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## Review Article

## Monkeypox infection: An update for the practicing physician

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## ABSTRACT

As of August 5, 2022, >26,000 cases of monkeypox have been diagnosed worldwide and the steep increase of cases has spurred renewed concern about the risk for another viral pandemic. In this narrative review, we address etiology, epidemiology and virology of monkeypox, describing routes of transmission and modes of spread. We also describe the current clinical presentation of monkeypox, focusing on circumstances where the disease should be suspected, and the methods to diagnose it. Finally, we briefly describe available treatments and strategies for active immune prophylaxis.

## 1. What is Monkeypox?

Monkeypox (MPX) is a viral infectious disease characterized by symptoms that are similar to, but less severe than those of smallpox. It is caused by the monkeypox virus (MPXV) [1].

## 2. Is Monkeypox a new infection?

Monkeypox isn't at all a 'novel' infection. The first description of MPX dates back to the 1958, when a new virus, belonging to the Poxviridae family, was detected in captive monkeys at the State Serum Institute in Copenhagen [2]. After the initial discovery, several cases among different animal species were reported [3–5].

On September 1, 1970, a 9-month-old child, who had not been previously vaccinated for smallpox, and who was suspected of having the disease, was admitted to the Basankusu Hospital, Democratic Republic of Congo. Different specimens from the patient were sent to the WHO Smallpox Reference Center in Moscow, where a virus almost identical to MPXV was isolated. Only limited clinical information regarding this child illness was made available, with the exception of the presence of a skin eruption resembling that of smallpox [6]. In 1970, several MPX cases were diagnosed in Liberia and Sierra Leone. Subsequent serological examination of monkeys in the Congo region showed that these animals had had contact with an infectious agent belonging to the Poxviruses. This observation led to hypothesize that transmission from these animals to humans had occurred.

Early epidemiological analyses showed a low grade of

contagiousness to men, and no human-to-human transmission among households was reported [7]. Between 1970 and 1979, 47 human MPX cases were diagnosed in different countries of Africa [8]. An analysis from the Centers for Disease Control and Prevention showed significant epidemiological changes during the years 1970–1997: between 1970 and 79 primary cases, i.e. cases stemming from animal-to-human transmission, were 91% (43/47) with a fatality rate as high as 17%; between 1981 and 86, primary cases decreased to 72% (243/338) and fatality rate to 10%; very few cases were reported thereafter (due to surveillance failure), and in 1996–97 primary cases were only 22% (92/419) with a fatality rate of <5% [9].

MPX was not reported outside Africa until 2003. In June 2003, 47 cases of MPX were reported in Illinois, Indiana and Wisconsin [10,11]. Traceback investigation identified an international shipment of about 800 small mammals from Ghana to Texas as the probable source of MPXV introduction in the USA [12]. In recent years, travel-associated cases of MPX related to a Nigeria outbreak were reported in Israel [13], UK [14,15] and Singapore [16]. Between January and September 2020, 4594 suspected cases were reported from Democratic Republic of Congo [17], while the second most affected country was Nigeria [18].

## 3. What is the current epidemiologic scenario?

MPX received 'renewed' attention in May 2022, when an unprecedented outbreak of MPXV infection was reported in Europe, and beyond. At variance from the past, newly infected patients did not report any travel history to endemic regions or close contact with MPX confirmed

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or suspected cases, highlighting the emergence of a new area of endemic spread [19]. After the initial report, new cases were detected in different countries. On July 25, the WHO published an External Situation Report declaring this outbreak as a ‘public health emergency of international concern’ [20]. As of August 5, 2022, 26017 confirmed MPX cases were diagnosed, with 9 reported deaths (mortality <0.0005%). Cases were listed in >75 countries belonging to all six WHO regions (Fig. 1).

Current epidemiological data show an overwhelming predominance of affected males (>99%) and young adult (median age 36 years, interquartile range 31–43). Among cases with reported sexual orientation, 98% (5470/5561) self-identified as being gay, bisexual, or men having sex with men (MSM), and as many as 41% (1873/4614) of cases with reported HIV status were indeed living with HIV [20].

Genome analysis of current outbreak cases reveals a distinct monophyletic lineage of the current human MPXV. This lineage (B.1, belonging to clade 3) is characterized by heightened mutational signature comparing with its ancestors. This feature could explain the higher transmission rates observed and the related growing number of cases [21]. Phylogenetic analysis and the other MPXV clades are shown in Fig. 2 [22].

