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Letter to the Editor

Multi-country monkeypox outbreak: A quantitative evidence synthesis on clinical characteristics, potential transmission routes, and risk factors

Dear Editor,

The world is facing an outbreak of monkeypox. Since early May 2022, more than 60,000 cases of monkeypox have been reported from countries where the disease is not endemic. Monkeypox is a zoonotic virus that belongs to the *Poxviridae* family and is closely related to the smallpox virus. The disease has historically been limited to parts of Central and West Africa, but it has been suggested that waning population immunity associated with the discontinuation of smallpox vaccination from the 1970s onwards has established the landscape for the resurgence of monkeypox in nonendemic countries, particularly among individuals under 50 years of age [1].

Recently, we read with interest the narrative review by Patauner et al. [2] in this prestigious journal describing the epidemiological, clinical, and therapeutic aspects of monkeypox in the current outbreak. The authors report that the disease clinical presentation appears to have changed, and that virus mutations appear to have increased infectivity and favoured human-to-human transmission, particularly among men who have sex with men (MSM) as a sexually transmitted infection (STI). Epidemiological studies have shown that most cases of the 2022 monkeypox outbreak begin as whitish solid papules on the anogenital region and extremities, which may progress to a necrotic center over time. Patients may also have oral mucosal ulcers. Furthermore, systemic symptoms such as lymphadenopathy, fever, myalgia, asthenia, and headache have been frequently reported [3,4].

Because the current outbreak presentation of monkeypox and routes of transmission are novel, findings from a comprehensive systematic review can assist physicians and other health professionals in understanding the disease and making decisions based on the best available evidence. The narrative review by Patauner et al. [2] inspired us to conduct a quantitative evidence synthesis on clinical characteristics, potential transmission routes, and risk factors in monkeypox patients.

Searches were performed in the peer-reviewed literature (PubMed, Web of Science, and SCOPUS) from May 1 to August 21, 2022, without language restrictions. The search was updated on September 1 to include newly published articles. We included studies that provided epidemiological and clinical data on patients diagnosed with monkeypox in the current outbreak. We excluded single case reports, small case series (< 10 cases), publications with potentially overlapping reports, and studies where data extraction was not possible. In the case of potentially overlapping data, we selected the study with the most complete information. Titles and abstracts were screened first, followed by reading the full text of potentially eligible studies. To identify additional studies for inclusion, the reference lists of all eligible studies and reviews were also reviewed. The following search terms were used: “monkeypox”, “monkey pox”, and “monkeypox virus”.

Data from publications were extracted by two authors and crosschecked for accuracy. Our variables of interest were: country; number of cases; sex distribution; age; presence of mucocutaneous lesions and location (hands/feet, arms/legs, trunk, face, genital, anal/perianal, oropharynx/oral mucosa/lips); systemic symptoms (lymphadenopathy [inguinal, cervical, and axillary], fever, asthenia, headache, myalgia, sore throat or odynophagia); HIV infection and other concurrent STIs (gonorrhea, syphilis, and herpes simplex virus infection); occurrence of monkeypox among MSM; known contact with a confirmed monkeypox case or with people experiencing similar symptoms; travel abroad to endemic and non-endemic regions for monkeypox; prior vaccination against smallpox; hospital admission for clinical reasons; and deaths. The proportion of monkeypox cases according to the variables of interest was calculated using the variance-stabilizing Freeman-Tukey double-arcsine transformation with an inverse-variance random-effects model. Analyses were conducted in RStudio (version 0.98.1083).

