



Journal of Acute Disease

Review Article



jadweb.org

doi: 10.4103/jad.jad_91_24

Impact Factor® 0.5

Mpox re-emerges: Historical background, symptom overview, and contemporary treatment options

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ABSTRACT

As the global community continues to recover from the COVID-19 pandemic, the World Health Organization has issued a warning of another viral infection, mpox (monkeypox), that can pose a significant threat to public health. Mpox was once endemic in Africa but has spread globally, prompting the World Health Organization to declare it a public health emergency. In response, healthcare personnel must initiate timely, decisive, and robust action before the infection escalates. Moreover, accurate diagnosis is crucial, given the similarity between mpox and other rash-causing infections. This article provides a comprehensive overview of the symptoms, differentiating it from similar diseases, risk assessment, and treatment strategies. In addition, it aims to educate healthcare personnel with the necessary knowledge to educate others and take preventative measures when handling cases, thereby avoiding the spread of infection.

KEYWORDS: Mpox; Orthopoxvirus; Clade; Lymphadenopathy

1. Introduction

Mpox (monkeypox) is a distinct zoonotic disease categorized into two genetic clades, the Congo Basin Clade and West African Clade. These have been referred to as Clade I and II, with Clade I having two sub-clades, Clade Ia and Ib, while Clade II exists as Clade IIa and IIb. Clade IIb was identified as the variant most associated with the spread of infection[1]. Still, in August 2024, the first case of mpox caused by Clade Ib was reported in the European Union[2]. The mpox virus is a member of the *Orthopoxvirus* genus within the *Poxviridae* family. There exist 17 species of *Orthopoxviruses*, and they contain DNA of 170-40 bases

in length, which is folded and displays a brick-like appearance[1,3]. This DNA virus is similar to the smallpox virus and exhibits near identical clinical manifestations, which was a cause of concern during the outbreak. The incubation period for mpox ranges from 6 to 14 days, although this period can extend from 5 to 21 days. The contagious phase of mpox begins 1-2 days before the appearance of the rash and continues until all scabs have fallen off, a period that can span from 2 to 4 weeks.

The first documented case of mpox occurred in 1970 in a 9-month-old child in the Democratic Republic of Congo. Initially, mpox infections were confined to various African regions due to the dense tropical rainforests providing ideal animal-to-human transmission conditions. In Eastern and Central Africa, the disease was caused by the Clade I variant, while Clade II was responsible for infection in Western Africa[4,5]. Infection caused by the West African Clade has a much lower-case fatality rate of 1%. Also, mpox has re-emerged in Nigeria, with 985 suspected cases between May 2017 and August 2022[5,6]. However, the disease has spread to non-endemic areas in 2022-2023, indicating a significant geographical expansion[7].

The World Health Organization (WHO) recognized the global

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How to cite this article: Banji D, Banji OJ. Mpox re-emerges: Historical background, symptom overview, and contemporary treatment options. J Acute Dis 2024; 13(4): 127-134.

Article history: Received 18 August 2024; Revision 20 August 2024; Accepted 26 September 2024; Available online 30 September 2024

significance of mpox by declaring it a public health emergency on August 4, 2022. At that time, there have been approximately 87,858 confirmed cases worldwide, including 90 cases from the East Mediterranean region[8]. However, as the case numbers declined, the Director-General of WHO announced on May 11, 2023, that mpox was no longer considered a public health emergency of international concern. In a recent update, the WHO has reversed this decision, classifying mpox (caused by Clade Ib) as a public health emergency of international concern, as the disease severity could be higher[9]. When a public health emergency is declared, healthcare personnel must be well-informed, as they play a crucial role in guiding the general public on prevention and management strategies[3,10]. This was demonstrated during the COVID-19 pandemic, where healthcare personnel took on multifaceted roles. This review seeks to enhance the knowledge and readiness of healthcare professionals on the modes of transmission, clinical manifestations, potential complications, and strategies to prevent the spread of mpox.

