had previously been diagnosed with mpox, with samples collected in the context of prenatal care, STI screening or general vaginal complaints, such as discharge, with no reporting of genital ulcers [27]. Such findings highlight the potential role of sexual networks in mpox transmission dynamics, which might differ according to evolution of community transmission. For prompt recognition of mpox cases by healthcare providers, fighting stigma related to attachment of mpox diagnosis exclusively and pejoratively to MSM is essential [28].

Knowledge gaps remain regarding the impact of mpox on both cisgender and transgender women communities in non-endemic countries, such as epidemiological, behavior and clinical characteristics. This study aimed to compare characteristics of women diagnosed with mpox infection compared to men in Rio de Janeiro State, Brazil.

2. Methods

2.1. Study design and participants

In this cross-sectional study, we assessed all cases of mpox notified to the Rio de Janeiro State Health Department Notification System (surveillance data), since the first case on June 12, 2022, to December 15, 2022. Data were collected onto a standardized case report form from the Center for Emergency Operations (COE) of the Brazilian Ministry of Health. For this analysis, we included only mpox confirmed cases yielding a positive result by real-time RT-PCR from a sample collected at any body site.

2.2. Procedures

We assessed data on date of birth, gender identity and race according to Brazilian standard classification, education level, sexual partnerships (gender and multiple partners), HIV status, physical contact (including sexual) with a partner with unknown mpox status and non-sexual contact with a potential mpox case, both in the 21 days before mpox diagnosis. We also assessed date of signs and symptoms initiation that occurred in the previous 21 days, such as presence of genital and anal lesions, cutaneous rash (dichotomized in localized: rash on one segment [head/neck, trunk, trunk, pelvis, upper limbs, or lower limbs]; disseminated: rash on two or more segments), systemic sign and symptoms (report of fever, asthenia, myalgia, headache, sore throat or adenomegaly), hospitalization (reason and duration), and death. Reason for hospitalization was divided into three categories: clinical complication, investigation or isolation purpose.

We considered individuals born before 1975 as vaccinated for smallpox, as vaccination was compulsory in Brazil until then, with universal coverage through the Brazilian Ministry of Health Immunization Program.

2.3. Spatial analysis

We conducted a georeferencing exploratory analysis based on the Kernel estimator, with a radius of two km and Gaussian function, to obtain an overview of the spatial distribution of mpox confirmed cases and identify potential hot spots of occurrence stratified by gender. We considered the center of participants' zip codes using the 'cepR' API. We used the R software version 4.2.1 (www.r-project.com) and functions from the Spatial Analyst module in ArcGIS 10.4.

2.4. Statistical analysis

We compared sociodemographic, behavior and clinical characteristics of mpox cases according to gender (women vs. men). Gender identity data were collected using the following categories: cisgender woman, transgender woman, *travesti*, cisgender man, transgender man, non-binary, and ignored. We included any gender identification of the female spectrum in the women category (cisgender women, transgender women and *travesti*), while any gender identification of the male spectrum (cisgender or transgender men) were included in the men category. Individuals who self-identified as non-binary were not considered for gender comparisons. However, we provide characteristic of transgender women and non-binary persons separately in supplementary material. For comparisons, we used chi-squared test or Fisher's exact test for categorical variables and wilcoxon test for continuous variables. All analyses were performed using the R software version 4.2.1 (www.r-project.com).

2.5. Ethical considerations

We performed secondary data analysis using an unidentified database of mpox cases notified to Rio de Janeiro State Health Department Notification System. The database was unidentified before the analysis to guarantee the confidentiality of each notified case. The study project was conducted according to the National Health Council Resolution No. 466 (December 12, 2012).

