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Mpox (Monkeypox): A Comprehensive Review of Etiology, Epidemiology, Transmission, Clinical Presentation, Diagnosis, Treatment, and Prevention

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ABSTRACT

Introduction: The objective of this review is to provide a comprehensive overview of the current state of knowledge about mpox (monkeypox), its etiology, epidemiology, transmission, clinical features, diagnosis, treatment, and prevention.

Materials and Methods: A literature review was conducted in the PubMed database using the keywords: "monkeypox", "mpox", "MPXV", "tecovirimat", "VIGIV", "brincidofovir", and "cidofovir". We also used institutional websites: World Health Organization (WHO), Centers for Disease Control and Prevention (CDC), European Centre for Disease Prevention and Control (ECDC), Public Health England (PHE), and European Medicines Agency (EMA). All online resources were accessed in May 2025 and verified to be the most up-to-date at the time of analysis.

Summary: Mpox (monkeypox) is a zoonotic disease endemic in some regions of Central and West Africa. It is caused by monkeypox virus (MPXV). In May 2022, a large outbreak involving most EU/EEA (The European Union/European Economic Area) countries was announced. The mpox symptoms are divided into two phases: the prodrome (1 to 5 days) and the rash. The chosen method for detecting MPXV is nucleic acid amplification testing (NAAT), such as real-time or conventional polymerase chain reaction (PCR). For most patients, treatment is mainly supportive and symptomatic. Antiviral therapies such as tecovirimat, brincidofovir, cidofovir or vaccinia immune globulin intravenous (VIGIV) are reserved for patients with severe disease or those at high risk of complications. Mpox prevention includes isolation, public health control measures, and vaccination (both pre-and post-exposure).

Conclusions: Accurate recognition of mpox symptoms is crucial to helping control outbreaks. Swift diagnosis, surveillance, and access to treatments and vaccines are keys to effective management.

Keywords: monkeypox, mpox, emerging infectious diseases, zoonosis

Introduction

Mpox is a zoonotic disease caused by the monkeypox virus (MPXV) [1], which is classified into the genus Orthopoxvirus; the variola (smallpox) and vaccinia viruses are also a part of this genus, as classified by the International Committee on Taxonomy of Viruses (ICTV). [2] The disease was previously known as monkeypox but was renamed by the World Health Organization (WHO) on 28 November 2022 to avoid racist and stigmatizing language. [3] Mpox virus was isolated for the first time in 1958 at the State Serum Institute in Copenhagen, Denmark from a captive cynomolgus monkey, which resulted in the name of the disease. [4] The first human case was documented 12 years later in a nine-month-old child from the Democratic Republic of Congo. [5, 6]

The first outbreak outside Africa happened in the United States in 2003. Before that, mpox was an endemic disease in some parts of Central and West Africa. [1] In May 2022, a large outbreak involving most EU/EEA countries was announced. The monkeypox virus (MPXV) was

transmitted from human to human. Patients got infected via close physical contact with infected individuals. Most of the reported cases were among men who have sex with men. [7]

On 14 August 2024, the World Health Organization declared a Public Health Emergency of International Concern (PHEIC). It was due to a significant increase in mpox cases in the Democratic Republic of the Congo and its spread to neighbouring countries. [8] As of 31 March 2025, mpox remains a significant global public health concern with 12,531 cases reported in 66 countries in 2025 alone. [9] In order to manage the mpox epidemic efficiently, a deeper understanding and re-evaluation of the monkeypox virus is needed. [1]
The purpose of this review is to summarize knowledge concerning mpox's etiology, epidemiology, transmission, clinical manifestation, diagnostic strategies, treatment options, and preventive strategies.

Etiology
The monkeypox virus (Orthopoxvirus monkeypox) is a part of the Orthopoxvirus genus within the Poxviridae family. This genus also encompasses other well-known viruses, such as vaccinia virus, cowpox virus, variola virus, and some additional poxviruses that infect animals. MPXV is a double-stranded, enveloped DNA virus [2] and the genome of the MPXV is 197-300 kilobase pairs in size. [10, 11] Monkeypox virus (MPXV) has two genetic clades: the West African clade (WA, Clade II) and the Congo Basin clade (CB, Clade I), also called the Central African (CA) clade. [1] The CA clade causes more severe symptoms and is reported to have a higher fatality rate (10%) than the WA clade (4%). [12]