2. Historical context

Mpox, alongside other infectious diseases, has potentially ancient roots, with some researchers speculating that this disease may have been present among ancient Egyptian populations. This theory arises from studies of Egyptian mummies that displayed vesicular skin rashes, indicative of viral infections like mpox or smallpox. However, the scientific community has expressed caution in definitively attributing these symptoms to mpox due to the similarity in manifestations between mpox, smallpox, and other diseases. Despite these uncertainties, the frequent infectious diseases in ancient Egypt contributed to widespread mortality and resistance among survivors. Additionally, the possibility that mpox existed in a dormant or asymptomatic form among ancient Egyptians suggests that the disease could have a longer and more complex history within human populations than previously understood.

Later, the disease was suspected in gallery specimens of the African *Funisciurus* species (rope squirrel) in 1899. The first recorded outbreak of the disease occurred in 1958, and it was highlighted that mpox infection is usually transmitted through animal-human contact[11].

Mpox has been reported from endemic areas such as Central and Western Africa, but reports from non-endemic regions have also been received from 2022. Between January and June 2022, one death and 3413 laboratory-confirmed cases were reported to the WHO from 50 countries in five regions (Africa, Europe, Americas, Eastern Mediterranean, and Western Pacific)[12]. Since the last report of the disease episode was published on June 17, 2022, 1310 new cases have been reported, and 8 new countries were added to the

list[12]. A comprehensive search of the European surveillance system has yielded reports of 21,098 mpox cases from 36 countries in the European Region, with 99.3% (20,690 cases) of these cases being confirmed through laboratory testing[13]. In addition, cases were reported from the African region (2%), the Americas (11%), the Eastern Mediterranean region (<1%), and the Western Pacific region (<1%)[14].

3. Risk assessment

The risk of mpox is assessed using historical data and recent findings, focusing on the likelihood of infection and its potential severity. With recent widespread reports of mpox cases across multiple WHO regions, the disease is now recognized as a global threat. However, the outbreak of mpox in 2022 exhibited a heterogeneous risk profile across various geographic areas. Specifically, the European and American regions were characterized by elevated risk levels, whereas Africa, Southeast Asia, and Mediterranean regions displayed moderate risk. The Americas region maintained a high risk even eight months post-outbreak, whereas the risk level decreased to moderate in the European region over the same period[15]. The Eastern Mediterranean region contributed to less than 1% of the global cases[15], which could reflect variations in epidemiological patterns and the capacity for outbreak detection and management.

The risk can also be assessed by identifying the travel history of the affected individuals. Without travel history to endemic areas, it is crucial to identify cases, implement isolation, and conduct contact tracing[16]. Patients presenting with atypical rashes in community healthcare settings should be thoroughly investigated, and necessary precautions should be taken to prevent secondary cases.

The risk assessment of mpox transmission is informed by the primary mode of transmission, which involves prolonged, direct contact with an infected individual or their contaminated personal items. Epidemiological data suggests that brief, casual interactions, such as short conversations, do not constitute a significant risk for transmission.

Mpox infections have been identified predominantly among men who engage in sexual activities with new or multiple male partners[17,18]. This suggests potential underreporting by surveillance systems and the possibility of unrecognized human-to-human transmission[19].

4. Pathways of infection

Transmission mechanisms include direct contact with infectious skin lesions or mucosal surfaces, respiratory droplets, and contact

with contaminated objects. Direct contact with the infected rash, scabs, body fluids, or through inhalation of secretions, prolonged face-to-face interaction, intimate physical contact, or touching items used to clean infectious rash or body fluids can facilitate the spread of infection[20,21]. Intrauterine transmission from mother to child has also been reported[22]. Although the disease has been predominantly observed within a specific community, including gay men, bisexuals, and other men who have sex with men[23], it has the potential to spread beyond this group, much like HIV. Patients with oozing pustules are particularly likely to transmit the virus.

5. Clinical Manifestations

Flu-like symptoms, which may occur several days to weeks after direct exposure, are the first signs and symptoms of mpox. Mpox infection occurs in two phases: the invasion phase (affects 0-5 days), which is characterized by high fever, lymphadenopathy, back pain, myalgia, sore throat, cough, and extreme asthenia; and the rash phase (usually 1-3 days after the onset of high fever) with a deeply rooted, vesicular or pustular rash that progresses gradually from blemishes

Table 1. The stages and symptoms of mpox.

