Is Monkeypox the Next Pandemic? A Global Review of Emerging Trends and Challenges

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Abstract

Monkeypox (mpox), a zoonotic orthopoxvirus traditionally confined to Central and West Africa, has emerged as a global public health concern following widespread outbreaks in non-endemic regions since 2022. The unexpected global transmission, alongside evolving viral mutations and waning population immunity due to the cessation of smallpox vaccination, has raised urgent questions regarding the pandemic potential of mpox. This review explores the virological characteristics, epidemiological shifts, transmission dynamics, and clinical presentations of mpox, with a focus on its re-emergence as a globally relevant pathogen. It also evaluates public health responses, vaccination strategies, and the role of social and environmental drivers in the rapid spread of the virus. Drawing on data from recent outbreaks, especially the escalating crisis in Central Africa and the emergence of more virulent clade I variants, this article critically assesses the likelihood of mpox evolving into a sustained pandemic. The review highlights existing challenges such as vaccine inequity, misinformation, surveillance limitations, and global health disparities. Finally, it offers strategic recommendations for preparedness, including One Health approaches, equitable vaccine distribution, and enhanced genomic surveillance. Understanding the complex interplay of factors influencing mpox's spread is essential to inform global responses and prevent its escalation into the next pandemic.

Keywords: Monkeypox, mpox, emerging infectious diseases, pandemic potential, zoonosis, orthopoxvirus, viral evolution, global health, vaccine equity, outbreak surveillance, One Health, public health preparedness, clade I, human-to-human transmission, global pandemic risk

Introduction

In recent decades, the world has witnessed a resurgence of zoonotic diseases with the potential to disrupt global health systems. Among these, monkeypox, officially renamed *mpox* by the World Health Organization (WHO)—has re-emerged as a significant public health concern. Initially identified in 1958 in laboratory monkeys and first reported in humans in 1970 in the Democratic Republic of the Congo (DRC), mpox was historically considered a rare and geographically confined viral disease, limited largely to rural regions of Central and West Africa (Ladnyj et al., 1972; Bunge et al., 2022). However, the 2022–2023 global outbreak marked a critical epidemiological shift, with over 87,000 confirmed cases reported in more than 110 countries, many of which had no prior history of mpox transmission (Centers for Disease Control and Prevention [CDC], 2023).

Mpox is caused by the monkeypox virus, a double-stranded DNA virus belonging to the Orthopoxvirus genus, which also includes the variola virus responsible for smallpox. With the eradication of smallpox in 1980 and the subsequent discontinuation of smallpox vaccination, global immunity to orthopoxviruses has declined significantly, creating a vulnerable population that is increasingly susceptible to mpox infection (Rimoin et al., 2010; Nguyen et al., 2021). The virus is known to transmit through close physical contact, respiratory droplets, and contaminated fomites, with more recent outbreaks highlighting potential sexual transmission routes, particularly among men who have sex with men (MSM) (Thornhill et al., 2022).

The recent emergence of distinct viral clades, including Clade I (Congo Basin) and Clade II (West African), and sublineages with varying transmissibility and virulence, has further complicated the public health response (Isidro et al., 2022). In particular, Clade I has demonstrated a higher case fatality rate and expanded human-to-human transmission, raising serious concerns about the virus's pandemic potential. In 2023 and 2024, the outbreak in Central Africa intensified, with international spillovers indicating the potential for broader dissemination (World Health Organization, 2024).

Despite these warning signs, the global response to mpox has been inconsistent, with stark disparities in testing, vaccination access, and surveillance infrastructure between high-income and low-income countries. The rapid spread of the virus has exposed critical gaps in global preparedness, particularly in the face of novel variants and emerging zoonoses. Given these developments, a comprehensive examination of mpox’s epidemiology, virology, transmission dynamics, and public health impact is essential to assess its potential to become the next pandemic. This review aims to synthesize current scientific evidence, identify emerging trends and challenges, and offer informed recommendations for strengthening the global response to mpox.

