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Mpox: An Emerging Undetected Public Health Threat

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Abstract:
The emergence of viral infectious diseases is an enormous challenge for global public health systems to protect their communities. By March 5, 2024, there were greater than 94,297 cases of Mpox infections, including 198 deaths in non-endemic parts of the globe. As of this writing, Mpox has caused greater than 100,000 cases in 122 countries. The number of new infections continues to rise and currently represents 115 countries where Mpox was not previously observed (CDC, December 2025). This article provides an overview of the monkeypox virus, as the virus may be circulating not only undetected in communities across the Unted States, but globally.

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Introduction

The emergence of viral infectious diseases is an enormous challenge for global public health systems to protect their communities [1]. Smallpox affected humans for centuries and remains the only endemic human disease to be successfully eradicated. The World Health Organization (WHO) initiated a global smallpox eradication campaign in 1967, focusing specifically in countries with high rates of endemic smallpox such as Africa, Asia, and South America [2]. As the world recovers from Covid-19 that has killed millions of people, another infectious disease poses a public health threat. Mpox (formerly known as monkeypox) has been identified as a serious global public health threat of international concern by the World Health Organization (WHO) as Mpox is spreading beyond endemic regions. The paper presents a review of Mpox viral transmission, pathogenesis, clinical presentation and treatment options as the virus may be circulating not only in communities across the United States undetected, but globally that may result in the next pandemic.

Identified in 1958 in laboratory monkeys in Denmark, monkeypox (Mpox) is a double-stranded DNA zoonotic virus caused by the Monkeypox virus (Figure 1). The virus is part of the Orthopoxvirus genus in the family Poxviridae and is related to cowpox, vaccinia and variola (the virus that causes smallpox) [3, 4]. Mpox is endemic in Africa and is classified into two basics clades: Central African (also referred to as Congo Basin or Clade I) and West African (Clade II). Clade II is divided into two groups: IIa and IIb. IIb is now spreading internationally through human transmission.

Figure 1

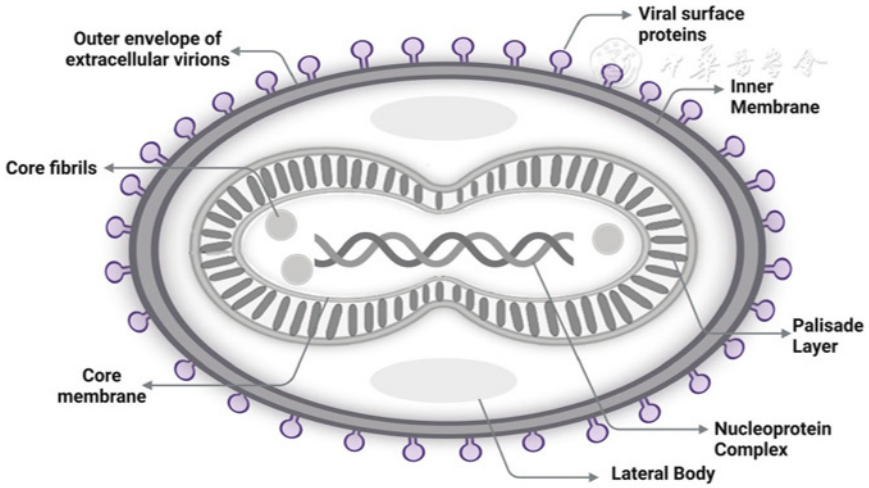

Figure 1: Schematic Representation of Mpox Virus Particle Structure. (CDC, 2025).

In 1970 the first human Mpox infection was confirmed in the Democratic Republic of Congo (DRC) in a nine-month-old boy that was suspected of contracting smallpox [5]. Since the first case report, more cases have been reported in African countries due to a decline in herd immunity against the smallpox virus [6]. Based on WHO data, 102,977 confirmed cases of Mpox triggered by clades I and II involving 219 fatalities have been recorded across 121 countries between 2022 and July 31, 2024.

The 2022 outbreak of Mpox in over 70 non-endemic countries continues to threaten global public health [7,8]. In the United States and Europe, there were greater than 80,000 cases of Mpox that continues to increase [9, 10]. By April 12, 2023, there were 30,344. confirmed cases in the United States, more than any other country [11,12]. By March 5, 2024, 94,297 individuals were infected with Mpox, including 198 deaths in non-endemic parts of the globe [13].