3. Results

By December 15, 2022, a total of 1306 mpox cases were reported in Rio de Janeiro State. Of these, 1188 (91.0%) were among men [99.8% (n = 1186/1188) cisgender, 0.2% (n = 2/1188) transgender], 108 (8.3%) in women [87.0% (n = 94/108) cisgender, 13.0% (n = 14/108) transgender], and 10 (0.8%) in non-binary persons. The overall median age was 33 years (IQR: 27–40), most were Black or *Pardo* (mixed-Black) [n

Table 1
Sociodemographic, behavior and clinical characteristics of the mpox cases, according to gender (N = 1306), Rio de Janeiro State, Brazil.

	Women (n = 108, 8.3%)		Men (n = 1188, 91.0%)		Overall (N = 1306[1])		p-value
	n	%	n	%	n	%	
Age (years)							
Median (IQR)	32	(24, 45)	33	(28, 40)	33	(27, 40)	0.5[a]
<18	11/108	10.2	20/1188	1.7	31/1306	2.4	<0.001[b]
18–24	20/108	18.5	136/1188	11.4	157/1306	12.0	
25–29	19/108	17.6	232/1188	19.5	257/1306	19.7	
30–39	21/108	19.4	500/1188	42.1	523/1306	40.0	
≥40	37/108	34.3	300/1188	25.2	338/1306	25.9	
Transgender							<0.001[c]
Yes	14/108	13.0	2/1188	0.2	16/1306	1.2	
Race							0.2[c]
Black	10/89	11.2	212/1097	19.3	225/1196	18.8	
Pardo (mixed-Black)	36/89	40.4	412/1097	37.6	451/1196	37.7	
White	38/89	42.7	441/1097	40.2	483/1196	40.4	
Asian	5/89	5.6	30/1097	2.7	35/1196	2.9	
Indigenous	0/89	0.00	2/1097	0.2	2/1196	0.2	
Education							0.004[b]
Primary	12/81	14.8	59/991	5.9	72/1082	6.7	
Secondary	37/81	45.7	416/991	42.	458/1082	42.3	
Post-Secondary	32/81	39.5	516/991	52.1	552/1082	51.0	
Vaccinated for smallpox[d]							<0.001[b]
Yes	26/108	24.1	106/1188	8.9	132/1306	10.1	
No	82/108	75.9	1082/1188	91.1	1174/1306	89.9	
Sexual Partnership							0.025[c]
With men	47/52	90.4	465/631	73.7	516/690	74.8	
With men and women	3/52	5.8	76/631	12.0	82/690	11.9	
With women	2/52	3.8	90/631	14.3	92/690	13.3	
Multiple Partnerships							<0.001[b]
Yes	5/46	10.9	286/522	54.8	294/574	51.2	
No	41/46	89.1	236/522	45.2	280/574	48.8	
Sexual contact with a potential mpox case[e]							<0.001[b]
Yes	17/92	18.5	487/1134	42.9	509/1232	41.3	
No	75/92	81.5	647/1134	57.1	723/1232	58.7	
Non-sexual contact with a potential mpox case[e]							0.004[b]
Yes	15/70	21.4	68/694	9.8	85/770	11.0	
No	55/70	78.6	626/694	90.2	685/770	89.0	
HIV Infection							<0.001[b]
Yes	08/97	8.3	508/1097	46.3	519/1204	43.1	
No	89/97	91.7	589/1097	53.7	685/1204	56.9	
Genital lesions [e,g]							<0.001[b]
Yes	28/88	31.8	529/914	57.9	562/1011	55.6	
No	60/88	68.2	385/914	42.1	449/1011	44.4	
Anal lesions [e]							0.2
Yes	6/89	6.7	101/904	11.2	110/1002	11.0	
No	83/89	93.3	803/904	88.8	892/1002	89.0	
Cutaneous rash [e]							0.7[b]
Localized	29/73	39.7	312/826	37.8	342/907	37.7	
Disseminated	44/73	60.3	514/826	62.2	565/907	62.3	
Systemic signs and symptoms [e,f]							0.015[b]
Yes	41/108	38.0	595/1188	50.1	642/1306	49.2	
No	67/108	62.0	593/1188	49.9	664/1306	50.8	
Fever [e]							0.002[b]
Yes	47/108	43.5	695/1188	58.5	750/1306	57.4	
No	61/108	56.5	493/1188	41.5	556/1306	42.6	
Adenomegaly							<0.001[b]
Yes	18/108	16.7	513/1188	43.2	536/1306	41.0	
No	90/108	83.3	675/1188	56.8	770/1306	59.0	
Days between first signs and symptoms and clinical assessment							0.15[a]
Median (IQR)	6.0	(3.0, 8.0)	6.0	(4.0, 9.0)	6.0	(4.0, 9.0)	
Hospitalization							0.3[b]
Yes	8/103	7.8	61/1166	5.2	69/1278	5.4	
No	95/103	92.2	1105/1166	94.8	1	94.6	
Death							–
Yes	0/108	0	5/1188	0.4	5/1306	0.4	
No	108/108	100	1183/1188	99.6	1301/1306	99.6	