Epidemiology & Transmission Dynamics

The epidemiological profile of mpox (formerly monkeypox) has undergone a significant transformation over the past five decades. Initially considered a rare zoonotic infection confined to forested regions of Central and West Africa, mpox has now become a globally recognized public health concern due to its increasing incidence, evolving transmission routes, and geographic expansion.

Historical Overview and Endemic Patterns

Monkeypox was first identified in humans in 1970 in the Democratic Republic of the Congo (DRC) and remained largely endemic to Central and West Africa, particularly in the DRC, Nigeria, Republic of the Congo, and Cameroon (Ladnyj et al., 1972; WHO, 2019). Human infections were sporadic and typically associated with direct contact with infected animals, particularly rodents and non-human primates. Between 1980 and 2000, fewer than 1,000 cases were reported globally, mainly in rural and forested settings where communities had close contact with wildlife (Rimoin et al., 2010).

Re-emergence and Global Spread (2003–2022)

The first recorded outbreak outside Africa occurred in the United States in 2003, linked to the importation of infected Gambian pouched rats from Ghana. This outbreak resulted in over 70 human cases and highlighted the potential for international spread

via wildlife trade (Reed et al., 2004). Following a resurgence in Nigeria in 2017—where over 500 suspected cases were reported—monkeypox re-emerged as a public health priority, with increasing concern about its capacity for sustained human-to-human transmission (Yinka-Ogunleye et al., 2018).

2022–2023 Global Outbreak and Shift in Transmission Dynamics

In May 2022, a multi-country outbreak of mpox was reported in countries without endemic transmission, including the United Kingdom, Spain, the United States, Brazil, and Canada. By the end of 2023, more than 87,000 confirmed cases were reported in over 110 countries, with sustained community transmission evident in many regions (CDC, 2023; WHO, 2023a). The dominant viral lineage involved was Clade IIb (previously West African clade), which exhibited relatively low mortality (<0.2%) but high human-to-human transmissibility (Isidro et al., 2022).

Transmission in the 2022–2023 outbreak was marked by a significant epidemiological shift. Unlike earlier outbreaks driven by zoonotic spillover, the global outbreak was predominantly characterized by close contact transmission among men who have sex with men (MSM), with over 95% of cases reported in this demographic (Thornhill et al., 2022). This highlighted sexual contact as a major route of transmission, although mpox is not currently classified as a sexually transmitted infection (STI). Additional transmission routes include direct contact with skin lesions, respiratory droplets during prolonged face-to-face interactions, and fomites such as bedding and clothing (WHO, 2022).

2023–2025 Central African Epidemic and Viral Evolution

While the global case count declined in late 2023 due to vaccination and behavioral modifications, a new and concerning trend emerged: a sharp increase in Clade I (Congo Basin) infections across Central Africa. In 2023–2025, over 29,000 cases and 800 deaths were reported across the DRC, Republic of the Congo, and South Sudan, with isolated cases detected in Europe and Asia (Sweden, Thailand), indicating the spread of more virulent strains beyond traditional boundaries (WHO, 2024; Le Monde, 2024). Clade I is associated with higher case fatality rates (up to 10%) and increased potential for human-to-human transmission, including nosocomial spread and household transmission (Jezek et al., 1987).

This ongoing epidemic led WHO to declare a Public Health Emergency of International Concern (PHEIC) for Central Africa in August 2024. Contributing factors included limited vaccine access, weak surveillance infrastructure, conflict-related displacement, and ecological disruption from deforestation and mining activities, all of which facilitated zoonotic spillover and human spread (Vox, 2024; FT, 2024).

Zoonotic Reservoirs and Environmental Drivers

Mpox is a zoonotic virus, and its reservoir hosts include a wide range of rodents such as rope squirrels (*Funisciurus spp.*), dormice (*Graphiurus spp.*), and Gambian pouched rats (*Cricetomys spp.*) (Hutson et al., 2007). Human encroachment into wildlife habitats, driven by logging, agriculture, and mining, has increased the frequency of human–animal interactions, thereby raising the likelihood of spillover events. Moreover, the illegal wildlife trade remains a persistent risk factor for the international spread of orthopoxviruses (Olival et al., 2017).