Clinical features	Incubation (7–14 days)	First stage – Prodrome (1–5 days)	Skin involvement (Rash)
Fever	/	/	Seen within 1-3 days of fever onset, lasts for 2-4 weeks
Lymphadenopathy	/	Occurs typically with fever onset Periauricular, cervical, axillary or inguinal Unilateral or bilateral	Occurs typically with fever onset
Stage of rashes	/	Enanthem: First lesions on tongue and mouth	Slow evolution
		Headache, muscle aches and exhaustion	Macules: Start from the face, spreading to arms, legs, palms, and soles (centrifugal distribution) within 24 hours
		Chills and sweats	The rash appears macular, papular, vesicular, and pustular. The classic lesion is vesico-pustular.
		Sore throat and cough	In most cases, the face (98%) is primarily affected, followed by the palms and soles (95%) Oral mucous membranes (70%), genitalia (28%), and conjunctiva (20%) can also be affected. Skin rashes are prominently seen on the limbs and face.
		Lesion progression	By the 3rd day, lesions progress to form papules. By 4th to 5th day, lesions develop into vesicles (raised and fluid-filled). By 6th to 7th day, lesions become pustular, raised, filled with opaque fluid, and deep-seated. Lesions may appear confluent. By the end of 2nd week, lesions dry up and crust. The scabs remain for one week before falling off. The lesion heals with hyperpigmented atrophic scars, hypopigmented atrophic scars, patchy alopecia, hypertrophic skin scars, and contracture/deformity of facial muscles after healing of ulcerated facial lesions.
Other factors	/		The vaccination status, age, nutritional levels, and HIV status can impact the manifestation. Mpox is predominantly seen in societies affected by malnutrition and parasitic infections, making prognosis difficult.
Lesion burden	/		The burden of lesions can be high (>500 lesions)

to somewhat enlarged, firm lesions called papules, vesicles filled with clear fluid, pustules filled with yellow colored fluid, and crusts that eventually dry up and flake off[24–26]. The disease usually lasts for 2–4 weeks (Table 1). Also, infection of the mucous membranes may be associated with extremely painful proctitis, urethritis, phimosis and balanitis[27].

Diagnostic testing plays a crucial role in preventing the transmission of infection. Since several other conditions, such as chickenpox, measles, bacterial skin infections, scabies, syphilis, and drug-induced allergic reactions, can also present with a rash, a thorough and scientific differential diagnosis is essential. Clinically, mpox can be differentiated from smallpox or chickenpox by the presence of lymphadenopathy during the prodromal stage of the disease (Table 2). Nucleic acid testing using real-time polymerase chain reaction is a vital diagnostic tool[28]. Swabs collected from vesicles, or the throat are analyzed to detect viral DNA, specifically targeting non-variola Orthopoxvirus DNA, such as the mpox virus. The most effective specimens for identifying mpox include skin lesions, especially dry crusts, and fluid from vesicles and pustules. The clade-specific polymerase chain reaction test assays can be used to determine the genetic clade[29]. Additionally, the detection of antibodies, which are present at higher levels when lesions appear, and immunohistochemistry of the viral antigens are other available methods but have their challenges. Additionally, a biopsy may also be considered when available.

6. Associated complications

Mpox primarily presents with skin lesions, but there is also a risk of other complications. Affected individuals may experience symptoms such as anorexia, vomiting, and abdominal pain along with diarrhea[30]. In some instances, anorectal pain, proctitis, and bleeding have also been found[31].

Adults and children under 10 years old with mpox could develop ocular symptoms such as blepharitis[30], conjunctivitis[32], and keratitis. In one study, photophobia was reported in 22% of the infected cases[33], and in some instances, corneal scarring, which could lead to blindness, has also been reported.

Secondary bacterial infections associated with mpox can often be mild and resolved with appropriate treatment. However, there exist reports of genital lesions leading to cellulitis and lesions on the hands causing paronychia and lymphangitis[30]. Differentiating between mpox and secondary bacterial infections can be challenging, but careful evaluation of balanitis and purulent exudate can serve as potential indicators of bacterial involvement[34].

Unvaccinated individuals could be at risk of developing bronchopneumonia with respiratory distress. Immunocompromised patients with mpox are more susceptible to viral infections such as

influenza and SARS-CoV-2[35].

