

# Monkeypox virus infection: A clinical review based on the 2022 global outbreak

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## ABSTRACT

Monkeypox (mpox) is a zoonotic infection caused by an orthopox DNA virus of the family which causes smallpox. The new outbreak of mpox was first reported in Europe in May 2022, which led to cases being reported in non-endemic countries across the globe. The main modes of human-to-human transmission are through bodily secretions or contact with skin sores. More than 83,000 cases of mpox have been reported globally in 110 affected countries, with 72 confirmed deaths. The predominant mode of transmission is through animal-to-human infected body fluids. The main clinical presentation of patients with mpox is with mucocutaneous manifestation with a range of recorded descriptions of the skin lesions. Most of the patients recover without any medical intervention as mostly the disease is self-limiting. The usual supportive care is needed. Although there is no specific treatment, yet antivirals are used for the treatment of mpox which were originally developed for use in patients with smallpox. At present, there are two available vaccines which can mitigate the risk of developing mpox. The timely global collaboration between the World Health Organization and different countries has helped to mitigate the public health impact of mpox.

**Key words:** Monkeypox, Orthopox DNA virus, Global outbreak, Zoonotic infection, Endemic

Monkeypox (mpox) is a zoonotic infection caused by an orthopox DNA virus of the family which causes smallpox. It has rarely been reported out of Africa until early 2022, when sporadic cases were reported all over the world since April 2022.<sup>1</sup> It was first reported in 1970 in Zaire (now called the Democratic Republic of Congo [DRC]) [1].

As of December 22, 2022, more than 83,000 cases have been reported globally in 110 affected countries, with 72 confirmed deaths. [2] Initially, the World Health Organization (WHO) declared mpox an “evolving threat of moderate public health concern” on June 23, 2022. However, due to the rapidly evolving situation, the WHO declared it a global health emergency on July 23, 2022, a designation which was previously used to describe only two other diseases, COVID-19 and Polio [3]. After a series of consultations with global experts, the WHO decided on November 28, 2022, to use the preferred name for monkeypox as “Mpox”. The new name will be simultaneously used with the original term of monkeypox for 1 year until the old name is phased out [4].

Due to significant public health importance, it is imperative that a literature review is carried out on this topic. Hence, the epidemiology, pathogenesis, clinical presentation, diagnosis, management, complications, and prognosis are reviewed below.

## ETIOLOGY AND EPIDEMIOLOGY

Mpox is a zoonotic infection which is caused by an orthopox DNA virus. It belongs to the same family of viruses which causes smallpox (the variola genus) – hence a similarity in appearance and pattern of the rash to smallpox. However, both the human spread and mortality related to mpox are less as compared to smallpox infection. Mpox has two strains identified – clade one (I) with predominance in Congo and clade two (II) in Western Africa. During the global pandemic, two subclades of clade two (II) have been identified as clade IIa and IIb.

It was in the 1950s that mpox was first isolated in Denmark. The mpox virus was identified and isolated from a colony of laboratory monkeys from Singapore. Originally, these monkeys were going to be used for poliovirus research at the time [5]. Despite the discovery of the virus in 1950s, the first community spread of mpox was identified nearly two decades later in the 1970s in the DRC. Since then, there have been steady and sporadic reports of infection outbreaks in the African region. Since 2007, there has been an exponential (nearly twenty times) increase in the incidence of mpox in the DRC as compared to the decade of 1980s [6]. The latest figures from the WHO indicate that mpox is endemic in many sub-Saharan African countries, including Benin, Cameroon, the Central African Republic, the DRC, the

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Republic of Congo, Gabon, Ghana, Ivory Coast, Liberia, Nigeria, Sierra Leone, and South Sudan – the geographic maps indicating that all these countries are located in the central-to-western region of the sub-Saharan Africa. Reported literature from Africa documented both animal-to-person and person-to-person transmission of mpox. The human-to-human transmission mainly occurs through either infected lesions on the skin or through body fluids. Moreover, surface contact with infected materials can also be a potential source of infection.

## **PUBLIC HEALTH PERSPECTIVE OF MPOX DURING THE GLOBAL OUTBREAK IN 2022**

The new outbreak of mpox was first reported in Europe in May 2022, which then led to cases being reported in non-endemic countries across the globe [7]. The first reported case was from the UK on May 6, 2022, in a patient travelling back to the UK from Nigeria [8]. Despite initial reports of travel-related cases, the vast majority of subsequent cases had no apparent link to travel to endemic areas, leading to the possibility of local transmission of mpox [9-12].