Climate change and urbanization also play critical roles in expanding the ecological range of animal reservoirs and vectors. These environmental shifts, compounded by

socioeconomic instability, create ideal conditions for viral transmission in both rural and urban settings.

Virology & Viral Evolution

Mpox (formerly monkeypox) is caused by the monkeypox virus (MPXV), a double-stranded DNA virus of the genus *Orthopoxvirus* within the family *Poxviridae*. It is closely related to other orthopoxviruses, including the variola virus (smallpox), vaccinia virus, and cowpox virus. MPXV is notable for its zoonotic potential, environmental stability, and increasing ability to adapt to human hosts, raising important concerns regarding its potential for pandemic spread.

Viral Structure and Genome

The MPXV virion is large (200–250 nm), brick-shaped, and enveloped, with a linear double-stranded DNA genome of approximately 197 kilobase pairs encoding around 190 genes (McCollum & Damon, 2014). The virus replicates exclusively in the cytoplasm of host cells, utilizing a complex viral transcription and replication machinery. MPXV shares high genomic similarity (~96%) with the variola virus, although it is less virulent and historically associated with lower case fatality rates.

Key genomic regions are responsible for immune evasion (e.g., complement-binding proteins), host range factors, and virulence modulation. These genomic features make MPXV particularly adept at crossing species barriers, especially in settings where human–animal interfaces are common (Likos et al., 2005).

Clade Classification and Genetic Lineages

Historically, MPXV has been divided into two main genetic clades: Clade I (Congo Basin clade) and Clade II (West African clade). In 2022, WHO adopted a non-discriminatory naming system that reclassified these clades as follows (WHO, 2022a):

- **Clade I (formerly Congo Basin)**: Known for higher virulence and transmissibility, with reported case fatality rates (CFRs) up to 10%. This clade has caused recurrent outbreaks in Central Africa, especially the DRC.
- **Clade IIa and IIb (formerly West African)**: Clade IIb was responsible for the 2022–2023 global outbreak. It shows a CFR of <1%, but demonstrated increased capacity for sustained human-to-human transmission.

Phylogenetic analyses have identified ongoing divergence within these clades. For instance, the 2022 global outbreak lineage—designated B.1 within Clade IIb—accumulated ~50 single nucleotide polymorphisms (SNPs) compared to its closest 2018 ancestor, suggesting accelerated microevolution (Isidro et al., 2022).

Mechanisms of Viral Evolution and Adaptation

While DNA viruses typically evolve more slowly than RNA viruses due to higher replication fidelity, recent studies suggest that MPXV may be undergoing **adaptive evolution**. APOBEC3-mediated mutagenesis, a host antiviral defense mechanism, has been proposed as a driver of accelerated MPXV mutation in the 2022–2023 strains (O'Toole et al., 2022).

This evolutionary trajectory may be facilitating enhanced transmissibility and immune evasion, particularly in immunologically naïve populations. The emergence of truncated genes in Clade IIb linked to reduced host immune recognition further supports the possibility of viral adaptation to human hosts (Gigante et al., 2022).

Implications of Viral Evolution on Pathogenicity and Transmission

Clade I, now at the center of the 2023–2025 Central African epidemic, is especially concerning due to its historically higher pathogenicity and new reports of sexual and nosocomial transmission. The appearance of Clade I cases in non-endemic countries (e.g., Sweden, Thailand) suggests either cryptic global circulation or international importation, signaling a potential expansion of high-virulence lineages (WHO, 2024; Jezek et al., 1987).

These observations raise the possibility that MPXV is evolving toward more efficient person-to-person transmission, which could fulfill key characteristics required for pandemic classification: sustained global spread, widespread susceptibility, and significant morbidity or mortality.

Moreover, the co-circulation of multiple clades and the possibility of **recombination events** between them—although not yet observed—remain a theoretical concern, particularly in areas with poor surveillance and high zoonotic exposure.