In addition, individuals infected with mpox may experience impaired platelet function and an increased risk of coagulopathy[36].

7. Treatment Strategies

Currently, no specific treatments are approved for mpox; however, certain antiviral drugs are being repurposed for compassionate use. Tecovirimat, initially developed for smallpox, is available under the Expanded Access program of the FDA, particularly for immunocompromised individuals, pregnant women, lactating mothers, infants, and those with compromised skin integrity [37,38]. Additionally, the antivirals cidofovir and brincidofovir have demonstrated efficacy against orthopoxviruses and are utilized in managing cytomegalovirus retinitis in AIDS patients. Brincidofovir, a prodrug of cidofovir, received approval for smallpox treatment in adults and children in 2021 and is safer due to its lower risk of renal toxicity[38,39]. Animal and in vitro studies have confirmed their effectiveness against orthopoxviruses, making it a potential option for mpox treatment. However, its use requires a single-patient investigational new drug (e-IND) application submitted by the clinician to the FDA. Also, the simultaneous use of brincidofovir and cidofovir is not recommended.

Vaccinia Immune Globulin can only be used in case of outbreaks to manage infections caused by orthopoxviruses[40].

Over-the-counter medications are recommended for symptomatic relief, and antibiotics may be prescribed to prevent secondary bacterial infections. Supportive care remains the primary approach for managing the majority of mpox cases.

At present, two vaccines are available for use against mpox. Jynneos is fully licensed for smallpox, and ACAM2000, initially developed for smallpox, has been utilized for mpox under the Expanded Access Investigational New Drug (EA-IND) protocol. Jynneos is a customized third-generation Ankara vaccine (MVA-BN), which is relatively safe and administered subcutaneously in two doses at least four weeks apart. Jynneos has demonstrated a low replicative capacity and reduced neuropathogenicity in human and animal studies while retaining strong immunogenic properties, including protective immune responses against various orthopoxviruses[40]. Protection begins seven days after the second dose and lasts up to 24 months.

As of September 8, 2022, the FDA has issued an Emergency Use Authorization for Jynneos, allowing its use in individuals under 18, though the specific age limit has not been defined. Jynneos is not recommended for use during pregnancy and in individuals with atopic dermatitis, as they may experience local and generalized reactions. Under an Emergency Use Authorization, Jynneos can also be administered *via* the intradermal route, providing flexibility

Table 2. Comparative features of monkeypox, smallpox, chickenpox, and measles.