Further cases were reported from Portugal, Spain, and other countries in the Western European region and other parts of the world. Since the onset of the global outbreak in May 2022, the cases continued to spread all over the world (including regions such as North America, South America, South-east Asia, the Middle East/North Africa, and Australia). Hence, on July 23, 2022, the WHO declared this outbreak of mpox a public health emergency of international concern.<sup>8</sup> In the USA, there have been 29,740 confirmed cases of mpox with 20 deaths (as on December 21, 2022) [13].

## **TRANSMISSION**

The predominant mode of transmission for mpox is animal to human through infected animal body fluids. Many types of animals have been found to carry mpox: Namely, squirrels, rats, and monkeys, with rodents being the most likely reservoirs [14].

The human-to-human transmission of mpox became more prominent during the current global outbreak since mid-2022, as majority of cases in Europe and USA were not related to travel to sub-Saharan Africa and/or exposure to animals. The main modes of human-to-human transmission are through bodily secretions, or contact with skin sores, which could be the result of direct sexual contact or non-sexual close intimate contact for a relatively long period of time [14]. A vast majority of cases reported from the non-endemic countries were noted in men who have had sex with men, though any form of intimate contact is a known risk [14,15]. Viral transmission through contact with infected materials (clothing and bed linen) or fomites as well as through respiratory secretions is also reported, though prolonged face-to-face contact is required for respiratory spread [14,16]. Maternal-to-fetal transmission of the virus across the placenta (vertical transmission) or during close contact around the time of childbirth is possible which can cause congenital disease, but the overall rates of transmission are not fully known [14].

## **CLINICAL PRESENTATION**

The incubation period for mpox infection is variable between 5 and 13 days, although it can range from as low as 4 days to as high as 21 days [17-20]. Mpox has a predominantly biphasic clinical presentation. The initial prodromal phase, which can last up to 5 days, is characterized by fever, malaise, chills, sweats, lymphadenopathy, and headache. This is almost invariably followed by the cutaneous eruption phase which usually follows 3–4 days after the prodromal phase.

The main clinical presentation of patients with mpox is with mucocutaneous manifestation with a range of recorded descriptions of the skin lesions. The main sites of distribution of these lesions are face, palms, soles, oral mucosa, conjunctivae, genitals, and anus or perineal area [21]. The duration of infectiousness is considered to be from the onset of clinical lesions to the time; all the lesions have healed (scabbed).

The cutaneous lesions are usually firm and well circumscribed. They are painful and have central umbilication. The rash typically evolves through stages (macules, papules, vesicles, and pustules) before getting crusted and falling off by around day 14 (Fig. 1). The mucocutaneous rash has been reportedly indistinguishable from other vesicular eruptions seen in variola (smallpox), varicella, and herpes simplex.

Other than mucocutaneous symptoms, the most common reported systemic symptoms are fever, chills, myalgias, and lymphadenopathy. Asymptomatic infections seem to be less common as compared to the predominantly symptomatic presentation [22].

## **DIAGNOSIS**

The WHO has published case definitions for suspected, probable, and confirmed cases of mpox infections (Table 1) [23]. Diagnostic testing requires viral testing on clinical specimen from the lesion samples for polymerase chain reaction or the development of immunoglobulin (Ig) M antibodies.

## **MANAGEMENT**

Most of the patients recover without any medical intervention as mostly the disease is self-limiting. The usual supportive care is needed like any other viral prodromal illness, i.e., symptomatic management with antipyretics, analgesics, antiemetics, good hydration, and rest. However, patients may require hospitalization, in case, the symptoms are not controlled, or if the disease leads to any complications.

Patients who should be considered for treatment include those with severe disease (leading to complications such as encephalitis, hemorrhagic disease, or sepsis), patients with systemic complications (e.g., secondary bacterial skin infection, gastroenteritis, acute kidney injury, pneumonia, etc.), patients who may be at high risk of severe disease like with immunocompromised states (primary or secondary due to malignancies, medications, post-transplant, etc.), and patients with a previous history of dermatological conditions such as



**Figure 1:** Examples of monkeypox rashes in different stages (photo credit: Courtesy of UK Health Security Agency (Content available under Open Government Licence v3.0.))

