

Review

Clade Ib Mpox Virus: How Can We Respond?

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ABSTRACT

In recent years, mpox virus Clade Ib has emerged as a significant global public health threat due to its rapid transmission and potential for severe disease outcomes. This strain was first identified in the Democratic Republic of the Congo (DRC) in September 2023 and began spreading to neighboring African countries by July 2024. It was subsequently imported through international travel to 12 non-African countries across Asia, Europe, and the Americas. Clade Ib exhibits increased transmissibility, and current data suggest that infections may lead to more severe symptoms, with higher risks of severe illness and mortality, particularly among vulnerable populations such as children, pregnant individuals, and immunocompromised groups (e.g., people living with HIV/AIDS). Epidemiologically, Clade Ib primarily spreads through sexual contact, close household contact, and healthcare-related exposure. This review aims to provide an overview of the current understanding of mpox virus Clade Ib, including its genetic characteristics, epidemiological patterns, and prevention and control strategies. Additionally, it discusses the strategies and interventions needed to address this emerging threat.

The mpox virus (MPXV) comprises two lineages: Clade I (Central African/Congo Basin strain) and Clade II (West African strain) (1), which have traditionally been associated with zoonotic transmission and limited human-to-human spread (2). The 2022–2023 global Clade II outbreak marked a significant shift, representing the first international emergence of MPXV, predominantly affecting male-to-male sexual networks in Europe and the Americas (3). Concurrently, the emergence of the Clade Ib variant in the Democratic Republic of Congo in 2023 triggered a substantial surge in Clade I infections across Africa (4–5). Following the World Health Organization (WHO)’s declaration of a public health

emergency in August 2024 (6), intensified research on Clade Ib MPXV has become imperative to address critical knowledge gaps in viral evolution, outbreak prediction, and development of effective countermeasures. These research efforts are vital for enhancing global surveillance systems and optimizing containment strategies against MPXV dissemination.

The Harm of Mpox Virus Clade Ib to Human Health

Following the decline of Clade II, Central Africa’s forest zones have experienced rising Clade I prevalence linked to zoonotic spillover and intrahousehold transmission (7). Clade Ib strains exhibit heightened virulence with a case fatality ratio (CFR) of 5.3% as of May 2024, characterized by distinctive clinical manifestations including disseminated eruptions, pharyngitis, persistent fever, and lymphadenopathy (8). Surveillance data indicate expanding geographic spread across 23 of 26 provinces in the Democratic Republic of Congo, disproportionately affecting pediatric populations (under 15 years) with severe outcomes (6). The 2023 epidemiological shift reveals novel transmission clusters in previously unaffected regions, underscoring intensified human-to-human spread alongside more than 700 suspected infections reported in 2024 (9).

The Genetic Characteristics of Mpox Virus Clade Ib

Genomic characterization has identified a distinct Clade Ib variant in South Kivu, originating from independent zoonotic transmission (3). While Clades I and II share high conservation (99.3% identity), accurate lineage differentiation requires insertion/deletion (INDEL) profiling (10). Although phylogenetically grouped within Clade I, these strains lack the CDC-endorsed diagnostic target due to a 1,114-nucleotide deletion (OPG032 loss), which compromises PCR reliability (5). Significant evolutionary divergence is evident between subclades, with Clade Ib exhibiting 16.7% APOBEC3-driven

SNPs compared to just 0.3% in Clade Ia, suggesting distinct evolutionary trajectories (11). The deletion of the C3L gene in Clade Ib, a key Clade I marker, presents critical diagnostic challenges that may result in false-negative results, particularly during periods of Clade II co-circulation (5,10,12).

Epidemiological Characteristics of Mpox Virus Clade Ib

Epidemic regions: Clade Ib emerged in South Kivu, Democratic Republic of Congo (September 2023) as a phylogenetically distinct lineage (12), rapidly expanding to 14 health zones within 11 months and crossing borders into four neighboring nations (Burundi, Rwanda, Uganda, Kenya) by August 2024 (13). The World Health Organization reissued its mpox Public Health Emergency of International Concern following this accelerated transnational spread, with travel-associated cases subsequently reported in Sweden (14) and Thailand (15) in August 2024. By autumn, autochthonous transmission was documented in India (September) (16), Germany (October) (17), England (October/November) (18–19), the United States (November) (20), and Brazil (November) (21), demonstrating Clade Ib's significant global dispersal capacity despite ongoing questions regarding its transmissibility.