[1] Including 10 cases in non-binary persons, described in supplementary table 1.
[a] Wilcoxon test.
[b] Chi-squared test.
[c] Fisher's exact test.
[d] Individuals born before 1975.
[e] Previous 21 days.
[f] Reported at least one sign or symptom (fever, asthenia, myalgia, headache, sore throat, adenomegaly).
[g] Excluding anal/perianal lesions.

Table 2
Demographic, behavioral and clinical characteristics of hospitalized mpox cases in women, Rio de Janeiro, Brazil.

ID	Age (years)	Race	Gender identity	Reason of Hospitalization	Hospitalization time (days)	Systemic signs and symptoms[a, b]	Rash distribution	Anogenital lesions	HIV Status	Pregnancy	Sexual Partnership	Multiple Partnerships	Sexual contact with a potential mpox case[a]	Non-sexual contact with a potential mpox case[a]
1	13	Pardo	Cisgender Woman	Isolation	7	No	Disseminated	No	No	No	NA	No	No	Yes
2	58	White	Cisgender Woman	Clinical Complication	10	Yes	Localized	No	No	No	With men	NA	No	NA
3	29	White	Cisgender Woman	NA	4	Yes	Disseminated	No	No	No	With men	No	NA	NA
4	18	Black	Cisgender Woman	Clinical Complication	6	Yes	Localized	Yes	No	No	NA	NA	Yes	No
5	20	Black	Cisgender Woman	Investigation	3	No	Localized	Yes	No	No	NA	No	No	No
6	48	Black	Cisgender Woman	Clinical Complication	3	Yes	Disseminated	Yes	No	No	NA	No	Yes	No
7	25	Pardo	Cisgender Woman	Investigation	7	Yes	Disseminated	Yes	No	No	With men	Yes	No	Yes
8[1]	69	Pardo	Cisgender Woman	Clinical Complication	4	No	NA	Yes	No	No	NA	NA	No	NA

[1] Death due to other clinical reasons (not mpox). Patient with immunosuppression.
[a] Previous 21 days.
[b] Reported at least one sign or symptom (fever, asthenia, myalgia, headache, sore throat, adenomegaly).

= 676/1196 (56.5%)], and had post-secondary education [n = 552/1082 (51.0%)] (Table 1).

Compared to men, women were more frequently of older age (40+ years: 34.3% vs. 25.3%; $p < 0.001$) and presumably vaccinated for smallpox (24.1% vs. 8.9%; $p = 0.001$). More women reported sexual partnership with men only (90.4% vs. 73.7%; $p < 0.025$) and non-sexual contact with a potential mpox case (21.4% vs. 9.8%; $p = 0.004$), but fewer multiple partnerships (10.9 vs. 54.8%; $p < 0.001$) and sexual contact with a potential mpox case (18.5% vs. 43.0%; $p < 0.001$) (Table 1).