**Table 1:** Surveillance case definitions for the current monkeypox outbreak in non-endemic countries (adopted from the WHO)<sup>1</sup>

**Suspected case:**

A person of any age presenting in a monkeypox non-endemic country<sup>(\*)</sup> with an unexplained acute rash

AND

One or more of the following signs or symptoms, since 15 March 2022:

- Headache
- Acute onset of fever ( $>38.5^{\circ}\text{C}$ ),
- Lymphadenopathy (swollen lymph nodes)
- Myalgia (muscle and body aches)
- Back pain
- Asthenia (profound weakness)

AND

for which the following common causes of acute rash do not explain the clinical picture: Varicella zoster, herpes zoster, measles, Zika, dengue, chikungunya, herpes simplex, bacterial skin infections, disseminated *gonococcus* infection, primary or secondary syphilis, chancroid, lymphogranuloma venereum, granuloma inguinale, molluscum contagiosum, allergic reaction (e.g., to plants); and any other locally relevant common causes of papular or vesicular rash

**Probable case:**

A person meeting the case definition for a suspected case

AND

One or more of the following:

- Has an epidemiological link (face-to-face exposure, including health workers without eye and respiratory protection); direct physical contact with skin or skin lesions, including sexual contact; or contact with contaminated materials such as clothing, bedding, or utensils to a probable or confirmed case of monkeypox in the 21 days before symptom onset
- Reported travel history to a monkeypox endemic country<sup>1</sup> in the 21 days before symptom onset
- Has had multiple or anonymous sexual partners in the 21 days before symptom onset
- Has a positive result of an *orthopoxvirus* serological assay, in the absence of smallpox vaccination or other known exposure to orthopox viruses
- Is hospitalized due to the illness

**Confirmed case:**

A case meeting the definition of either a suspected or probable case and is laboratory confirmed for monkeypox virus by detection of unique sequences of viral DNA either by real-time polymerase chain reaction (PCR) and/or sequencing.

N.B. It is not necessary to obtain negative laboratory results for listed common causes of rash illness in order to classify a case as suspected.

<sup>(\*)</sup>Monkeypox endemic countries are Benin, Cameroon, the Central African Republic, the Democratic Republic of the Congo, Gabon, Ghana (identified in animals only), Côte d'Ivoire, Liberia, Nigeria, the Republic of the Congo, and Sierra Leone. Benin and South Sudan have documented importations in the past. Countries currently reporting cases of the West African clade are Cameroon and Nigeria. With this case definition, all countries except these four should report new cases of monkeypox as part of the current multicountry outbreak.

<sup>1</sup>Source: The WHO: Monkeypox outbreak toolbox: Available: <https://www.who.int/emergencies/outbreak-toolkit/disease-outbreak-toolboxes/monkeypox-outbreak-toolbox>

atopic dermatitis or other exfoliative skin conditions and pregnant or breastfeeding women [24].

Although there is no specific treatment approved for mpox virus infections, it is deemed prudent to use antivirals developed for use in patients with smallpox. Most experts suggest tecovirimat as the drug of choice, with some suggesting concomitant use of cidofovir, especially in patients with severe disease. However, the lack of data on efficacy of cidofovir and the high incidence of nephrotoxicity limit its initial use. It is advisable to involve expert opinion from the infectious disease specialists and/or local public health officials, whichever the case may be, as per the institutional policies.

Tecovirimat potentially inhibits the orthopoxvirus protein which is essential for the viral spread in the infected patient. Both oral

and intravenous preparations are available for its use with dosing calculated as per the patient's weight. The recommended duration of treatment with tecovirimat is 14 days. The side effects are generally mild (nausea, abdominal pain, and headache) [25].

## VACCINES

At present, there are two available vaccines which can mitigate the risk of developing mpox both in pre-exposure and post-exposure phases. The vaccines are the modified vaccinia Ankara (MVA) vaccine (JYNNEOS in the United States, IMVANEX in the European Union, and IMVAMUNE in Canada) and ACAM2000 vaccine [26]. The former (MVA vaccine) is made from a highly

**Table 2: Interim Community Exposure Risk Assessment and Recommendations for Monitoring and Post-exposure Prophylaxis in Individuals Exposed to monkeypox Virus in a Community Setting (adopted from the CDC)<sup>1</sup>**