Epidemiology
Mpox is an endemic disease in parts of Central and West Africa [1] and its first documented case was in a nine-month-old child from DRC in 1970. [5, 6] The spread to Europe and North America was limited. [13] Between 1970 and 1990 more than 400 mpox patients were reported in Africa, most of them in the DRC. [1] Small viral outbreaks regularly occur in equatorial Central and West Africa, with the Democratic Republic of the Congo reporting 500 cases between 1991 and 1999. [13]
The first outbreak outside Africa happened in the United States in 2003. Before that, mpox was an endemic disease in parts of Central and West Africa. During the outbreak, all the 47 reported cases were traced to contact with pet prairie dogs (Cynomys spp.). They had been infected through exposure to small mammals imported from Ghana. [1]
On May 6th, 2022, a case of monkeypox virus infection was reported in a British citizen returning from Nigeria who developed characteristic mpox symptoms. Soon after, case numbers rose rapidly, surpassing 1,500 across 43 countries - including those in Europe and North America - by June 10, 2022. The emergence of mpox in high-income regions raised serious concerns about its potential for global spread. [13] In response, the World Health Organization (WHO) declared the mpox outbreak a Public Health Emergency of International Concern (PHEIC) on 23 July 2022. [14] By 13 September 2022, over 57,995 laboratory-confirmed mpox cases had been reported across more than 100 countries or territories in all six WHO regions

with a total of 18 deaths. [1] Clade IIb of the monkeypox virus (MPXV) has been responsible for a major, ongoing outbreak that began in 2022 and continues to the present. [9]

29,607 mpox cases were reported across 47 countries and territories in the WHO European Region in a period from 7 March 2022 to 14 April 2025. Most cases (98%) occurred in males, with the most affected age group being individuals aged 31–40 (40%). Among men with reported sexual behaviour, 97% identified as men who have sex with men (MSM). Of those informed about their HIV status, 37% were HIV-positive. [15]
On 14 August 2024, the World Health Organization declared a Public Health Emergency of International Concern (PHEIC). It was due to a significant increase in mpox cases in the Democratic Republic of the Congo caused by a newly identified strain, Clade Ib, and its cross-border spread to neighbouring countries. [8]

Transmission
The monkeypox virus' transmission occurs through animal-to-human and human-to-human routes. Animal-to-human transmission occurs through direct contact with diseased parts or fluids of infected animals, and even via contaminated surfaces, through scratching, biting, or eating infected meat. Person-to-person transmission occurs through direct contact with skin lesions or bodily fluids, respiratory droplets, aerosolized respiratory secretions, or even via contact with a mpox patient's bedding or clothing. [1, 16] MPXV can be passed from pregnant women to the fetus, during delivery and in the postpartum period. [17]
Transmission of MPXV can occur through both homosexual and heterosexual contact. During the 2022 outbreak, most cases were reported among men who have sex with men (MSM). The high number of mpox cases among MSM has been attributed to the virus's accidental entry into the community and then sexual behaviour constituting "close contact" rather than through the sexual transmission of the virus itself. [16, 17, 18]

Clinical Presentation
The incubation period for the monkeypox virus is from 1 to 21 days, with symptoms appearing approximately one week after exposure. Symptoms usually last two to four weeks and are divided into two phases: the prodrome (1 to 5 days) and the rash. The prodromal phase is typically associated with fever, headache, chills, fatigue, myalgia, back pain, lymphadenopathy, and general weakness. Within about three days of the onset of these symptoms, a centrifugal maculopapular rash usually occurs at the site of primary infection and rapidly spreads to other parts of the body. Involvement of the palms and soles is a distinctive and characteristic feature of mpox. The skin lesions progress for 2-4 weeks through several stages: macules, papules, vesicles, pustules, scabs, and ultimately shedding. The rash is different in every individual - it can vary from a few to several thousand skin lesions. Greater numbers of lesions typically reflect more severe disease. Most mpox infections are characterized by mild to moderate symptoms and typically result in full recovery with supportive care. [1, 7, 19, 20] Differential

diagnoses include smallpox, chickenpox, syphilis, herpes simplex infection, impetigo, and cellulitis. [21, 25]

Some possible complications of monkeypox are encephalitis, keratitis, pneumonitis, and secondary bacterial infection. Additional possible complications are pain or difficulty swallowing, gastrointestinal symptoms such as vomiting and diarrhea leading to dehydration or malnutrition, sepsis, myocarditis, proctitis, balanitis, and urethritis. [1, 19] Severe complications and sequelae have been discovered to be more prevalent in unvaccinated individuals (74%) compared to those who were vaccinated (39.5%). [22]