#### 4. What characterises the MPX causative agent and how does it spread?

MPXV is a 197 kb linear DNA genome Orthopoxvirus, member of the Poxviridae family, which includes smallpox, cowpox and vaccinia viruses. MPXV is 200–250 nm in size with virions enveloped into a lipoprotein outer membrane. A recognised cause of zoonosis endemic in West Africa and the Congo Basin [23], MPXV may spread via animal-to-human or human-to-human transmission.

Before the current outbreak, major risk factors for human-to-human transmission were identified in sharing the same bedroom or bed or household, and drinking or eating from the same dish. In contrast, behaviors implying increased exposure to animals were related to a higher risk of animal-to-human transmission [24]. Transmission occurs

through direct skin/mucous membranes contact or inhalation of contaminated aerosols. Upon entry, MPXV infection starts via dermis or respiratory epithelium invasion, followed by lymphatic and then hematogenous spread [25]. In light of the high prevalence in MSM groups during the current outbreak, a sexual transmission also appears obvious. Indeed, analysis of samples obtained from infected patients showed high viral loads in saliva, rectal swab, semen, urine and fecal samples [26]. A preliminary study about transmissibility showed an  $R_0 > 1$ , with the highest figure of 1.60 for the Spanish study group. However, it should be kept in mind that in this early phase of outbreak  $R_0$  estimation has many limitations [27]. Miura et al estimated mean incubation period as 8.5 days [28].

#### 5. Clinical presentation of monkeypox in the current outbreak

Before the current outbreak, symptoms of MPX included an initial febrile prodrome (1–4 days) followed by appearance of characteristic, deep-seated, well circumscribed skin lesions, typically showing a centrifugal distribution. Lesions on one area of the body were often synchronous in their development and in rash progression (macule → papule → vesicle → pustule → crust) to desquamation, which occurred 14–24 days after rash onset. Lymphadenopathy was seen in many MPX patients [29].

Since the first report of the ongoing (2022) outbreak, a copious amount of case descriptions were published. We summarized in Table 1 the chief epidemiological and clinical features from the three major studies published by July 25, 2022 [30–32].

The WHO reported data from 9099 patients [20]. The clinical presentation of some MPX cases associated with this outbreak was atypical, and many cases were not presenting with the clinical picture and timing of signs and symptoms previously described. Any rash was described in 90% of cases (8216/9099) and genital rash in 37% (3426/9099); fever was present in 48% of cases (4429/9099) but no specific information was available about its timing. Other major signs and symptoms were: lymphadenopathy (32.8%), fatigue (24%), headache (21.7%) and oral