Transmission route: Genomic epidemiology reveals Clade Ib's sustained human-to-human transmission through host-adaptive mutations (12), contrasting with Clade Ia's predominantly zoonotic and household transmission patterns (22). The absence of a defined core transmission group — combined with unsubstantiated associations between sexual orientation and transmission risk — creates potential for stigmatization and undermines surveillance effectiveness in non-endemic regions (12,23). Clade Ib demonstrates distinct transmission dynamics from Clade IIb, which primarily affects men who have sex with men (MSM) populations (23). In the Democratic Republic of Congo, Clade Ib infections show a demographically balanced sex distribution, with 72% [95% confidence interval (CI): 65%, 78%] linked to sexual networks, disproportionately affecting adolescents (15–19 years) and young adults (20–24 years), including sex workers (23). While sexual contact frequency significantly increases infection risk [odds ratio (OR)=3.4, $P<0.01$], no specific sexual practices or orientations show significant association (12), challenging assumptions that conflate particular

intimate behaviors with Clade Ib transmission.

Susceptible population: Epidemiological data confirm two distinct Clade Ib outbreak patterns in the DRC: 1) clusters among adult female sex workers (24), and 2) pediatric populations exhibiting heightened susceptibility and mortality (25). Surveillance records from 2024 document over 7,000 suspected cases with a case fatality ratio of 5.3%, with children aged ≤ 15 years constituting 67% of cases and 84% of fatalities (9). Infants under 5 years demonstrate a fourfold higher mortality risk compared to older age groups (26), highlighting household and community transmission as the predominant infection pathway.

Detection on Clade Ib Mpox

The high genomic conservation between MPXV Clades I and II (>99% nucleotide identity in core regions) and broad *Orthopoxvirus* homology (>90%) presents significant challenges for lineage-specific assay development (10). Phylogenetic convergence necessitates structural variation analysis, with validated INDEL polymorphisms serving as critical Clade-discriminatory markers (10).

PCR remains the gold standard for MPXV confirmation. CDC-endorsed real-time PCR assays effectively distinguish Clades I/II from other *Orthopoxvirus* species (27–28), though some C3L-adjacent assays demonstrate uncertain reliability for Clade Ib differentiation (29). Recent advancements include a Clade Ib-specific TaqMan probe targeting C3L deletions, which enhances transmission network tracking in non-endemic regions (30).

Whole genome sequencing (WGS) analyses of Clade Ib strains have revealed seven hotspot mutations (C9L-B21R) and consistent OPG032 (D14L) deletions, establishing a novel subgroup (VI) within Clade I through phylogenetic clustering (31). These findings underscore the necessity for enhanced genomic surveillance in endemic regions.

Serological surveillance complements molecular diagnostics by detecting subclinical infections. African studies demonstrate 6.3% *Orthopoxvirus* IgG seropositivity in asymptomatic populations (32), while 2022 outbreak data revealed 10.2% asymptomatic transmission-capable cases (33). Recent investigations identified 8.1% (91/1,119) suspected undiagnosed infections through serology (34). Modern immunoblot techniques improve Clade-specific antibody detection, overcoming cross-reactivity challenges inherent to conventional enzyme-linked immunosorbent assay (ELISA) (35). Neutralization assays differentiate

vaccine-derived from natural infection antibodies, which is critical for epidemiological mapping (36–37). Integrated sero-genomic surveillance could refine pandemic models by quantifying gaps in symptom-based reporting systems.

Prevention and Control Measures

Effective prevention and control of MPXV, particularly Clade Ib, requires a comprehensive strategy encompassing enhanced surveillance, public education, and isolation protocols (38). Robust surveillance systems are essential for early detection and rapid outbreak response (39). Healthcare settings should implement rapid diagnostic testing, complemented by targeted public health campaigns that educate high-risk populations — including healthcare workers and individuals in close contact with infected animals — about transmission mechanisms, symptom recognition, and preventive measures (24,40).

Vaccines

Vaccination remains the cornerstone of mpox prevention, particularly given the high pediatric mortality rates associated with Clade Ib infections (41). Three live-attenuated smallpox vaccines are currently available:

Routine vaccines: MVA-BN (JYNNEOS®/Imvamune®/Imvanex®). This non-replicating vaccine is globally approved and safe for immunocompromised individuals, pregnant women, and those with dermatologic conditions. It requires a two-dose regimen with a 4-week interval and demonstrated 62%–85% efficacy during the 2022 outbreaks, significantly reducing disease severity (42–44).