In October 2025, the California Department of Public Health (CDPH) reported clade Ib Mpox infection in three males, ages 25–40 years. All were gay or bisexual and frequented associated social networks. Most disturbing, all three men denied recent international travel or contact with one another, suggesting community transmission of the virus [14]. None of the men were vaccinated against Mpox or received antiviral medication and recovered from Mpox with supportive care. As of this writing, Clade II Mpox has caused greater than 100,000 cases in 122 countries. The number of new infections represents 115 countries where Mpox was not previously observed [15].

Viral Transmission

Transmission between animals and humans is the main source of infection and occurs through contact of infected body fluids from animals [16]. Human-to-human transmission of the Mpox virus occurs through direct contact of infected body fluids, skin, and lesions of the mucous membrane and contaminated clothing [17,18]. Testing for the virus revealed elevated levels of Mpox DNA in lesions of the skin, anus/rectum, pharynx and in semen [19]. The risk of viral transmission is low after lesions have healed with scab formation.

Pathogenesis

The incubation period of Mpox is 5-21 days. Lesions progress through four stages: macular, papular, vesicular, and pustular, before the scab phase [20]. The virus initially infects its hosts by entering the skin (Figure 2), oropharynx, and nasopharynx [21-23]. From the site of infection, the virus is capable of entering lymphatic channels to infect distant organs such as the lungs, spleen, liver, kidney, resulting in a second wave of viremia.

Figure 2

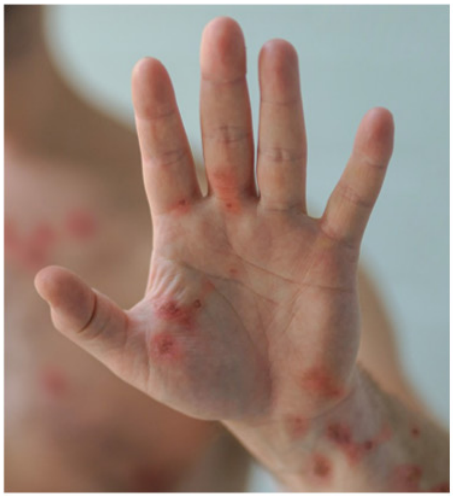

Figure 2 : Mpox skin lesions on the hand. Lesions can be present on any part of the body- head, face, oral cavity, hands, feet, genitals, and anus. (Courtesy CDC Image library).

Mpox infection manifests as fever, headache, itching, chills, and myalgia [24-26]. The prodromal phase starts 4–17 days after virus exposure, characterized by lymphadenopathy of the cervical, maxillary and inguinal lymph nodes. Cutaneous rashes and lesions spread throughout the body that are observed on the head, face, oral cavity (Figure 3), genitals, hands, and feet [24,25]. The contagious period occurs from the initiation of symptoms until all cutaneous lesions have completely healed [27]. However, scabs retain significant levels of Mpox DNA after lesions have disappeared. In a study by Suñer et al. [28] using quantitative polymerase chain reaction (PCR), viral DNA was detected in cutaneous lesions 25 days post-infection.

Figure 3

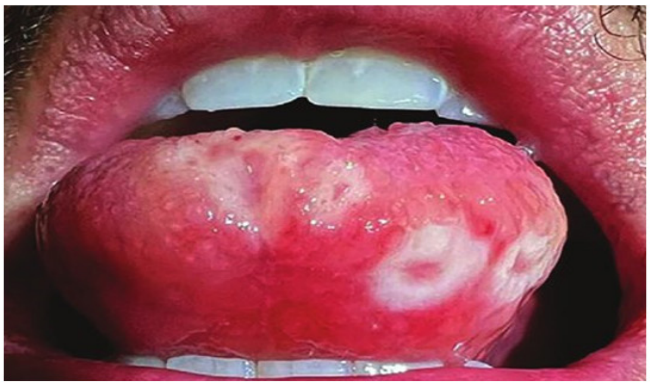

Figure 3: Painful tongue ulcerations from the Mpox virus. (Courtesy of Benslama et al, 2022).