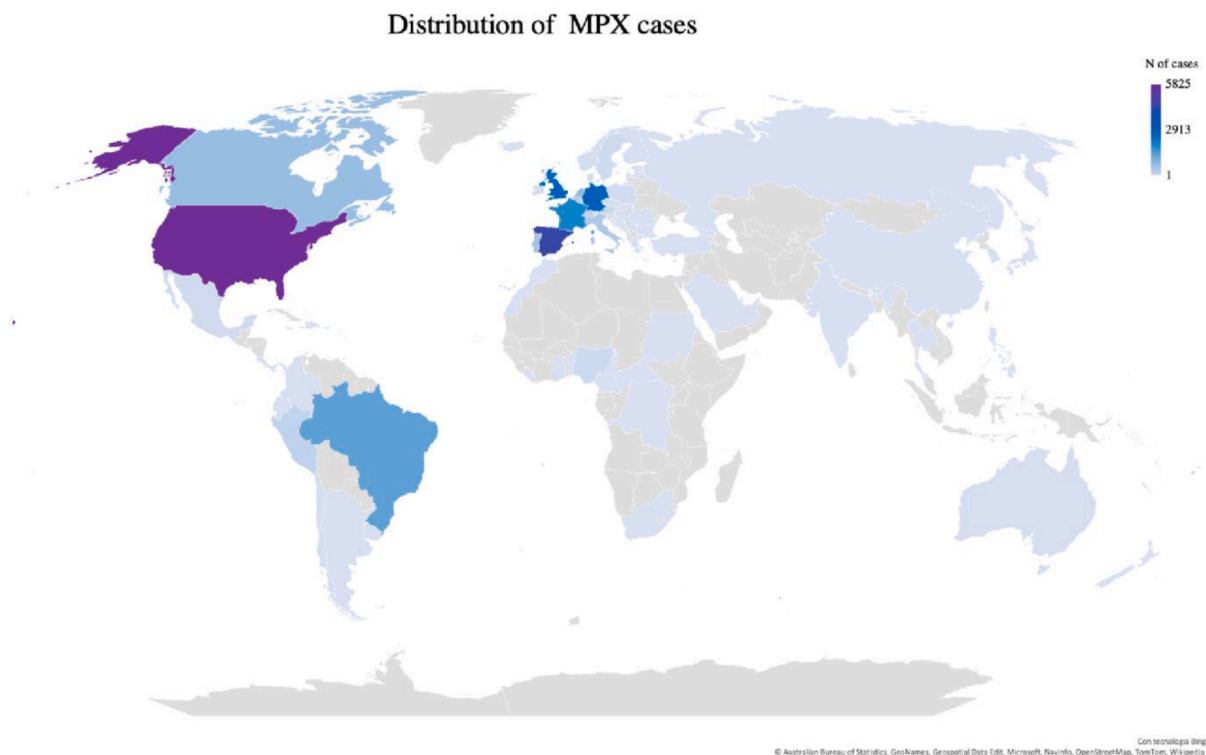
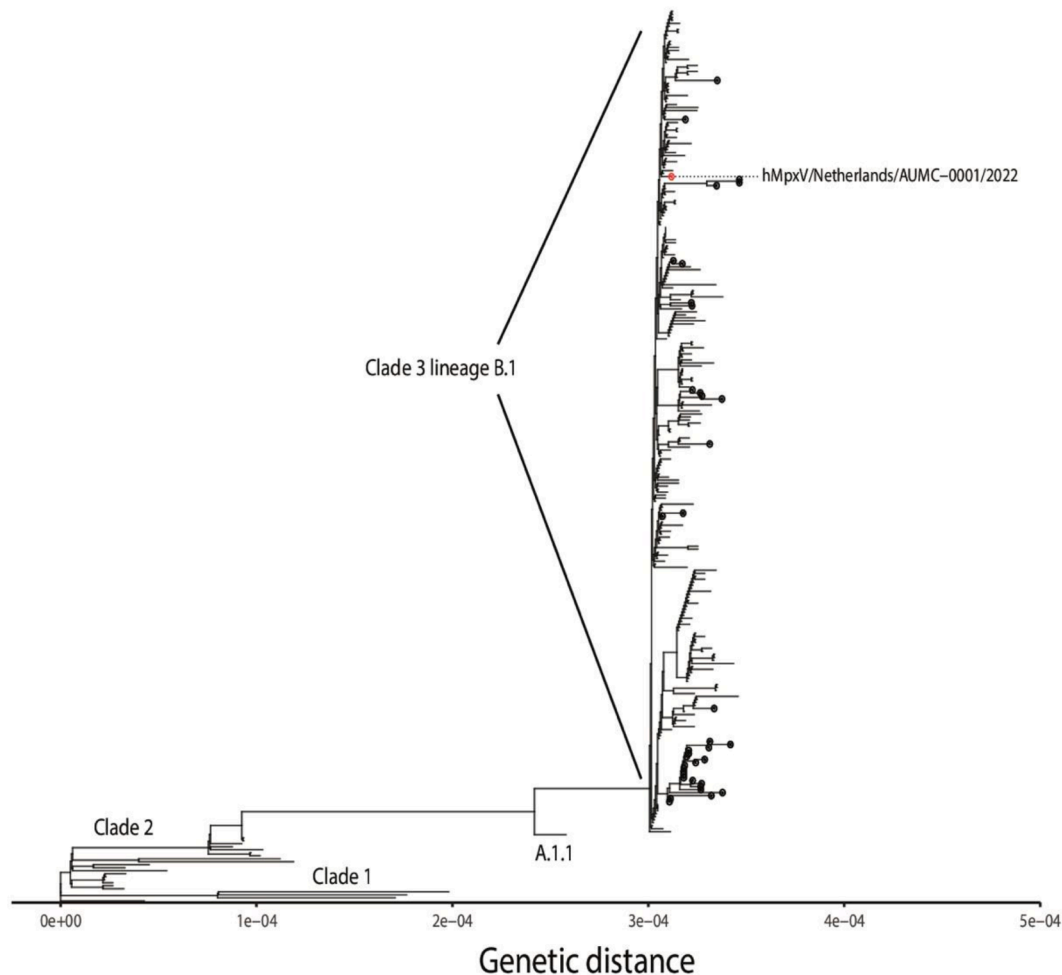


Fig. 1. Distribution of Monkeypox cases from January 1, 2022 through August 3, 2022. Prevalence map constructed based on WHO data [[https://worldhealthorg.shinyapps.io/mpx\\_global/](https://worldhealthorg.shinyapps.io/mpx_global/), Accessed 6 August 2022].