Degree of Exposure: Higher
Recommendations
<ul style="list-style-type: none"> <li>• Monitoring: Yes</li> <li>• PEP<sup>†</sup>: Recommended</li> </ul>
Exposure Characteristics
<ul style="list-style-type: none"> <li>• Contact between an exposed individual's broken skin or mucous membranes with the skin lesions or bodily fluids from a person with monkeypox -OR-</li> <li>• Any sexual or intimate contact involving mucous membranes (e.g., kissing, oral-genital, oral-anal, vaginal, or anal sex (insertive or receptive)) with a person with monkeypox -OR-</li> <li>• Contact between an exposed individual's broken skin or mucous membranes with materials (e.g., linens, clothing, objects, sex toys) that have contacted the skin lesions or bodily fluids of a person with monkeypox (e.g., sharing food, handling, or sharing of linens used by a person with monkeypox without having been disinfected<sup>‡</sup> or laundered)</li> </ul>
Degree of exposure: Intermediate
Recommendations
<ul style="list-style-type: none"> <li>• Monitoring: Yes</li> <li>• PEP<sup>†</sup>: Informed clinical decision making recommended on an individual basis to determine if the benefits of PEP outweigh the risks</li> </ul>
Exposure characteristics
<ul style="list-style-type: none"> <li>• Being within 6 feet for a total of 3 h or more (cumulative) of an unmasked person with monkeypox without wearing a surgical mask or respirator -OR-</li> <li>• Contact between an exposed individual's intact skin with the skin lesions or bodily fluids from a person with monkeypox -OR-</li> <li>• Contact between an exposed individual's intact skin with materials (e.g., linens, clothing, sex toys) that have contacted the skin lesions or bodily fluids from a person with monkeypox without having been disinfected<sup>‡</sup> or laundered -OR-</li> <li>• Contact between an exposed individual's clothing with the person with monkeypox's skin lesions or bodily fluids, or their soiled linens or dressings (e.g., during turning, bathing, or assisting with transfer)</li> </ul>
Degree of exposure: Lower
Recommendations
<ul style="list-style-type: none"> <li>• Monitoring: Yes</li> <li>• PEP<sup>†</sup>: None</li> </ul>
Exposure characteristics
<ul style="list-style-type: none"> <li>• Entry into the living space of a person with monkeypox (regardless of whether the person with monkeypox is present) and in the absence of any exposures above</li> </ul>
Degree of exposure: No risk
Recommendations
<ul style="list-style-type: none"> <li>• Monitoring: No</li> <li>• PEP<sup>†</sup>: None</li> </ul>
Exposure characteristics
<ul style="list-style-type: none"> <li>• No contact with the person with monkeypox, their potentially infectious contaminated materials, nor entry into their living space</li> </ul>

PEP: Post-exposure prophylaxis. <sup>†</sup>JYNNEOS and ACAM2000 are available for PEP.

<sup>1</sup>Source: adopted from the CDC: Available: <https://www.cdc.gov/poxvirus/monkeypox/clinicians/monitoring.html>



attenuated, non-replicating vaccinia virus administered as two doses, 4 weeks apart. The ACAM2000 is actually a smallpox vaccine that can only be used in select patients. In general, MVA vaccine has a much better safety profile than the ACAM 2000 vaccine. In the United States, ACAM2000 is approved for the prevention of smallpox. It can be used for mpox under an expanded access investigational new drug application through the centers for disease control (CDC) [26]. The selection of high-risk, intermediate-risk and low-risk exposures has been defined by the United States CDC and prevention in Table 2 [27].

## COMPLICATIONS

In addition to the classical presentations discussed under the clinical presentation above, patients can also present with complications such as proctitis (history of perianal pain, discharge, or bleeding, especially in patients with a history of anal sex). Other complications/presentations include pharyngitis, tonsillitis, and ocular disease (conjunctivitis, keratitis, etc.) [1]. Other systemic complications include encephalitis, myocarditis, bronchopneumonia, cellulitis, and sepsis [1,21].

## PROGNOSIS

In a vast majority of cases, mpox is a largely self-limiting illness, which like many other viral infections, resolves in 2–4 weeks without any sequelae. Some patients may develop local or systemic complications as discussed earlier. Clade one (I), the classical form, reportedly has a higher case fatality rate of around 10% [28,29]. In contrast, Clade two (II) variant has a milder disease with less than 1% case fatality rate. The presence of immunocompromised state confers a higher risk for complications and mortality - this specially applies to patients with advanced stages of human immunodeficiency virus infection [30].

## CONCLUSION

The global spread of mpox infection, beyond its accustomed endemic areas, is yet another stark reminder of the abilities of viral strains to defy the usual norms of disease epidemiology and the typical geographical “boundaries”. Like COVID-19 pandemic, a concerted global response, led by the WHO, enabled health-care systems all over the world to share clinical and epidemiological information as well as best practices to everyone’s mutual benefit. This collaboration has invariably identified the key areas of mutual collaboration to mitigate the public health impact of mpox: Public health education and awareness (particularly in high-risk population), early detection and prevention, and in the strengthening of treatment modalities and vaccination protocols.

## AUTHORS’ CONTRIBUTION

All authors have made a significant contribution to this work, be it in the conception, implementation, and literature review or in all

these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be responsible for all aspects of the work.

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