Risk Factors & Drivers of Spread

The re-emergence and international spread of monkeypox (mpox) are driven by a complex interplay of biological, environmental, behavioral, and sociopolitical factors. Unlike previous outbreaks confined largely to zoonotic spillovers in endemic regions, recent transmission patterns underscore the role of global mobility, behavioral risk networks, ecological disturbances, and immunity gaps in accelerating human-to-human spread.

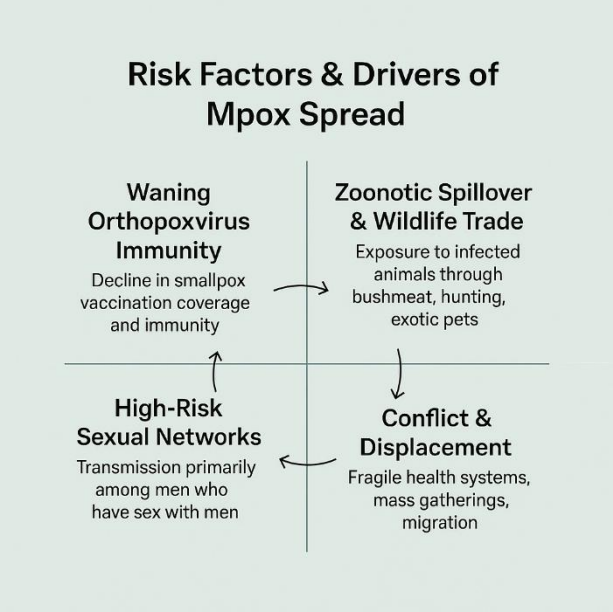

Figure 1: Risk Factors and Drives of Mpox Spreads.

1. Waning Orthopoxvirus Immunity: One of the most significant factors contributing to the spread of mpox is the global cessation of smallpox vaccination following the eradication of smallpox in 1980. The smallpox vaccine (Vaccinia virus-based) provided cross-protective immunity estimated at 85% against mpox (Fine et al., 1988). As a result, generations born after 1980 are immunologically naïve to orthopoxviruses. Studies suggest that the decline in herd immunity has led to increasing susceptibility, particularly among younger, urban populations in both endemic and non-endemic regions (Nguyen et al., 2021; Rimoin et al., 2010).

2. Zoonotic Spillover and Wildlife Trade: The natural reservoir of mpox is believed to be rodents such as rope squirrels (*Funisciurus spp.*), dormice (*Graphiurus spp.*), and Gambian pouched rats (*Cricetomys spp.*). Human exposure to these animals, through bushmeat consumption, hunting, or the exotic pet trade, significantly increases the risk of zoonotic spillover (Hutson et al., 2007). The 2003 outbreak in the United States—traced to imported African rodents that infected prairie dogs sold as pets—underscored the risk posed by unregulated wildlife trade (Reed et al., 2004).
Environmental disruption, such as deforestation and mining, also brings humans into closer contact with wildlife, facilitating viral crossover. Deforestation in Central Africa has been associated with increased human–animal interface, particularly in areas with limited public health surveillance (Olival et al., 2017).

3. International Travel and Globalization: Global mobility is a key factor in the transcontinental spread of mpox. The 2022 outbreak revealed how air travel facilitated the rapid dissemination of the virus to more than 110 countries within weeks of initial detection (Bunge et al., 2022). Many index cases had no travel history to endemic areas, suggesting asymptomatic or undetected transmission during travel. High-volume international hubs acted as conduits for viral exportation, especially from Western Europe to the Americas and Asia (WHO, 2022a).

4. High-Risk Sexual Networks and Urban Transmission: Unlike previous outbreaks, the 2022–2023 mpox outbreak demonstrated sustained human-to-human transmission in urban settings, primarily among men who have sex with men (MSM). Epidemiological investigations revealed that over 95% of cases occurred in MSM populations, with transmission often linked to close, skin-to-skin contact during sexual activity (Thornhill et al., 2022). Events such as pride festivals, nightclubs, and private gatherings were identified as superspreader contexts.