After screening 1130 titles and abstracts, 35 full-text articles were assessed for eligibility and 21 studies were excluded, nine of which were due to potentially overlapping data. Fourteen studies were included, and data from 3097 patients were analysed (supplementary data). The median age in most studies was between 30 and 40 years, and the prevalence of monkeypox among men and MSM was 99.9% (95% CI 99.4 – 100.0) and 98.7% (95% CI 96.5 – 99.9), respectively. The prevalence of HIV infection was 37.9% (95% CI 32.7 – 43.1) among 1646 individuals with monkeypox and HIV status data available. Furthermore, the prevalence of other concurrent STIs, such as gonorrhea, syphilis, and herpes simplex virus infection, was 22.1% (95% CI 15.5 – 29.4). A recent history of travel abroad was reported by approximately ¼ of the patients (27.3%; 95% CI 16.8 – 39.2), but only two had visited monkeypox-endemic areas (West Africa). A small frequency of individuals reported having known contact with a confirmed monkeypox case or people experiencing similar symptoms (16.7%; 95% CI 5.8 – 31.4).

Fever (63.5%; 95% CI 59.4 – 67.5), inguinal lymphadenopathy (55.4%; 95% CI 36.7 – 73.5), and asthenia (47.4%; 95% CI 34.5 – 60.6) were the most common systemic symptoms. Mucocutaneous lesions were found in approximately 99% of individuals (98.8%; 95% CI 93.6 – 100.0), with a higher prevalence in the genital (56.2%; 95% CI 48.6 – 63.7) and anal/perianal (45.4%; 95% CI 37.0 – 53.8) areas. Other regions had a prevalence of lesions ranging from 16.5% (oropharynx/oral cavity/lips) to 44.7% (arms/legs). The hospitalization rate in patients with monkeypox was 7.2% (95% CI 3.9 – 11.2) and no deaths were reported. One hundred and sixteen of the 839 individuals with available vaccination data described prior smallpox vaccination (12.3%; 95% CI 9.3 – 15.5) (Table 1).

To the best of our knowledge, this is the first quantitative evidence synthesis on clinical characteristics, potential transmission routes, and risk factors of the multi-country monkeypox outbreak in 2022. Based on

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Table 1
Clinical characteristics, transmission routes, and risk factors in monkeypox patients.

Variables	Events / total	Prevalence (%) (95% CI)	I^2 (%)
Male sex	3069 / 3097	99.9 (99.4 – 100.0)	46.0
Systemic symptoms			
Lymphadenopathy	1370 / 2191	64.9 (56.9 – 72.4)	87.6
Inguinal	483 / 996	55.4 (36.7 – 73.5)	87.0
Cervical	151 / 976	12.9 (6.0 – 21.6)	87.0
Axillary	12 / 976	0.3 (0.0 – 1.0)	4.7
Fever	1430 / 2236	63.5 (59.4 – 67.5)	60.3
Asthenia	899 / 1769	47.4 (34.5 – 60.6)	93.3
Headache	880 / 2134	33.5 (24.2 – 43.3)	93.3
Myalgia	785 / 1760	30.9 (19.6 – 43.2)	93.6
Sore throat/odynophagia	312 / 1236	23.2 (17.5 – 29.5)	77.2
Mucocutaneous lesions	2051 / 2081	98.8 (93.6 – 100.0)	87.1
Location			
Hands/feet	575 / 1952	25.9 (16.1 – 37.0)	94.2
Arms/legs	993 / 1751	44.7 (31.1 – 58.7)	97.2
Trunk	510 / 1751	30.4 (24.0 – 37.3)	86.3
Face	691 / 1964	30.3 (23.2 – 37.9)	74.2
Genital	1136 / 2036	56.2 (48.6 – 63.7)	88.4
Anal/perianal	906 / 2012	45.4 (37.0 – 53.8)	95.2
Oropharynx/oral mucosa/lips	262 / 1204	16.5 (10.6 – 23.3)	76.1
Hospitalizations	186 / 2682	7.2 (3.9 – 11.2)	83.3
Prior vaccination against smallpox	116 / 839	12.3 (9.3 – 15.5)	49.4
Known contact with a confirmed case	266 / 1173	16.7 (5.8 – 31.4)	96.3
Travel abroad	373 / 1770	27.3 (16.8 – 39.2)	94.2
Men who have sex with men	2005 / 2069	98.7 (96.5 – 99.9)	84.1
HIV infection	641 / 1646	37.9 (32.7 – 43.1)	68.4
Undetectable viral load	86 / 104	85.1 (76.6 – 92.3)	0.0
Concurrent STI	115 / 490	22.1 (15.5 – 29.4)	64.4
Syphilis	21 / 370	4.2 (1.4 – 7.9)	38.7
Gonorrhoea	54 / 405	13.2 (3.5 – 27.1)	91.8
Herpes simplex virus infection	14 / 374	2.4 (0.02 – 7.1)	65.3

