Editorial

*Discovery Medicine* 2024; 36(190): 2309–2312
https://doi.org/10.24976/Discov.Med.202436190.212

# Monkeypox Resurgence: A Global Health Challenge Navigating Zoonotic Spillover, Genomic Evolution, and Strategic Response

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Published: 20 November 2024

In recent years, the global health landscape has been marked by the resurgence of infectious diseases that were once considered under control. Among these viruses, Monkeypox (Mpox), a zoonotic virus from the *Orthopoxvirus* genus, has emerged as a significant public health concern. Originally confined to central and western African regions, this zoonotic viral disease has spread to multiple countries, igniting discussions about its epidemiology, prevention, and control. Mpox has been declared a Public Health Emergency of International Concern by the World Health Organization [1], highlighting concerns over its global spread, zoonotic transmission, and evolving nature.

## Epidemiology and Transmission Dynamics

Historically, Mpox cases were reported primarily in rural African regions, where close contact with wild animals, particularly rodents and nonhuman primates, facilitated zoonotic transmission. However, recent outbreaks have demonstrated that the virus can spread more effectively through human-to-human transmission than other ways, especially close contacting with bodily fluids, skin lesions, or contaminated materials [2]. The 2022 multicountry outbreak revealed that the virus could thrive in urban environments with dense populations, exacerbating the difficulty of containment (Fig. 1, Ref. [3]). Importantly, researchers have identified environmental transmission factors, including the potential for Mpox to persist in contaminated water or surfaces, further complicating efforts to halt its spread [4].

A recent study emphasized the role of environmental factors in transmission, with Mpox viral particles detected in wastewater in various locations, including Chicago and cities in Canada, offering valuable early warnings of outbreaks [5]. This highlights the importance of incorporating environmental surveillance into traditional case reporting.

## Symptoms of Mpox

Fever, headache, myalgia, exhaustion, and lymphadenopathy are the initial signs of Mpox, crucial characteristics that distinguish it from smallpox. Mucosal lesions appear in the mouth within two days, quickly followed by skin lesions on the face and extremities. The rash may or may not extend to other parts of the body [6]. The lesions progress through the macular, papular, vesicular, and pustular phases in two-day increments during the next two to four weeks. The lesions are hard, deep-seated, and range from 2 to 10 mm in size, progressing synchronously across the affected regions. Prior to crust formation, lesions remain in the pustular phase for five to seven days. In most cases, the illness resolves within three to four weeks following the commencement of symptoms, with crusts forming and desquamating over the next 2 weeks. Furthermore, the vaginal area is commonly afflicted and shows lesion clustering due to the sexual transmission of the disease [7].

## Genetic Evolution, Viral Variability and Host Factors

The rapid spread of Mpox has been accompanied by significant viral mutations which may play a role in viral viability and adaptation to new hosts [8,9]. Genomic research has identified two distinct clades of the virus: Clade I (Congo Basin) and Clade II (West Africa), with the former resulting in more severe outcomes and higher mortality rates [10]; their differences are also reflected in the virus's viability in various environments and hosts. In particular, studies have also revealed genomic variability, including gene duplications and deletion events, which may contribute to the ability of viruses to adapt to new environments or hosts [11,12]. Regarding host factors, specific immune responses are critical in determining disease severity. A previous study has shown that immunocompromised individuals, including those with HIV/AIDS or other immune-suppressive conditions, are at higher risk for severe Mpox outcomes [13]. This interplay between viral variability and host susceptibility poses challenges for vaccine development. The diversity in viral strains and host immune responses necessitates a multi-pronged approach to vaccine design, ensuring coverage across both viral clades and accounting for varying levels of host immunity. Vacci-