While mpox is not classified as a sexually transmitted infection (STI), the detection of viral DNA in semen and genital lesions indicates the possibility of sexual transmission, especially when mucosal contact is involved (Peiró-Mestres et al., 2022).
5. Population Density and Urbanization: The rapid growth of densely populated urban centers, particularly in Africa and Asia, has intensified the risk of mpox transmission. Urbanization promotes conditions favorable to viral spread: crowded housing, inadequate sanitation, and greater human mobility. This is particularly problematic in informal settlements and refugee camps, where access to healthcare is limited and surveillance systems are weak (WHO, 2023).

6. Conflict, Displacement, and Health System Fragility: Political instability, armed conflict, and mass displacement—especially in Central Africa—have severely compromised the ability of local health systems to detect and respond to mpox outbreaks. Internally displaced persons (IDPs) and refugees often lack access to vaccination, healthcare, and isolation facilities, creating hotspots for uncontained spread (UNHCR, 2023).

In 2024, WHO declared a Public Health Emergency of International Concern (PHEIC) for the Central African epidemic after Clade I mpox spread in conflict-affected regions, including South Sudan and the DRC, with limited containment capacity (WHO, 2024).

7. Misinformation, Stigma, and Delayed Health-Seeking Behavior: Social stigma surrounding mpox—particularly its perceived association with LGBTQ+ populations—has discouraged individuals from seeking testing and care. Misinformation on social media has exacerbated fears, promoted conspiracy theories, and undermined public trust in vaccination and health authorities (Aramburu et al., 2023). As with COVID-19, communication failures have hampered early detection and community-based response.

8. Climate Change and Environmental Shifts: Climate change is altering the ecological dynamics of zoonotic reservoirs. Changes in rainfall, temperature, and habitat fragmentation may expand the range of mpox host species, thereby increasing the risk of spillover in new geographic areas. This environmental unpredictability underscores the importance of integrating One Health approaches to monitor and mitigate emerging infectious threats (Carlson et al., 2022).

Clinical Presentation & Diagnostics

The clinical spectrum of mpox (monkeypox) ranges from a self-limiting febrile illness with characteristic skin lesions to more severe complications in vulnerable populations. Understanding the evolving presentation and improving diagnostic strategies is essential for early detection, containment, and clinical management.

1. Classical Clinical Features: The incubation period of mpox is typically 6 to 13 days but can range from 5 to 21 days (WHO, 2022). The classical presentation closely resembles smallpox but with less severity and includes:

- Prodromal phase: fever, intense headache, lymphadenopathy, myalgia, and fatigue.
- Eruption phase: a centrifugal rash appears 1–3 days after fever onset, beginning on the face and spreading to the palms, soles, and mucous membranes. The rash progresses synchronously through macular, papular, vesicular, pustular, and crusting stages over a period of 2–4 weeks (McCollum & Damon, 2014).

Lymphadenopathy is a key clinical feature that distinguishes mpox from smallpox and other vesiculopustular illnesses like varicella (Ježek et al., 1987).

2. Evolving Atypical Presentations: During the 2022–2023 outbreak, clinical features evolved significantly, particularly among non-endemic populations. Many patients presented with:

- Fewer lesions, often localized to the genital, perianal, or oral areas.
- Painful anorectal ulcers, proctitis, and penile edema, mimicking sexually transmitted infections (STIs).
- Absence of prodromal symptoms in some cases.
- Lesions at different stages of development in a single patient (Thornhill et al., 2022).

These atypical patterns suggest that host immunity, viral adaptation, and mode of transmission (e.g., sexual contact) may influence clinical manifestations. Additionally, co-infections with HIV and other STIs have been reported, complicating diagnosis and management (Tarín-Vicente et al., 2022).

3. High-Risk Populations and Severe Disease: Certain groups are more likely to experience severe disease or complications:

- Children: higher risk of encephalitis, sepsis, and secondary bacterial infections.

- Pregnant women: potential for vertical transmission and fetal demise.
- Immunocompromised patients: including those with HIV/AIDS, organ transplants, or cancer therapy (Ogoina et al., 2020).

Case fatality rates have historically ranged from 1–10% depending on the clade, with Clade I (Congo Basin) being more severe (Bunge et al., 2022).

