PUBLIC HEALTH SYSTEMATIC REVIEW

Mpox (Monkeypox) as a Recurrent Global Public Health Emergency: Epidemiology, Clade Ib Emergence, Vaccine Deployment Challenges, and Lessons for Pandemic Preparedness

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ABSTRACT

Mpox (formerly monkeypox) re-entered global consciousness in May 2022 with an unprecedented multi-country outbreak — the first sustained human-to-human transmission documented outside sub-Saharan Africa — prompting the WHO to declare it a Public Health Emergency of International Concern (PHEIC) in July 2022. Although the 2022 multi-country outbreak (predominantly Clade IIb) was ultimately controlled through targeted vaccination campaigns, behavior change, and infection control measures, the emergence of Clade Ib — a genetically distinct and potentially more pathogenic variant first identified in the Democratic Republic of Congo (DRC) in 2023 — prompted the WHO to re-declare mpox a PHEIC in August 2024. This systematic review examines the epidemiology and clinical characteristics of both outbreak waves, compares the virological and clinical features of Clade IIb versus emerging Clade Ib, evaluates the efficacy and real-world effectiveness of the modified vaccinia Ankara (MVA-BN; Jynneos) vaccine, analyzes the structural barriers to equitable vaccine access in endemic African regions, and extracts actionable pandemic preparedness lessons.

Keywords: *mpox, monkeypox, Clade Ib, MPXV, Jynneos, MVA-BN, public health emergency, DRC, vaccine equity, pandemic preparedness, orthopoxvirus, Africa CDC*

1. INTRODUCTION

Mpox is a zoonotic disease caused by monkeypox virus (MPXV), an orthopoxvirus phylogenetically related to the variola virus (smallpox) and vaccinia virus (the basis of the smallpox vaccine). First identified in 1958 in captive monkeys and in humans in 1970 in the DRC, mpox was for decades considered a geographically confined disease of Central and West African rainforest ecozones, transmitted through contact with infected rodents (the true reservoir hosts) or nonhuman primates, and occasionally through close human-to-human contact.

The waning of population-level immunity conferred by the global smallpox vaccination campaign — which ended in 1980 following eradication — has been progressively recognized as a permissive factor for mpox resurgence, given the cross-protective immunity provided by orthopoxvirus vaccines. The 2022 multi-country outbreak, characterized by efficient sexual network transmission predominantly among men who have sex with men (MSM), reached 87,000 confirmed cases in 110 countries within 12 months and fundamentally transformed understanding of MPXV's pandemic potential.

The emergence and rapid spread of Clade Ib MPXV in eastern DRC from late 2023, associated with both sexual transmission networks and broader household transmission — including a

concerning proportion of pediatric cases and deaths — represents a qualitative shift in mpox epidemiology warranting urgent systematic analysis. This review addresses the full scope of the contemporary mpox public health challenge, from virology to vaccine equity.

2. VIROLOGY AND CLADE COMPARISON

MPXV is classified into two distinct clades: Clade I (formerly the Congo Basin/Central African clade) and Clade II (formerly the West African clade), with Clade II further subdivided into IIa (historically endemic in West Africa) and IIb (the 2022 global outbreak strain). A newly characterized subvariant designated Clade Ib was identified by the Africa Centres for Disease Control and Prevention (Africa CDC) and INRB genomic surveillance programs in 2023, primarily in South Kivu Province of eastern DRC.

Genomic analyses of Clade Ib isolates reveal a pattern of APOBEC3-driven hypermutation — the same evolutionary signature observed in Clade IIb — superimposed on a Clade I genomic background, suggesting parallel adaptive evolution toward enhanced human-to-human transmissibility. Additionally, several Clade Ib isolates harbor novel recombination events not previously observed in MPXV, raising concerns about accelerated viral evolution under conditions of sustained human transmission.

Feature	Clade IIb (2022 Global)	Clade Ib (2023–Present, DRC)
Primary transmission route	Sexual contact (MSM networks)	Sexual + household/community
Pediatric cases (%)	<5%	~32%
Case fatality rate (estimated)	0.1–0.3%	3.6–5.4% (DRC, 2024)
Rash distribution	Genital/perigenital predominant	Generalized; face/oral involvement
Geographic spread	110 countries (2022–23)	DRC, Burundi, Rwanda, Uganda
Vaccine effectiveness (Jynneos)	~78–85% (observational)	Limited data; trials pending
Genomic signature	APOBEC3 hypermutation	APOBEC3 + novel recombination events

Table 1. Comparative epidemiological and clinical features of Clade IIb vs. Clade Ib MPXV.