Diagnosis of Mpox

As the clinical presentation of Mpox appears similar to other diseases with rash, fever, cutaneous lesions and lymphadenopathy (such as scabies, measles, smallpox, chickenpox, chancroid, allergic reactions, herpes zoster, syphilis, and varicella-zoster), correct diagnosis is critical to initiate treatment [29,30]. Diagnosis of the Mpox virus can be detected using several different laboratory methods simultaneously, as it provides the best chance for correct diagnosis [31]. Diagnostic methods include the following: histopathology (Figure 4); quantitative PCR, electron microscopy (Figure 5A, 5B), culture of Mpox lesions, immunohistochemistry, and testing for viral antigens and antibodies [32,33].

Figure 4

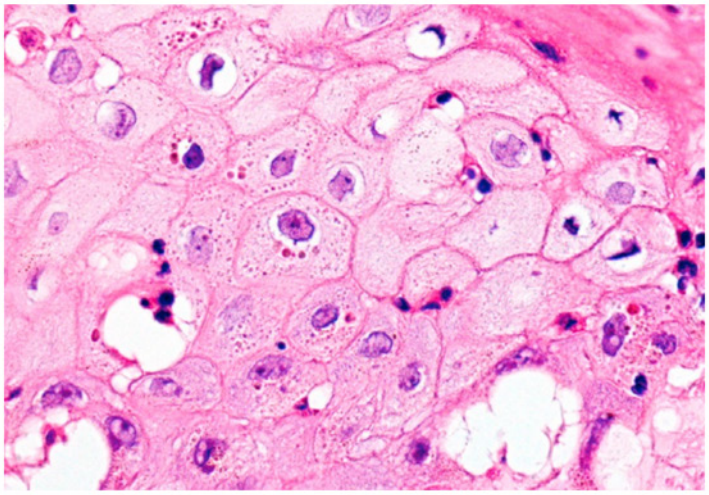

Figure 4: Histopathology of Mpox infected human skin. High-power view. Guarnieri's inclusion bodies in keratinocytes of the epidermis with balloon cell changes. (H & E stain. Original magnification x 400). (Courtesy of Rodriguez-Cuadrado, et al., 2022).

Figure 5A

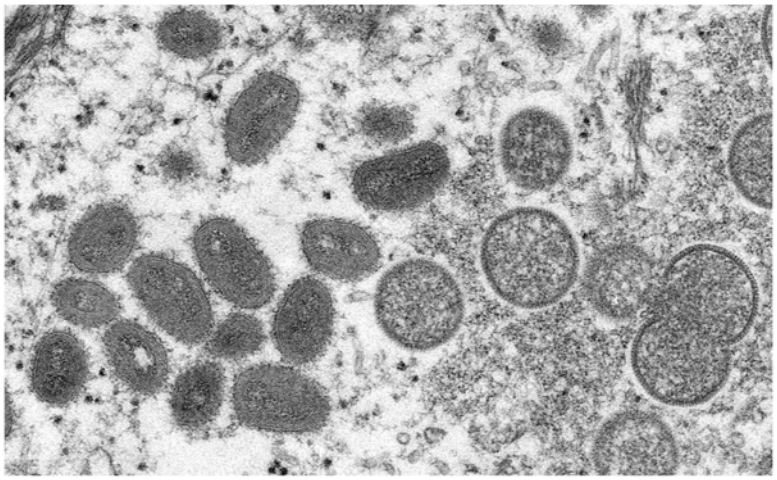

Figure 5A: Transmission electron micrograph from infected Mpox human skin. Mature, oval shaped virus particles and circular shaped immature virus particles. (Courtesy of CDC Image library/Cynthia S. Goldsmith and Russell Regnery).