**Fig. 2.** Phylogenetic analysis of the currently spreading MPXV and the other MPXV clades. Reprinted under CC-BY license from Tutu van Furth et al. [22].

lesions (11%). Asymptomatic cases were 780 (8.6%) [20].

These data clearly indicate the current disease is different from prior outbreaks. There is no longer a clear distinction between prodromal symptoms and the appearance of skin lesions, and systemic symptoms are described in only about half of cases. Skin lesions are often asynchronous. In addition, the new evidence of genital and perineal lesions pinpoints the route of transmission. In this regard, it is interesting to analyse the case of two MSM patients having both anal and oro-anal sex [33]. Twenty-four hours after sexual intercourse, the receptive partner developed perioral white spots and painful perianal blistering lesions. Forty-eight hours later, the insertive partner had symptoms of perioral papules which blistered and ulcerated, with subsequent papules on the mons pubis and penis which evolved into painful ulcers. Neither individual reported prodromal symptoms; rather, skin eruptions were followed by systemic manifestations of lymphadenopathy, fever, headache and diarrhoea [33].

A macroscopic and microscopic description of skin lesions was reported by Maronese et al. [34]. Skin lesions were represented by multiple vesicular-pustular lesions with marked umbilication and brownish central crusting and perilesional erythema at dermoscopy. Histology revealed a central area of full-thickness epidermal necrosis with adjacent acanthosis and keratinocyte degeneration. Full-thickness inflammatory infiltrate and cytopathic changes on vascular walls were found in the underlying dermis [34].

## 6. When to suspect and how to diagnose monkeypox

According to the ECDC, a *confirmed case* is a person with a

laboratory-confirmed MPX infection: this implies a positive result on MPXV-specific PCR assay or an orthopoxvirus-specific PCR positive result plus confirmation of the detected virus as MPXV by nucleotide sequence determination. A *probable case* is defined as either A) a person with an unexplained rash on any part of the body AND one or more additional symptom(s) of MPXV infection (fever higher  $>38.5$  °C, headache, backache, fatigue, localized or generalized lymphadenopathy) PLUS one of the following: 1) positive laboratory test result for orthopoxviral infection; 2) epidemiological link to a confirmed or probable case of MPXV in the 21 days before symptom onset; 3) travel to MPXV endemic countries in the 21 days before symptom onset; 4) multiple or anonymous sexual partners in the 21 days before symptom onset; 5) man having sex with men, or B) a person with an unexplained generalized or localized maculopapular or vesiculopustular rash with centrifugal spread, with lesions showing umbilication or scabbing, lymphadenopathy and one or more additional MPX-compatible symptoms [35].

At present, there is no role for serology in the diagnosis of MPX.

## 7. Is there any treatment for monkeypox?

In the attempt to avert a potential bioterrorism threat, a few drugs were recently developed in the US to treat smallpox infection. These antiviral agents are also active against MPXV. The FDA approved tecovirimat in 2018 and oral brincidofovir in 2021. Another active antiviral, already available since decades, is cidofovir, both in topical and intravenous formulations. Tecovirimat was also approved by the EMA in 2021 [36]. It acts inhibiting the viral protein p27, thereby preventing

**Table 1**  
Current clinical features of MPXV as described in 3 recently-published, large case series.

Reference	Number of patients	Country	Age range	Sex (%)	Sexual behaviour, (%)	HIV status, (%)	Concomitant STI, (%)	Systemic symptoms, (%)	Distribution of lesion	Lymphadenopathy, (%)	Complications, (%)	Source of MPXV DNA detection (%)	Antiviral treatment, (%)	Hospitalization, (%)	Mortality, (%)
[30]	508	Spain	20-69	M 503 (99)	MSM 397 (78)	225 (44)	N/A	Fever (63) Asthenia (47) Myalgia (36) Odynophagia (28) Proctitis (16)	Genital and perineal 71% Legs and arms 44% Face 39% Chest abdomen 31% Palms and soles 24%	311 (61)	Parapharyngeal abscess, mouth ulcers, bacterial superinfection (1.3)	Vesicular lesion (100)	0 (0)	19 (3.7)	0 (0)
[31]	27*	Portugal	22-51	M 27 (100)	MSM 18 (95)	14 (52)	N/A	Fever (48) Exanthema (52)	Genital ulcers 22%	14 (52)	0 (0)	Vesicular lesion (100)	0 (0)	3 (11)	0 (0)
[32]	528	16 countries	18 (68%)	M 527 (99)	MSM 509 (96) Heterosexual 9 (2) Bisexual 10 (2)	218 (41)	109 (29)	Fever 330 (62) Pharyngitis 113 (21) Proctitis or anorectal pain 75 (14) Rash 500 (95)	Anogenital area 383 (73%) Trunk or limbs 292 (55%) Face 134 (25%) Palms and soles 51 (20%)	295 (56)	Epi- glottitis 1 (<1) Myocarditis 2 (<1)	Skin or anogenital lesion (97) Semen (29)	25 (5)	70 (13)	0 (0)