HIV infection and genital lesions were less frequent among women (8.3% vs. 46.3%; $p < 0.001$; 31.8% vs. 57.9%; $p < 0.001$ respectively), than in men. Fewer women presented mpox systemic signs and symptoms (38.0% vs. 50.1%; $p = 0.015$), including fever (43.5% vs. 58.5%; $p = 0.002$) and adenomegaly (16.7% vs. 43.2%; $p < 0.001$). Cutaneous rash and hospitalization frequencies did not differ according to gender. However, all deaths notified due to mpox in Rio de Janeiro State during this period (n = 5) occurred in men (Table 1).

Eight women were hospitalized, all of them cisgender, with median hospitalization time of five days (IQR: 3.5–7) and age ranging from 13 to 69 years. Hospitalization occurred due to clinical complications (n = 4/8) and isolation or investigation purposes (n = 3/8); the hospitalization reason for one case was unknown. None of the mpox-related hospitalizations in women were in people living with HIV or pregnant. Anogenital lesions were frequent (n = 5/8), with most presenting disseminated cutaneous rash (n = 4/8), and systemic signs and symptoms (n = 5/8). One patient was an adolescent (13 years) who reported non-sexual contact with a potential mpox case and presented a disseminated rash, but had no mpox-related complications and was hospitalized for isolation purposes. One participant died due to clinical complications not related to mpox. Information on sexual behavior was incomplete; 3/3 had a sexual partnership with men, 1/5 reported multiple partnerships and 2/7 denied sexual contact with a potential mpox cases in the previous 21 days, while 2/5 reported non-sexual contact with a potential mpox case. (Table 2).

Among transgender women (n = 14) and non-binary persons mpox cases (n = 10), most were in individuals aged 25–29 years or older (n = 12/14 and n = 9/10, respectively), self-identified as *Pardo* (n = 10/14 and n = 3/10, respectively) or Black (n = 2/14 and n = 3/10, respectively), and half had secondary education (n = 9/13 and n = 5/10, respectively). About half reported sexual partnerships with men only (n = 7/8 and n = 4/7, respectively), and the majority (n = 10/14 and n = 5/6, respectively) reported sexual contact with a potential mpox case. Transgender women accounted for all HIV cases registered among women (n = 8/14) whereas non-binary persons accounted for three HIV cases. No hospitalization was registered among transgender woman or non-binary persons (Supplementary Table 1).

Geographically, the distribution of cases did not differ by gender, although there was a hotspot of men cases in Rio de Janeiro city (downtown and part of the South and North regions), a pattern that was not observed for women cases (Fig. 1).

Among men, the distribution of cases by epidemiological week of notification showed an increase starting on week 24, with the highest number recorded in week 31, followed by a gradual decrease in the number of cases. The distribution of cases among women seemed to follow a similar pattern, but with differences in delay of diagnosis. Among women, the highest number of cases was notified in epidemiological week 34, when the number of cases among men started to decrease (Figs. 2 and 3).

4. Discussion

In this study we described the profile of mpox cases in Rio de Janeiro State, stratified by gender and focusing on cases among women, who represent a considerably smaller proportion of total cases. We identified that women and men might present differences in epidemiological,