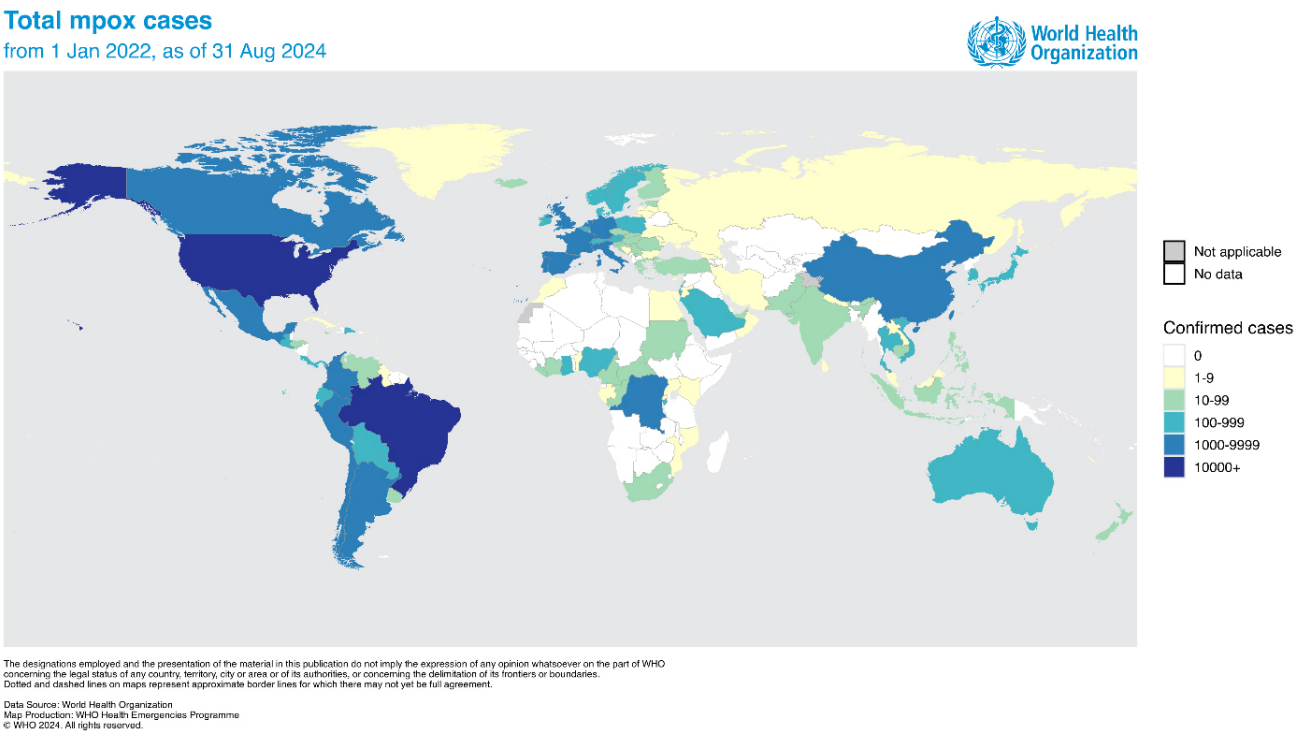


**Fig. 1. Geographic distribution and spread of Monkeypox (Mpox) from 1 January 2022, as of 31 August 2024, according to the World Health Organization [3].**

nation strategies may need to consider boosting immunity in populations with high-risk profiles, especially those with pre-existing immunodeficiencies.

## Therapeutic Strategies and Vaccine Development

The effective management of Mpox relies on both therapeutic interventions and vaccines. Antiviral treatments such as Tecovirimat, which target the viral envelope protein, have shown promise in reducing disease severity, but access to such treatments in many regions remains limited, particularly in low- and middle-income religions [14]. In addition to Tecovirimat, Brincidofovir (Tembexa) has emerged as another potential treatment. Approved by the U.S. Food and Drug Administration for smallpox in 2021, Brincidofovir has shown efficacy in animal models of Orthopoxvirus infection, making it a promising candidate for Mpox treatment [15]. Both Tecovirimat and Brincidofovir are being further evaluated through ongoing clinical trials, such as the Study of Tecovirimat for Human Mpox Virus (STOMP) trial, to determine their effectiveness in treating severe cases of Mpox, especially in immunocompromised individuals and high-risk populations.

Vaccination remains the most effective long-term strategy for preventing the spread of Mpox. Modified Vaccinia Ankara vaccines, which were originally developed for smallpox, have proven effective in providing immunity against Mpox, although their long-term efficacy remains uncertain [16]. Emerging technologies, such as CRISPR-based diagnostics, allow for rapid detection and differentiation of Mpox from other viruses [17]. These advances in diagnostic tools offer a way to manage outbreaks more efficiently, particularly in areas with limited healthcare infrastructure.

## Challenges in Control and Zoonotic Spillover

Despite advancements in treatment and prevention, eradicating Mpox remains challenging due to its zoonotic reservoirs, which continue to serve as a source of infection. Various animals, including rodents and nonhuman primates, have been identified as carriers of the Mpox virus, making it difficult to fully eliminate the disease [18]. To effectively address this issue, a comprehensive “One Health” approach is crucial, integrating human, animal, and environmental health strategies [19]. Successful applications of the “One Health” strategy have been demonstrated in several regions, particularly in West and Central Africa. However, executing the “One Health” approach requires overcoming significant challenges, such as the need for cross-sector collaboration, resource sharing, and consistent communication across international borders. These hurdles often limit the full potential of the strategy, particularly in low-resource settings. Addressing these obstacles requires sustained commitment from governments, international organizations, and local communities to ensure equitable access to healthcare, vaccines, and surveillance tools.

Another key challenge is the lack of equitable access to healthcare resources, particularly in developing nations where the burden of Mpox is highest. In regions with limited infrastructure, delayed diagnosis and insufficient access to vaccines and treatments can lead to higher transmission rates and increased mortality. Addressing these disparities requires a concerted effort from international organizations and governments to ensure that all populations have the necessary tools to combat this virus [20]. Moreover, the cessation of smallpox vaccination programs has left populations vulnerable to infection, contributing to the resurgence of the virus. Reintroducing vaccination programs, particularly in high-risk populations, is crucial for preventing future outbreaks [21].

In summary, Mpox, once a localized threat, has evolved into a global public health challenge that demands coordinated international efforts. Controlling this virus will require a comprehensive approach, from understanding its genetic evolution and transmission dynamics to addressing gaps in vaccine distribution and zoonotic spillover from animal reservoirs. By integrating human, animal and environmental health, and prioritizing equitable healthcare access, vaccination, antiviral treatments, and innovative surveillance, the global community can mitigate the spread of Mpox and protect vulnerable populations. Early and comprehensive action is critical to preventing future outbreaks and averting the next global health emergency.

## Availability of Data and Materials

Not applicable.

## Author Contributions

AA and MS conceived this study. AA and MS were involved in the drafting and critical revision of the manuscript. Both authors have read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.

## Acknowledgment

Not applicable.

## Funding

This research received no external funding.

## Conflict of Interest

Abdelazeem Mohamed Algammal is serving as one of the Editorial Board members of this journal. We declare that Abdelazeem Mohamed Algammal had no involvement in the peer review of this article and has no access to information regarding its peer review. Muhammad Shafiq has no conflicts of interest.

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