4. Diagnostic Approaches

a. Clinical Diagnosis: Initial assessment is based on clinical suspicion, especially in patients presenting with rash, lymphadenopathy, and epidemiological risk factors (e.g., travel history, contact with confirmed cases, MSM exposure). However, due to overlap with other diseases such as varicella, herpes, molluscum contagiosum, syphilis, and hand-foot-mouth disease, laboratory confirmation is essential.

b. Laboratory Diagnosis: The gold standard for mpox diagnosis is real-time polymerase chain reaction (RT-PCR) testing of lesion-derived specimens (fluid, crusts, or swabs from the lesion base) (CDC, 2022). RT-PCR provides high specificity and sensitivity and distinguishes mpox from other orthopoxviruses.

Key considerations include:

- Multiple specimens from different lesions should be collected.
- Blood and respiratory samples may be useful in systemic or early-stage cases but are less reliable for diagnosis.

c. Serology and Antigen Detection: Serological testing (e.g., ELISA for IgM and IgG) may indicate recent or past orthopoxvirus exposure but lacks specificity due to cross-reactivity with other poxviruses. It is not recommended for primary diagnosis (Hutson et al., 2009).

Antigen detection methods, such as lateral flow assays, are under development but are not yet widely available or validated.

5. Diagnostic Innovations and Challenges

- Point-of-care diagnostics: Several rapid molecular assays are under evaluation, including mobile PCR devices that may assist outbreak containment in remote or low-resource settings (Peiró-Mestres et al., 2022).
- Genomic surveillance: Whole genome sequencing (WGS) has become a critical tool for tracking viral evolution, detecting clade shifts, and monitoring antiviral resistance (Isidro et al., 2022).
- Diagnostic gaps: Many African regions lack adequate testing infrastructure, resulting in underreporting and delayed outbreak responses (Wenham & Eccleston-Turner, 2022).

Public Health Response Strategies

The global spread of monkeypox (mpox) has challenged public health systems to respond with a combination of containment, vaccination, surveillance, communication, and cross-sectoral coordination. The experience of COVID-19 has informed some of these responses, but the mpox epidemic has also revealed persistent gaps in preparedness, particularly in low- and middle-income countries (LMICs). This section reviews the core public health strategies implemented to mitigate mpox spread and identifies ongoing challenges.

1. Vaccination Strategies

a. Types of Vaccines

Two primary vaccines are being used or evaluated for mpox prevention:

- Modified Vaccinia Ankara–Bavarian Nordic (MVA-BN): A third-generation, non-replicating vaccine marketed as JYNNEOS (US), Imvanex (EU), and Imvamune (Canada). It is approved for prevention of both smallpox and mpox in several countries.
- ACAM2000: A live, replicating second-generation smallpox vaccine used in emergency settings but associated with greater risk of adverse events, especially in immunocompromised individuals (Karem et al., 2007).

Clinical data suggest MVA-BN offers 85% protection against mpox, though effectiveness data specific to the 2022–2023 outbreak are still being assessed (Huhn et al., 2022).

b. Vaccine Deployment and Coverage

During the 2022–2023 outbreak, vaccination efforts were initially focused on high-risk populations, especially men who have sex with men (MSM), healthcare workers, and laboratory personnel. However, logistical challenges—including limited global supply, dose-sparing strategies, and cold chain requirements—hindered equitable access.

By late 2023, high-income countries had secured most available doses, while endemic countries in Africa remained underserved. This inequity continues to raise ethical and strategic concerns, especially as virulent Clade I outbreaks intensify in Central Africa (Le Monde, 2024; WHO, 2024).

2. Surveillance, Case Finding, and Contact Tracing

Early detection and isolation remain key pillars in mpox outbreak control.