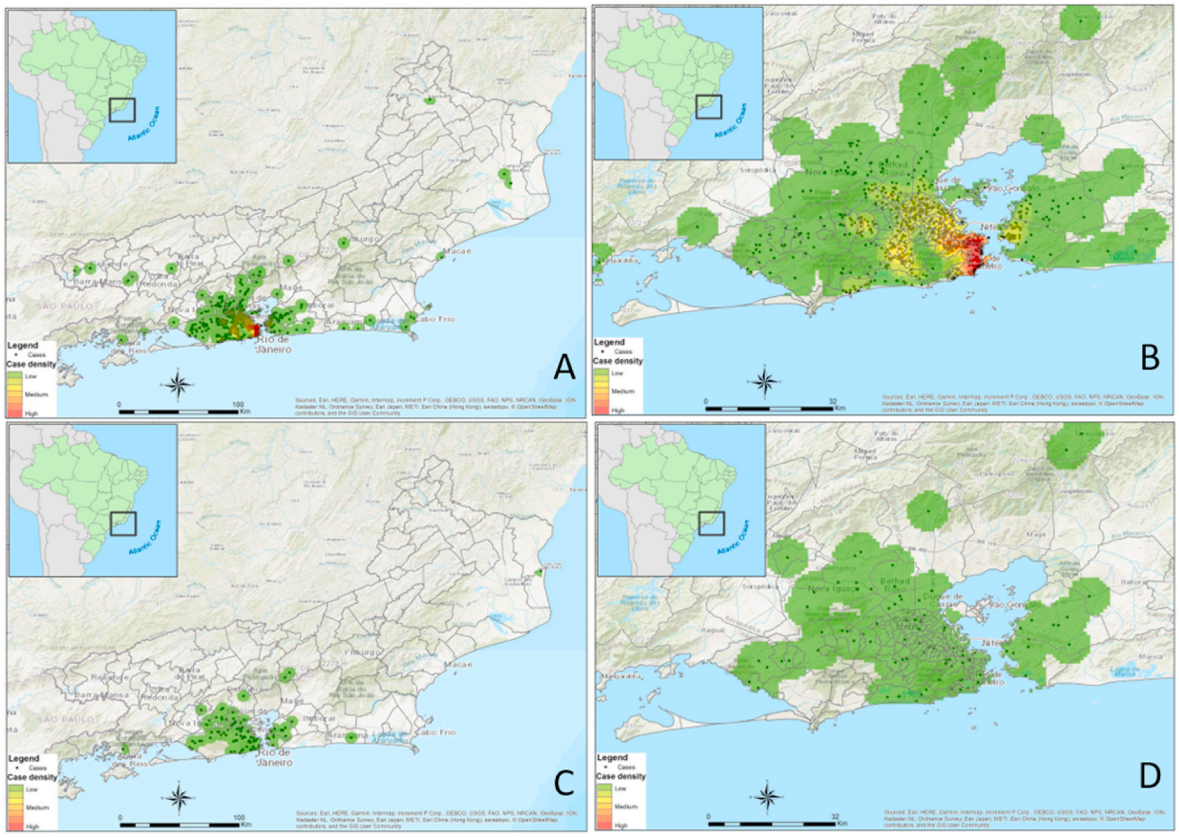

Fig. 1. Kernel density maps of mpox cases by gender, until December 15, 2022, Rio de Janeiro, Brazil. Confirmed cases among men (A) and hot spot (B). Confirmed cases among women (C) and hot spot (D).