Features	Mpox	Smallpox	Chicken pox	Measles (Rubeola)
Virus	Mpox	Variola	Varicella Zoster	Paramyxovirus
Genus	Orthopoxviruses	Orthopoxviruses	Varicellovirus	Morbillivirus
Family	Poxviridae	Poxviridae	Orthoherpesviridae	Paramyxoviridae
Forms	Clade I and II	Variola minor & variola major	Seven genotypes	20 different types
Genetic material	Double stranded DNA	Double stranded DNA	DNA	RNA
Mode of spread	Animal to human and human to human spread. Sexual contact between men, contact with infected skin/lesions or contaminated materials	Human to human. Droplet infection, indirect contact with contaminated materials. No animal as a reservoir.	Spreads through direct contact with rash or through the air by respiratory droplets	Transmitted through respiratory droplets or direct contact with nasal or throat secretions of infected persons.
Incubation period	6-14 days but may extend to 21 days	7-17 days	14-16 days	11-12 days
Communicability	During the prodrome phase and till scabs fall off.	First week of illness and until scabs fall off.	1-2 days before rash appears and until they form crusts.	4 days preceding the appearance of rash and until four days after it emerges.
Characteristic feature	Lymphadenopathy	No lymphadenopathy	No lymphadenopathy	Lymphadenopathy is seen
Symptoms	The prodromal phase is characterized by fever which might appear 1-5 days before the appearance of rash, headache, lymphadenopathy, and lethargy. Following this initial phase, lesions appear 1-3 days later. Sores are large, painful, filled with fluid as well as pus and last for 2-4 weeks.	The initial symptoms include fever, back pain, fatigue, abdominal pain, and vomiting. These are followed by a rash that progresses through several stages: it begins as macules, then transforms into papules, and finally develops into pustules, with each stage lasting approximately 2-3 days.	Mild prodrome with fever for 1-2 days before the appearance of rash. Pruritic rash occurs within 24 hours and can be seen as macules, papules and vesicular rash. Sores are itchy and last for around 2 weeks. The primary infection with the varicella-zoster virus leads to varicella (chickenpox). When the virus becomes latent, it can later reactivate to cause herpes zoster (shingles).	The prodromal phase of the illness lasts 2-4 days and is marked by symptoms such as high fever, cough, conjunctivitis, runny nose (coryza), and distinctive Koplik spots on the buccal mucous membranes. This phase is followed by a rash that persists for 5-6 days, affecting the face, neck, hands, and feet.
Location of lesions	Hands, feet, face, genitalia, cornea.	Face, hands, oral, anorectal and vaginal sites. Occasionally on hands & feet.	Face, scalp and trunk as well as the mu-cous membranes.	Face, ears and then spreads to the trunk and extremities.
Associating complications	Secondary infections, bronchopneumonia, sep-sis, encephalitis, and corneal infection with potential loss of vision.	Severe scarring, blindness, arthritis, and even death in severe cases.	Bacterial infections of the skin, pneumonia, and encephalitis (rarely)	Otitis media, severe diarrhea, pneumonia, encephalitis, blindness, seizures, and a rare but fatal disease called subacute sclerosing panencephalitis (SSPE)
Laboratory testing	With real-time or usual polymerase chain reac-tion (PCR), Nucleic acid amplification testing (NAAT). Additionally, sequencing could be done to identity the clade.	PCR	Real time PCR, ELISA, serological tests	Real time reverse transcriptase PCR or serology testing for IgM or IgG antibodies.
Fatality rate	Low (10 %)	High (30-50%)	Can vary but is around 1-2 %	About 3-5 %
Cause of mortality	Occurs only in severely ill cases	Multi organ failure		
Prevention	Isolation, avoiding skin-to-skin contact with the infected and vaccination.	Isolation	Vaccination with Varivax® and MMRV (Mumps, Measles, Rubella & Varicella, ProQuad®)	Mumps, Measles & Ru-bella (MMR) or MMRV
Treatment	Supportive care, Ankara vaccine in 2 doses, 2 weeks apart, JYNNEOS vaccine	Tecovirimat, Brincidofovir, Cidofovir	Antivirals such as acyclovir	Vitamin A, antibiotics to treat pneumonia

during outbreaks.

Another vaccine approved against smallpox is the ACAM vaccine. Under the Expanded Access Investigational New Drug (EA-IND) protocol, the ACAM vaccine could be used for mpox; however, the toxicities associated with its use are high.

8. Recommendations for prevention & spread

Viral evolution affects the organism's virulence, leading to symptom variations and necessitating the development of new diagnostic tools. Sequencing virus-infected specimens and documenting the data in repositories can be of good support in managing cases effectively.

To prevent the spread of mpox, avoid close skin contact with individuals with an infection. Reducing contact with sick animals and minimizing human-to-human transmission are vital strategies to prevent the spread of mpox. Refraining from touching the rash or scabs of an infected person, avoiding intimate physical contact, avoiding touching contaminated bedding, and regular handwashing with soap and water or using an alcohol-based hand sanitizer, especially before eating or touching your face, is also crucial in reducing the risk of infection[41]. Contact tracing helps collect epidemiological data, and travel advice should be provided to anyone traveling to the affected regions[42].

9. Conclusion

The resurgence of mpox as a global health concern focuses on the need for vigilance and timely intervention to prevent and manage the infection. The transmission pathways and clinical manifestations emphasize the need for accurate diagnosis, effective treatment strategies, and preventive measures to control its spread. The availability of antiviral treatments and vaccines, such as Tecovirimat and Jynneos, is a hope in managing and preventing mpox infections. Still, their use must be carefully considered based on individual risk factors. Continued surveillance, research into antiviral therapies, and public health education will help combat this re-emerging threat.

Conflict of interest statement

The authors report no conflict of interest.

Funding

This study received no extramural funding.

Authors' contributions

Conception, literature review, writing, and final review: BD & BOJ.

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Edited by Liu JJ