- Surveillance: Many countries integrated mpox reporting into their existing notifiable disease systems. However, many African countries face underreporting due to poor diagnostic capacity and limited case investigation resources (Wenham & Eccleston-Turner, 2022).
- Contact tracing: Has been effectively implemented in countries like the UK and Canada, especially within defined social and sexual networks. However, stigma and privacy concerns often impede comprehensive contact tracing among MSM populations.
- Genomic surveillance: Next-generation sequencing (NGS) has been crucial in identifying mutations, tracking clade evolution (e.g., B.1 lineage in Clade IIb), and detecting importation events (Isidro et al., 2022).

3. Isolation and Quarantine Guidelines

Most national health authorities adopted WHO recommendations that confirmed cases self-isolate until all lesions are crusted and healed, usually lasting 2–4 weeks. Some countries, such as Germany and the UK, provided financial support for individuals in quarantine to encourage compliance (UKHSA, 2022).

However, strict isolation policies are difficult to enforce in settings with economic precarity or conflict displacement, particularly in African epidemic zones (UNHCR, 2023).

4. Risk Communication and Community Engagement

Given the concentration of early cases in MSM communities, targeted risk communication was critical.

- Public health agencies emphasized that mpox is not limited to any sexual orientation, to avoid stigma.

- Community-based organizations played a key role in delivering accurate messaging, especially during events such as Pride celebrations (Thornhill et al., 2022).
- WHO and CDC developed multilingual digital toolkits and launched social media campaigns to counter misinformation and reduce panic (CDC, 2023).

Despite these efforts, disinformation and stigma have persisted, particularly in regions where LGBTQ+ individuals face legal or social discrimination, discouraging affected individuals from seeking care.

5. Therapeutics and Clinical Management

No specific antiviral is approved for mpox, but several agents have been repurposed under investigational protocols:

- Tecovirimat (TPOXX): An antiviral targeting the orthopoxvirus VP37 protein, approved for smallpox and made available through expanded access for mpox cases. Observational studies suggest reduced symptom duration and viral shedding, but randomized controlled trial data remain limited (Desai et al., 2022).
- Cidofovir and brincidofovir: Broad-spectrum antivirals with in vitro activity against orthopoxviruses, though their nephrotoxicity and side effect profiles limit routine use (Chastel, 2001).

Clinical guidelines emphasize supportive care: hydration, analgesia, and management of complications such as bacterial superinfection or proctitis.

6. Global Governance and One Health Response

The mpox outbreak highlights the need for a One Health approach that addresses human, animal, and environmental interfaces:

- Efforts include limiting wildlife trade, monitoring animal reservoirs, and developing ecological surveillance platforms.
- WHO convened emergency meetings and declared a Public Health Emergency of International Concern (PHEIC) in July 2022 for global mpox and in August 2024 for Clade I outbreaks in Central Africa.
- The International Health Regulations (IHR) framework was activated to improve cross-border data sharing, harmonize responses, and coordinate vaccine donation mechanisms (WHO, 2022; 2024).
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7. Challenges and Gaps

- Vaccine inequity: Africa still lacks sufficient access despite being the most affected region historically.
- Misinformation: Undermines trust in public health messaging, particularly around vaccines and transmission routes.
- Weak health systems: Many endemic regions lack the laboratory and surveillance capacity to detect outbreaks early.
- Political inertia: Delays in mobilizing international aid and logistics have worsened response in conflict-affected areas.

Pandemic Potential Assessment

Assessing whether mpox (monkeypox) possesses the potential to escalate into a global pandemic requires evaluating it against the classical criteria for pandemics: (1) **emergence of a novel pathogen**, (2) **sustained human-to-human transmission**, (3) **geographic spread**, and (4) **significant impact on public health, economies, or**

healthcare systems (Morens et al., 2009). While mpox does not yet meet all these criteria in full, recent epidemiological shifts—particularly in viral transmission patterns and clade evolution—suggest that it may be approaching the threshold.
Although mpox is not a novel pathogen, the global population is largely immunologically naïve due to the cessation of smallpox vaccination since 1980. This has left more than 70% of the world's population without orthopoxvirus immunity, rendering them susceptible to mpox infection (Rimoin et al., 2010; Nguyen et al., 2021). The emergence of Clade IIb in 2022 demonstrated the virus's ability to sustain transmission chains in non-endemic regions—an unprecedented development.
The re-emergence of **Clade I** with higher virulence and wider geographic reach raises the concern of increased transmission efficiency and case fatality, especially in regions with limited healthcare infrastructure (WHO, 2024).