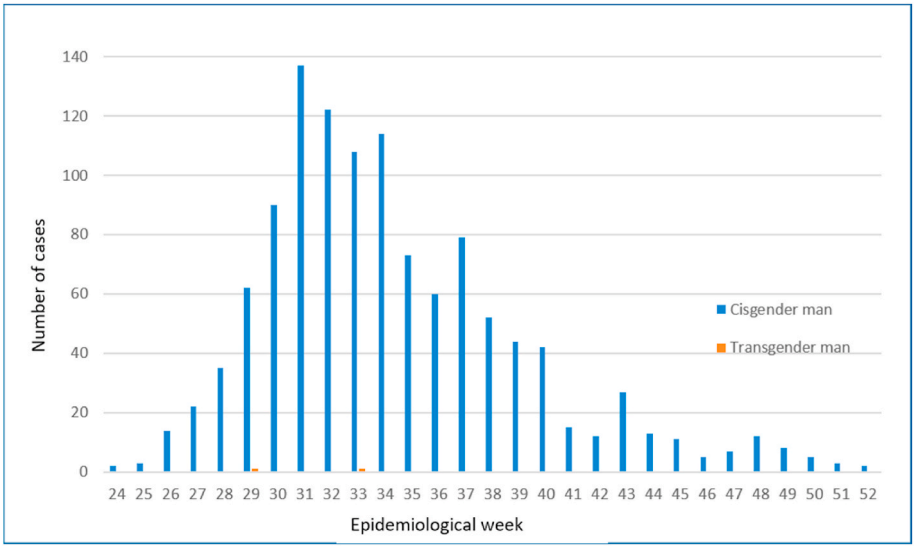

Fig. 2. Notified mpox cases among men by epidemiological week, until December 15, 2022, Rio de Janeiro, Brazil.

behavioral and clinical characteristics.

In general, women were older, had lower access to education, reported fewer sexual partnerships, and less sexual contact with potential mpox cases than men. Information on sexual behavior was frequently incomplete for women, possibly mirroring gender inequities and rights to sexual and reproductive health [29,30]. Women may avoid seeking sexual health services in contexts where women's sexuality is controlled and repressed. Moreover, for cultural reasons or due to the assumption that cisgender women are not at risk of STIs, health care providers frequently do not ask women about their sexual behavior [31]. This underscores the importance of including information about gender identity and sexual behavior during data collection for care and surveillance, to better understand sexual networks, engagement on risk behavior and possible prevention/treatment options.

The prevalence of HIV infection among women was high compared to the general population in Rio de Janeiro, but much lower than among men diagnosed with mpox [32]. Although we had no information on STI diagnosis among these participants, previous cohort studies showed

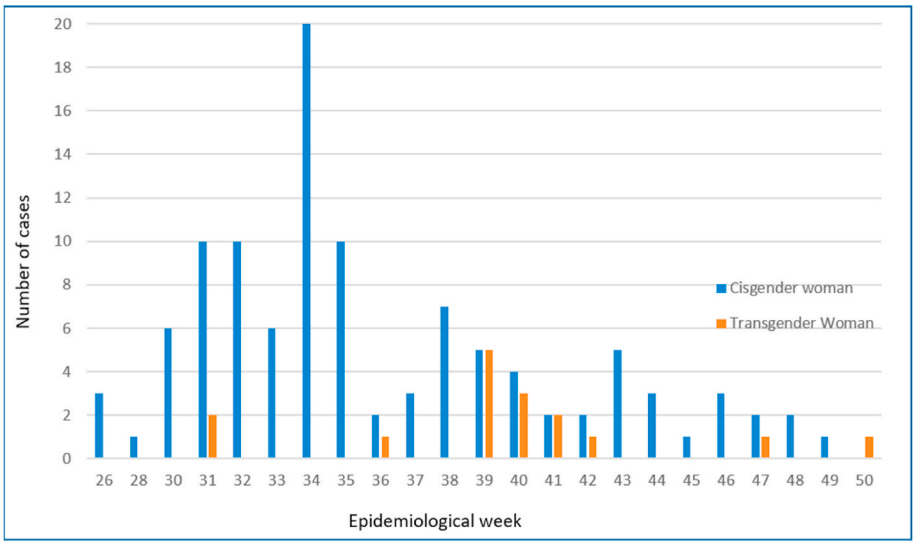

Fig. 3. Notified mpox cases among women by epidemiological week, until December 15, 2022, Rio de Janeiro, Brazil.

high rates of mpox coinfection with syphilis, chlamydia, gonorrhea and/or viral hepatitis, both globally and in Latin America [23,33,34]. Our study adds to evidence that mpox outbreaks pose the need for structuring integrated sexual health services to ensure they account for sexual and gender inequities. At the same time, it is important to not reinforce a risk-based approach, which contributes to increase stigma against the LGBTQIA+ community and to a structural invisibility of women's sexuality. We found fewer cases of mpox among transgender women than in a global study, possibly related to structural and socioeconomic barriers to accessing healthcare services [13,35]. Furthermore, we also registered differences in sexual behavior and HIV prevalence between transgender women and cisgender women when evaluated separately.