LC16m8. This low-replicating strain developed in Japan confers 100% protection in non-human primates (NHPs) against Clade I MPXV (45). It induces neutralizing antibodies with 70% seroconversion (46) and exhibits only mild side effects, including fever and lymphadenopathy (47). Over 90,000 individuals, including 50,000 children, have been vaccinated with LC16m8 without significant safety concerns (48).

ACAM2000. This replication-competent vaccine is authorized for emergency use but contraindicated in immunocompromised individuals due to risks of myopericarditis. It served as the primary mpox vaccine in the U.S. until 2019 (49–50).

Next-generation vaccines: Several innovative vaccine platforms are currently under development for mpox

prevention. Quadrivalent mRNA vaccines (e.g., mRNA-A/B-LNP) targeting A29L, A35R, M1R, and B6R have demonstrated robust neutralizing antibody production and T-cell responses in murine models (51).

Multivalent mRNA vaccines such as Mpoxac-097 induce protective CD8+ T-cell responses against vaccinia virus (VACV) challenge, representing a promising advancement in orthopoxvirus immunization (52).

Additional candidates include encapsulated mRNA vaccines targeting A35R/M1R antigens and multicomponent formulations, which elicit Th1-biased immune responses with efficacy comparable to traditional vaccines in preclinical murine studies (53–54).

Drugs and Clinical Treatment

Drugs: Tecovirimat, a broad-spectrum antiviral, inhibits the p37 protein (encoded by the C17L gene in VARV), a conserved *Orthopoxvirus* target essential for viral envelope formation and pathogenicity (55). Approved by the U.S. FDA in 2018 for smallpox treatment, it effectively blocks the production of enveloped virions across the *Orthopoxvirus* genus.

Brincidofovir, an oral cidofovir analog approved in 2021 for smallpox, offers reduced nephrotoxicity compared to its injectable predecessor (56). Both agents inhibit viral replication through DNA polymerase inhibition (57).

Clinical treatment: Interim analyses from the National Institute of Allergy and Infectious Diseases (NIAID)-sponsored PALM007 (NCT05559099) and STOMP (NCT05534984) trials demonstrated tecovirimat's safety but found no efficacy in accelerating lesion resolution compared to placebo. PALM007, which enrolled hospitalized adults and children receiving high-quality supportive care, reported 1.7% mortality (historically $\geq 3.6\%$), attributing improved outcomes to enhanced supportive measures rather than tecovirimat. Similarly, STOMP's double-blinded cohort (mild-to-moderate cases, 2:1 allocation) showed no significant lesion or pain reduction with tecovirimat. Both trials confirmed the drug's tolerability (no serious adverse events) but demonstrated limited clinical benefit in immunocompetent patients with low-severity disease (58). Subgroup analyses are ongoing for immunocompromised individuals, patients with advanced HIV coinfection, and those receiving early treatment initiation.

Brincidofovir, FDA-approved for smallpox across all age groups, has demonstrated efficacy against *Orthopoxvirus* in both in vitro and animal studies, though human data specific to MPXV remain limited (58).

Challenges and Future Prospects

The emergence of MPXV Clade Ib in China presents significant public health challenges alongside strategic opportunities. Key challenges include its potential to escape existing vaccines, which could compromise immunization strategies and outbreak containment efforts, and its elevated mutation rate, necessitating continuous real-time genomic surveillance and adaptive public health responses. Conversely, this emergence creates opportunities to accelerate development of Clade Ib-specific vaccines and therapeutics while strengthening cross-border collaborations for coordinated resource mobilization. The escalating transmission risks underscore the urgent need for targeted health communication strategies to enhance community-level outbreak preparedness.

CONCLUSION

In summary, MPXV Clade Ib has emerged as a significant strain with substantial impact on disease epidemiology. It poses a considerable public health threat due to its enhanced transmission potential and the severity of illness it causes. The strain's rapid geographic spread, coupled with its distinct clinical presentation and higher case fatality ratio, underscores the urgent need for coordinated global surveillance, targeted prevention strategies, and continued development of effective vaccines and therapeutics. As international cases continue to emerge, strengthening cross-border collaboration and implementing evidence-based public health measures remain essential to mitigate the impact of this evolving pathogen.

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