Historically, mpox required close contact for transmission, and outbreaks were largely self-limiting. However, the 2022–2023 outbreak revealed:

- Evidence of sustained **human-to-human transmission** within urban and international networks.
- Transmission via **skin-to-skin**, **fomite**, **respiratory droplets**, and probable **sexual contact**, especially among MSM (Thornhill et al., 2022).
- A reproductive number (R_0) estimated to be >1 in specific risk groups and geographies (Endo et al., 2022).

These changes suggest that mpox has overcome some of the biological and behavioral barriers that previously limited its pandemic potential.

Between May 2022 and December 2023, mpox spread to more than **110 countries**, many of which had no history of endemic transmission. Over 87,000 cases were confirmed globally, affecting all six WHO regions (CDC, 2023). The simultaneous emergence of local outbreaks in Europe, the Americas, and Asia, as well as cross-border transmission of Clade I into non-endemic countries, marks a shift toward **globalization of the pathogen**.
While the **case fatality rate (CFR)** of Clade IIb is low (<0.2%), Clade I presents a higher CFR (~10%) and more severe complications, including encephalitis, secondary infections, and fetal loss during pregnancy (Jezek et al., 1987). The potential for **co-circulation of multiple clades** complicates public health responses, vaccine deployment, and clinical management

In 2022, mpox overwhelmed sexual health services in parts of Europe and North America due to high demand for testing, post-exposure prophylaxis, and behavioral counseling. In Africa, the resurgence of Clade I has stretched already underfunded healthcare systems (Le Monde, 2024).
Recent analyses suggest that mpox is evolving more rapidly than expected for a DNA virus. APOBEC3-mediated mutations and microevolutionary changes have been documented in the 2022–2023 outbreak lineage (Isidro et al., 2022). Viral adaptation may enhance human infectivity or immune evasion, similar to how SARS-CoV-2 evolved variants of concern.

The potential for **increased transmissibility or reduced vaccine efficacy** through genetic drift or recombination (particularly in co-infection hotspots) underscores the need for ongoing genomic surveillance.

Based on current evidence, **mpox exhibits moderate-to-high pandemic potential**, particularly if:

- Clade I continues to expand globally,
- Human-to-human transmission intensifies across diverse populations,
- Surveillance and vaccine equity remain insufficient.

However, mpox is not yet a global pandemic. Its relatively low transmissibility (compared to respiratory viruses like SARS-CoV-2) and the availability of existing vaccines provide opportunities for containment—if addressed proactively.

Conclusion

The recent resurgence of monkeypox (mpox) and its unprecedented global spread have redefined the public health perception of this once-neglected zoonotic disease. Historically confined to Central and West Africa, mpox has now emerged as a global concern due to shifts in transmission dynamics, viral evolution, and widening geographical reach. The 2022–2023 outbreaks demonstrated that mpox can sustain human-to-human transmission in urban, non-endemic populations, especially within high-risk social networks. The concurrent escalation of Clade I infections in Central Africa—characterized by higher virulence and mortality—further amplifies the urgency for a globally coordinated response.

This review has shown that the pandemic potential of mpox lies not only in its biological capacity for spread but also in the vulnerabilities of global health systems: declining immunity, weak surveillance, vaccine inequity, and social stigmatization. The virus's ability to evolve, infect immunologically naïve populations, and spread silently in underserved regions poses an ongoing threat that could escalate if unaddressed. While mpox is not currently a pandemic in scope or severity, the indicators of risk are converging.

Effective control of mpox will require timely action: expanding vaccine access, enhancing surveillance and diagnostics, addressing misinformation, and applying a One Health approach to monitor zoonotic spillovers. The global health community must seize this moment—not only to contain mpox—but also to strengthen resilience against future zoonotic pandemics. The lessons learned from mpox should be integrated into broader pandemic preparedness frameworks to prevent history from repeating itself.

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