Figure 5B

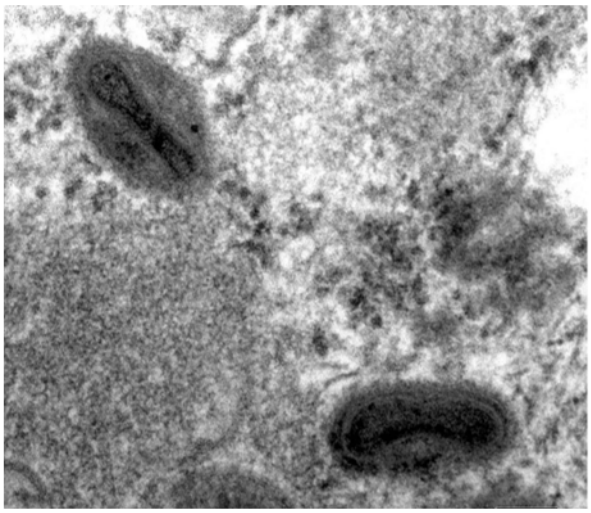

Figure 5B: Transmission electron micrograph of monkeypox virus particles from cell culture containing dumbbell shaped dense cores. (Courtesy of Ryan F. Relich, Ph.D.).

There is no specific treatment for Mpox (WHO, 2024). Virus infected individuals are treated with supportive care while in isolation to prevent viral transmission [34]. Fever and pain from lesions and myalgia are managed with NSAIDS and acetaminophen. Fluid resuscitation is important to correct dehydration and electrolyte imbalance. Wound care should also be initiated to prevent secondary infections, including the use of intravenous antibiotics. With severe respiratory compromise requiring oxygen, intubation with ventilation

support may be indicated.

Lesions of the oral cavity are extremely painful and can affect the quality of life. Elective oral surgical procedures should be postponed. Application of topical local anesthetics, such as viscous lidocaine may decrease the pain from aphthous ulcers and Mpox lesions. Oral antiviral medications, such as acyclovir, tecovirimat and cidofovir may provide postexposure and prophylaxis. The WHO [35] recommends oral rinses with salt water and antiseptic mouthrinses such as chlorhexidine.

Therapeutic Intervention (Table 1) Vaccination

WHO surveillance discovered that smallpox vaccination reduced secondary attack rates and symptoms with monkeypox infection [36,37]. Vaccination against smallpox provides 80-85% cross-protection against Mpox [37,38]. Vaccines activate the hosts immune system to identify specific viruses preventing viral transmission, severe illness and death. In the United States, two vaccines are approved for Mpox preventive measures: ACAM2000 and JYNNEOS/IMVANEX. The only vaccine approved for the prevention of Mpox by the FDA is JYNNEOS/IMVANEX [39,40]. Patients with immune deficiencies are prohibited from receiving ACAM2000 but may receive JYNNEOS/IMVANEX.

Table 1: Therapeutic Agents and Drug Action

Antiviral Agent	Category	Drug Class	Drug Action
ACAM2000	Vaccine	Live attenuated vaccine	Induces immunity
JYNNEOS	Vaccine	Modified live attenuated vaccine	Stimulates immune response
Imvamune	Vaccine	Live attenuated vaccine	Stimulates immune response
Tecovirimat	Antiviral	Orthopox inhibitor	Inhibits viral P37 protein, maturation, and release
Brincidofovir Cidovofir	Nucleotide analog	Orthopox inhibitor	Inhibits DNA polymerase enzymes
Vaccinia immune globulin	Immunotherapy	Polyvalent immunoglobulin	Neutralizes virus Provides passive immunity

Antiviral Medication

Antiviral medicines have a significant role in controlling Mpox infection. Antiviral medications such as Tecovirimat and Brincidofovir are two FDA-approved antiviral drugs used to treat smallpox that can also be used to treat Mpox [41]. Tecovirimat inhibits formation of the viral envelope by selectively targeting the viral protein, VP37 [42]. Brincidofovir targets the double-stranded viral DNA by inhibiting DNA polymerase [43]. Patients with severe Mpox infections can be treated with Vaccinia Immune Globulin (VIG), when combined with antiviral drugs such as Tecovirimat [44]. Vaccinia immune globulin is a purified human immunoglobulin derived from vaccinated donors.

Conclusion

Mpox infection may be circulating not only in communities across the United States undetected, but globally which has the potential to lead to the next pandemic after Covid-19. Clinicians must be familiar with the clinical and histopathologic features of Mpox lesions to make a correct diagnosis that will allow for immediate treatment.

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