3. CLINICAL FEATURES AND DISEASE SEVERITY

Classic mpox presents with a prodromal phase of fever, headache, myalgia, and lymphadenopathy (the latter distinguishing mpox from smallpox and chickenpox), followed 1–3 days later by a characteristic centrifugal rash beginning on the face and spreading to the trunk and extremities, progressing synchronously through macule, papule, vesicle, pustule, and crust stages. Clade I/Ib infection is typically associated with more severe disease including larger lesion burden, higher frequency of mucosal involvement (oral, genital, perianal, conjunctival), and more pronounced systemic illness compared to Clade IIb.

Complications include secondary bacterial superinfection of lesions, pneumonitis, encephalitis, keratitis threatening vision loss, and — particularly in Clade Ib — life-threatening hemorrhagic forms. HIV co-infection substantially worsens outcomes, with case fatality rates up to 15% in severely immunocompromised individuals. Pregnancy-associated mpox carries significant risk of pregnancy loss, premature delivery, and neonatal mpox with high neonatal mortality.

4. VACCINE EFFICACY AND DEPLOYMENT

4.1 MVA-BN (Jynneos)

The Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN) vaccine — marketed as Jynneos in the United States, Imvamune in Canada, and Imvanex in Europe — is a non-replicating, third-generation smallpox/mpox vaccine administered as a two-dose series 28 days apart. Observational effectiveness studies conducted during the 2022 outbreak estimated pre-exposure vaccine effectiveness of 78–85% against symptomatic mpox in MSM cohorts in the United States, United Kingdom, and France. Post-exposure prophylaxis effectiveness when administered within 4 days of exposure was estimated at approximately 89% in the UK Health Security Agency's contact tracing program.

4.2 Vaccine Equity — The DRC Crisis

The starkest failure of the mpox response has been the near-complete absence of MVA-BN vaccine availability in the DRC and neighboring countries bearing the greatest burden of disease. As of September 2024, fewer than 200,000 MVA-BN doses had been delivered to the African continent — a fraction of the tens of millions of doses secured by high-income countries during the 2022 outbreak and subsequently stockpiled. Manufacturing capacity for MVA-BN is effectively monopolized by Bavarian Nordic, creating structural supply constraints that echo the COVID-19 vaccine equity crisis. Vaccine donation pledges from the United States (1 million doses), European Union (215,000 doses), and Japan (3.5 million doses) — while welcomed — remain operationally constrained by cold chain requirements, delivery logistics, and health system capacity in affected regions.

5. PANDEMIC PREPAREDNESS LESSONS

The mpox experience across both outbreak waves generates several critical lessons: (1) Zoonotic spillover diseases with pandemic potential exist along a spectrum — the failure to aggressively control mpox in endemic African regions for five decades created the conditions for global emergence. Investment in endemic-region surveillance and outbreak control has direct global security value. (2) Vaccine nationalism and stockpiling by high-income countries during health emergencies has predictable and severe consequences for global equity and ultimately for global outbreak control. (3) The APOBEC3-driven hypermutation pattern in Clade IIb, and further genomic complexity in Clade Ib, demonstrates that orthopoxviruses are more evolutionarily dynamic than previously appreciated — sustained global genomic surveillance infrastructure is essential. (4) Clinical management capacity, including access to tecovirimat (TPOXX) and brincidofovir — the two licensed antiviral agents with activity against MPXV — remains extremely limited in endemic-region health systems. (5) Community engagement strategies that are non-stigmatizing, culturally appropriate, and co-developed with affected communities are essential for effective outbreak response across all transmission contexts.

Preparedness Domain	2022 Clade IIb Performance	2024 Clade Ib Performance	Priority Action
Genomic surveillance	Rapid global sequencing	Strong in DRC; limited neighbors	Fund Africa CDC genomics
Vaccine supply (endemic regions)	Near-absent	Near-absent	Mandate equitable allocation
Antiviral access	Limited (HIC only)	Very limited (LMIC)	Technology transfer urgently

Community engagement	Effective in MSM networks	Challenging (diverse affected groups)	Co-design with communities
Clinical case management	Good (HIC)	Very limited (DRC)	Train HCW, build capacity

Table 2. Pandemic preparedness assessment across key domains for mpox outbreak response. HIC = high-income countries; LMIC = low- and middle-income countries; HCW = healthcare workers.

6. CONCLUSIONS

Mpox has transitioned from a neglected tropical disease to a recurrent global public health emergency — a transition driven by biological factors (waning orthopoxvirus immunity, viral evolution), ecological pressures (deforestation, wildlife-human interface expansion), and structural global health failures (decades of neglect of endemic-region outbreak control and vaccine development). The emergence of Clade Ib with its broader transmission profile and higher case fatality rate demands an urgent and equitable global response. Sustainable control of mpox will require genuine partnership between high-income countries and DRC-region governments, massively scaled vaccine production and equitable distribution, robust antiviral access programs, and investment in African genomic and epidemiological surveillance infrastructure.

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