STI, sexually transmitted infection.

the results of 3097 patients, we found that cases of monkeypox have occurred predominantly among MSM in their fourth and fifth decades of life. A recent systematic review of reported data on human monkeypox outbreaks over time revealed that the majority of cases of disease in endemic areas of Central and West Africa are diagnosed in children and adolescents with no sex predilection [5]. These findings indicate a change in the disease's epidemiological profile in the current public health emergency of international concern.

On May 7, 2022, the first case of monkeypox in the ongoing outbreak was confirmed in an individual who travelled from London to Nigeria. On May 14, two additional cases were identified in London in individuals who lived in the same household but had no history of travel to Africa or contact with the index case (https://www.gov.uk/government/news/monkeypox-cases-confirmed-in-england-latest-updates). In our study, we collected information on travel to endemic areas from 1770 individuals, two of whom reported recent trips to West Africa, where the disease is endemic. However, we found a prevalence of 27.3% of individuals with monkeypox who described a history of travel to non-endemic areas, particularly countries in Europe and the Americas, and a low proportion of individuals who described known contact with a monkeypox confirmed case or people with similar symptoms. These findings indicate widespread and rapid community transmission of monkeypox in the months following the discovery of the first case outside the African continent.

There is growing evidence that the incubation period for most monkeypox cases occurs within 21 days after exposure [6] and that at least 50% of patients experience systemic symptoms before the onset of mucocutaneous lesions, particularly fever and inguinal lymphadenopathy. During the eruptive phase of disease, multiple lesions are found in approximately 90% of patients, and involvement of multiple sites (≥ 2) has been observed in 60–70% of patients [4,7]. Furthermore, 35% of lesions have a polymorphic appearance and do not necessarily progress through the four sequential stages (macules, papules, vesicles, pustules) before scabbing over and desquamation [4].

The higher prevalence of lesions in the anogenital region and oral mucosa among MSM suggests that the majority of lesions may initially appear at the inoculation site due to close skin-to-skin contact during unprotected sexual intercourse. Alternatively, the virus could spread hematogenously to regional lymph nodes or to distant sites. Although monkeypox is not considered a STI [8], recent evidence has found monkeypox virus DNA in the seminal fluid of 60% of individuals with the disease [9], suggesting the possibility of sexual transmission. In our study, we also found that two out of every five individuals with monkeypox in the current outbreak were living with HIV, and that the prevalence of concurrent STIs, such as syphilis, gonorrhea, and herpes simplex virus infection, was 22%. Despite the high prevalence of people living with HIV, most individuals had undetectable HIV-1 viral loads, and the role of immunosuppression as a risk factor for monkeypox could not be determined.

In addition, even among individuals living with HIV or with other ISTs, the rate of complications and hospitalization associated with monkeypox appears to be low. However, understanding the current epidemiological scenario and directing efforts to implement educational and preventive public policies aimed at specific risk groups based on the best available evidence is critical. Discrimination and homo-bis-transphobia can lead to stigma and increase health disparities in the LGBTQI+ community [10]. Because the majority of cases in the 2022 monkeypox outbreak appear to be associated with high-risk MSM sexual behavior, and these individuals have a high prevalence of HIV infection and other STIs, STI screening and contact tracing of sexual partners should be included in clinical guidelines for suspected monkeypox cases. Surveillance is needed to monitor the potential spread of the virus to other social networks and the general population.

Authors contributions

All authors contributed equally to this manuscript.

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This study did not receive financial source.

Declaration of Competing Interest

The authors declare they have no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2022.09.013.

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