The lethality of monkeypox infection varies depending on several factors, including the viral clade, the route of transmission, and the age of the patient. [1] Estimated overall case fatality rate (CFR) is estimated at 8.7%, with significant differences between clades: 10.6% (95% CI: 8.4%–13.3%) for the Central African clade and 3.6% (95% CI: 1.7%–6.8%) for the West African clade. [23] Up to 31 March 2025, a total of 317 deaths have been reported worldwide since the start of the 2022 outbreak, including 62 deaths in 2025 alone. [9]

Diagnosis

Monkeypox diagnosis is a combination of epidemiological background, clinical evaluation, and laboratory confirmation tests. [1] The World Health Organization (WHO) states that the primary specimen type for laboratory confirmation of MPXV infection are the skin lesion material such as swabs of lesion surfaces, exudates, or crust. In cases in which there are no skin or mucosal lesions, alternative samples such as oropharyngeal swabs may be collected, although these offer fewer sensitive results. [24]

The preferred method for detecting MPXV is nucleic acid amplification testing (NAAT), such as real-time or conventional polymerase chain reaction (PCR). It works by targeting specific viral DNA sequences. PCR is used alone or alongside sequencing to identify specific clades. The hemagglutinin gene, the acidophilic-type inclusion body gene, and the crmB gene are commonly targeted genes for PCR testing. [1]

Serology is not recommended as a single test because of its cross reactivity with antibodies to other orthopoxviruses as well as those elicited by vaccination. Serological testing can be used in cases where NAAT results are inconclusive. [24, 25] Point-of-care tests approved by the U.S. Food and Drug Administration (FDA) are also available and offer rapid diagnostic results with performance comparable to standard laboratory-based assays. [26]

Other diagnostic methods, such as electron microscopy and viral culture are available, but they are not routinely used in clinical settings. [24]

Treatment

There is currently no specific treatment approved for mpox, and most patients receive symptomatic and supportive care. Treatment may be considered for individuals with severe

disease or those at high risk of complications, including immunocompromised patients, children, pregnant or breastfeeding women, and individuals with skin conditions or with aberrant mpox infections (e.g., eyes, mouth) or regions where mpox infection could pose a threat (genitals or anus). While smallpox antivirals such as tecovirimat, brincidofovir, and cidofovir show potential due to genetic similarities between the viruses, the World Health Organization (WHO) notes that their effectiveness against mpox has not yet been conclusively demonstrated. [1, 19, 26]

Symptomatic treatment includes alleviation of fever and pruritus, pain management, and hydration. Prevention and treatment of secondary bacterial infections (treated with systemic or topical antibiotics) is also a part of mpox symptomatic treatment. Pain symptoms can be alleviated with usage of topical therapies - sitz baths or lidocaine gels for proctitis, and saltwater or viscous lidocaine gargles for pharyngitis. [7, 27] The only antiviral drug authorized for use in the European Union for the treatment of orthopoxvirus infections, including monkeypox, is tecovirimat. Marketed as Tecovirimat SIGA, the drug interferes with a VP37 protein on the surface of orthopoxviruses—such as smallpox, monkeypox, and cowpox—disrupting viral replication and thereby limiting the spread of infection. Clinical evaluations have shown the side effects to be generally well-tolerated, with the most common being headache (12.3%) and nausea (4.5%). [28] Cidofovir and its prodrug brincidofovir work as viral DNA polymerase inhibitors. While cidofovir has demonstrated efficacy against MPX in animal studies, brincidofovir has shown antiviral activity only against infections caused by Orthopoxvirus genus members. Highly immunosuppressed patients with severe symptoms of mpox disease can be treated with intravenous cidofovir. Cidofovir has also been applied topically as a cream or injected directly into skin lesions, with certain case reports noting clinical improvement. [27, 29]

Vaccinia immune globulin intravenous (VIGIV), an FDA-approved treatment for complications related to smallpox vaccination-such as eczema vaccinatum, progressive vaccinia, and vaccinia infections in individuals with skin conditions-has also been authorized by the CDC for use during mpox outbreaks. While its effectiveness in treating severe mpox remains unproven, VIGIV may be considered for immunocompromised patients who are unlikely to produce an adequate antibody response. VIGIV is usually used in combination with tecovirimat and either brincidofovir or cidofovir. [1,30]

Prevention

Mpox prevention includes isolation, public health control measures, and vaccination (both pre- and post-exposure). Patients with mpox infection should be isolated at home or in a healthcare facility, for the entire period of the infectious stage. Isolation should continue until all skin lesions are fully healed and scabs have dropped off completely, to ensure that the risk of transmission to others is minimized. They should take precaution to avoid contact with high-risk groups, including immunocompromised individuals, and follow public health guidelines. If going outside is necessary, a mask should be worn, and all the lesions should be covered. Sexual activity should be abstained until full recovery, and condoms are recommended for 12

weeks post-recovery as there is a possibility of viral presence in semen. During the infectious period patients should avoid contact with mammals. [7,19]