MSM: men having sex with men; HIV, human immunodeficiency virus; STI, sexually transmitted infection; MPXV, monkeypox virus. \* in this study the total number of MPXV cases was 96 but data were available only for 27 patients

viral egress from infected cells. In contrast, brincidofovir and cidofovir block viral DNA polymerase [37]. Two clinical trials had actually been planned before the current outbreak to evaluate tecovirimat in MPXV infected patients [38]. NIOCH-14 is an analogue of tecovirimat that showed efficacy in a small number of patients.

Recommended tecovirimat dose for adult patients is 600 mg twice daily for 14 days, given either orally or intra-venously. Co-administration with repaglinide may cause hypoglycaemia. Interference of tecovirimat with cytochrome P450 enzymes translates into numerous interactions with antiviral agents, including anti-retroviral agents for the treatment of HIV-infection. The intra-venous formulation should not be administered to patients with severe renal impairment. [39]

Due to limited supply of MPX-specific antivirals, these drugs should be considered solely for those patients at risk for severe disease (or those who present or develop severe MPX, as recommended by WHO. Pregnant women, children, immune compromised subjects should be considered to be at higher risk for complications [40].

Vaccina immune globulin (VIG) is a recently FDA-approved medicinal product showing efficacy in complications resulting from smallpox vaccination [41]. It could have a role against MPXV but no clinical data are presently available on the use of VIG in MPXV-infected patients.

In light of current clinical, morbidity and mortality data, the goals of MPX management are essentially represented by supportive care, pain management and treatment of uncommon complications such as bacterial superinfections.

### 8. Who should be prioritized for prophylaxis

The progressive waning of herd immunity against smallpox due to withdrawal of the relevant vaccine campaign is considered one of the main causes of the growing MPX incidence over the past decades [42]. Interestingly, median age of patients infected during the current MPX outbreak is about 10 years lower than that of latest smallpox vaccines.

Both pre- and post-exposure MPXV prophylaxis may be prescribed. Available vaccines include MVA-BN (Bavarian Nordic) and ACAM 2000. The former is fully market authorized for MPX prophylaxis in the US and Canada, while it is licensed for smallpox and authorized under exceptional circumstances in Europe. The latter is approved in the US for smallpox and as emergency drug under investigation by FDA for MPXV post-exposure prophylaxis. MVA-BN is a 3<sup>rd</sup> generation, attenuated, non-replicating orthopoxvirus; ACAM 2000 is a 2<sup>nd</sup> generation live vaccinia virus [39,43].

Post-exposure prophylaxis is recommended for high- and medium-risk contacts. These are respectively defined as: 1) Direct exposure of skin or mucous membranes to skin or respiratory secretions of a person with confirmed, probable or suspected MPX, their body fluids or potentially infectious materials if not wearing appropriate personal protection equipment; 2) No direct contact but close proximity in the same room or indoor physical space with a symptomatic MPX patient, if not wearing appropriate protection.

Pre-exposure prophylaxis is indicated only for health-care workers at risk of exposure, research laboratory personnel, clinical laboratory personnel performing diagnostic testing for orthopoxviruses, and designated response team members at risk for occupational exposure to MPX [43].

Some authorities have suggested studying optimal strategies for pre-exposure prophylaxis in subgroups with a high prevalence of infection, such as MSM and patients living with HIV [44].

### 9. Take home message

MPX is spreading fast in previously non-endemic countries, and now represents a reason for concern. Mutations in MPXV have likely increased infectivity and favored human-to-human transmission, which is mostly confined to MSM as a sexually transmitted infection. Clinical presentation appears to have changed, and translates into subtle

morbidity and exceedingly low mortality. For severe cases, active antivirals are available. Vaccine prophylaxis should be considered in at risk groups.

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