Several studies have demonstrated that sexual activity is associated with mpox and specific sexual practices are associated with lesion development [36–39]. The majority of mpox cases described in women presented genital and skin lesions associated with history of sexual contact [14–17,19–21]. In our study, genital lesions were less common in women than in men (31.8% vs. 58.9%; $p = 0.001$, respectively). In agreement with our results, a case series of 769 women diagnosed with mpox in the US showed that only 36% had genital lesions [9]. In a case series from Spain with 158 mpox cases among women (2.1% of the total cases), men presented more anogenital lesions than women (67.3% vs. 51.0%; $p = 0.001$, respectively), and more transmission during close sexual contact between men and women (92.9% vs. 65.7%; $p < 0.001$) [12]. Other transmission mechanisms than sexual contact may be driving women's mpox cases, especially in the context of augmented community transmission [12]. Overall, women presented with fewer systemic symptoms than men. This could be potentially related to mucosal exposure during sexual contact, which was more frequent among cisgender men, highlighting the possible differences in disease presentation related to different sexual contact routes [13,40].

We found no difference in hospitalization rate according to gender, and no deaths among women were reported. A recent study conducted in Rio de Janeiro, Brazil found similar hospitalization rates between men (11%) and women (13%), with pain control (90.7%) as the most common reason for hospitalization and all deaths in hospitalized cases among men living with HIV [41]. A global case series from 19 countries showed that overall mpox-related hospitalization among people living with HIV with CD4 cell count less than 350 cells per mm^3 was 28%, mostly among cisgender men [42]. Conversely, in our study HIV cases were more frequent among men and no hospitalized women were living with HIV. In individuals with uteruses, mpox presents a higher risk of severe congenital infections, pregnancy complications, and perinatal morbidity and mortality. The potential for underdiagnoses in asymptomatic pregnant persons and the underreporting of symptoms beyond genital ulcers emphasize the need to address mpox in women's healthcare [27]. Reproductive healthcare programs should incorporate mpox as a relevant public health concern, and investment in surveillance and diagnosis should be enhanced, particularly in countries in the Global South [43,44].

Our findings show no consistent trends in terms of temporal or spatial distribution in women diagnosed with mpox in Rio de Janeiro, in contrast with men's cases, which clustered in the capital city central area, in line with the findings of an internet-based survey conducted in Brazil in 2022 [45]. Also, as reported in Spain [12], despite showing similar time trends mpox diagnoses among women in Rio de Janeiro occurred after the men's outbreak. Further implications are limited by the low number of cases, however this might be related to the role of extremely interconnected and dense sexual networks among cisgender MSM [46]. It is still unclear how the different sexual networks overlap [47,48]. Thus, further studies are needed to better understand the dynamics of disease transmission in real life situations in settings where people's sexuality might be extremely diverse and sexual health demands might be a result of interaction between several structural and individual factors.

This study had limitations. We analyzed surveillance data, with limited granularity, especially about clinical features. Our results cannot be extrapolated to other Brazilian regions or other countries. However, our data include all mpox cases reported to the Rio de Janeiro state surveillance system (Rio de Janeiro is ranked second in number of mpox cases in Brazil), and are in line with limited existing data from women cases in international cohorts and cases series published so far.

5. Conclusions

Women diagnosed with mpox presented differences on epidemiological, behavioral, and clinical characteristics compared to men, including less severe clinical presentation of mpox and lower HIV prevalence than men, but had similar rates of hospitalization. It is imperative to raise clinical suspicion of mpox to avoid missing a potential diagnosis. Health services must provide a comprehensive clinical and epidemiological assessment that accounts for gender diversity to address the knowledge gaps regarding the impact of mpox on both cisgender and transgender women.

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CRediT authorship contribution statement

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Declaration of competing interest

All authors declare no competing interests.

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Appendix A. Supplementary data

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