The Mpox Global Strategic Preparedness and Response Plan by the World Health Organization outlines key priorities, which include enhancing surveillance, early case detection, and contact tracing; implementing targeted vaccination strategies focused on high-incidence areas and populations at risk such as household and sexual contacts of confirmed cases, front-line healthcare workers in affected regions, and vulnerable populations like sex workers and immunocompromised individuals. The strategy also emphasizes strengthening international collaboration to maximize vaccine access, especially in middle- and low-income countries. It also empowers communities to be actively engaged in risk communication, stigma reduction, and preventive efforts. [31]

The European Union authorized a third-generation, non-replicating smallpox vaccine Imvanex (Modified Vaccinia Ankara - Bavarian Nordic, MVA-BN) in July 2022 for use in adults for immunization against mpox. In September 2024, the European Medicines Agency (EMA) recommended its administration to be expanded to adolescents aged 12 to 17. The product information directs that a single 0.5 mL injection should be administered subcutaneously on a chosen date, and an additional single 0.5 mL injection at least 28 days after. For post-exposure prophylaxis the vaccination is ideally given within four days after exposure, but it can still be given up to 14 days later, provided that no symptoms have already occurred. The most frequent adverse reactions observed in clinical trials were injection site reactions and typical systemic responses seen with vaccines. These reactions were mild to moderate in intensity and resolved spontaneously within seven days following vaccination. [7, 32] Two pre-exposure doses of vaccine (PPV) have estimated efficacy of 82% (95% CI: 72–92), and one dose has 76% efficacy (95% CI: 64–88). In post-exposure vaccination (PEPV), efficacy is lower at an estimated 20% (95% CI: -24–65). [33] Moreover, individuals who developed mpox infection despite vaccination had milder illness than unvaccinated individuals. [34]

Summary

Mpox (monkeypox) is a zoonotic disease endemic in some regions of Central and West Africa, caused by the monkeypox virus. It was first identified in 1958 in monkeys and later in humans in 1970 in the Democratic Republic of Congo (DRC). In May 2022, a multi-country outbreak was declared, with locally acquired cases reported in most EU/EEA countries. Person-to-person transmission occurs through direct contact with skin lesions or bodily fluids, respiratory droplets, aerosolized respiratory secretions, or even via contact with a mpox patient's bedding or clothing. Most of the reported cases during the 2022 outbreak were among men who have sex with men. Symptoms usually last two to four weeks and are divided into two phases: the prodrome and the rash. The prodromal phase is typically associated with fever, headache, chills, fatigue, myalgia, back pain, lymphadenopathy, and general weakness. After three days a centrifugal maculopapular rash usually occurs. The patient is infectious until all skin lesions have fully healed, and the scabs have completely fallen off. Nucleic acid amplification testing (NAAT), particularly real-time or conventional polymerase chain reaction (PCR), is the gold standard for detecting MPXV. Most patients receive symptomatic and supportive care.

Treatment may be considered for individuals with severe disease or those at high risk of complications may. It includes antiviral drugs such as tecovirimat, brincidofovir, cidofovir, or vaccinia immune globulin intravenous (VIGIV) though data on efficacy remain limited. Mpox prevention involves isolation, public health control measures, and vaccination (both pre- and post-exposure). The vaccine effectiveness of two pre-exposure vaccine doses is 82%, and one pre-exposure vaccine dose provides effectiveness of 76%. Post-exposure vaccination effectiveness is 20%. Individuals with mpox symptoms despite vaccination had milder illness compared to unvaccinated individuals.

Conclusions

As of today, mpox is still a health problem globally. The monkeypox virus transmission occurs through a human-to-human route and it can cause severe disease, especially in at-risk patients. Even though previously endemic in West and Central Africa, the 2022 epidemic proved it possible to be exported worldwide with most of the recent cases occurring among men who have sex with men (MSM). The epidemiological pattern of mpox continues to change. New viral clades, such as Clade Ib, have emerged. These developments highlight the need for continuous surveillance, early detection, and strong public health interventions. There is no antiviral drug developed specifically for MPVX. Antivirals like tecovirimat can be used in severe cases or immunocompromised patients. Prevention remains the main way to control outbreaks, and it includes quarantine of the infected and vaccination campaigns. Education among communities, research, parity of vaccine distribution, and global partnerships are essential to alleviate mpox transmission and its long-term consequences.

Disclosure

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