

REVIEW ARTICLE

Monkeypox: An integrated review of virology, epidemiology, pathogenesis, diagnostics, therapeutics, vaccinology, and public health strategies

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Abstract

Monkeypox (Mpox), caused by monkeypox virus (MPXV), has shifted from an endemic zoonosis in Central and West Africa to a pathogen of global public health significance. Two World Health Organization (WHO) Public Health Emergencies of International Concern were declared and subsequently lifted. Clade Ib has continued to emerge in the Democratic Republic of the Congo and neighboring countries, recombinant MPXV strains have been detected, and inequities in access to diagnostics, vaccines, and therapeutics persist. These factors need critical synthesis to inform clinical practice and public health preparedness. This paper reviewed MEDLINE, Embase, WHO situation reports, the United States Centers for Disease Control and Prevention, and Prevention surveillance bulletins, prioritizing peer-reviewed literature and official reports, with preprints identified where cited. MPXV comprises two major clades with distinct epidemiological, clinical, and virological profiles. Clade Ib shows apolipoprotein B mRNA editing enzyme catalytic subunit 3 consistent mutational signatures indicating sustained human adaptation, and has driven a large ongoing

outbreak in Central and East Africa. Clade IIb drove the 2022 global outbreak, predominantly through sexual contact among men who have sex with men. Diagnosis relies on polymerase chain reaction of lesion specimens, with whole genome sequencing needed for subclade and recombinant characterization. Tecovirimat has shown no significant clinical benefit in randomized trials for clade I disease, leaving treatment guidance unresolved. JYNNEOS offers approximately 82% pre-exposure effectiveness against clade IIb, though direct clade Ib effectiveness data remain limited, and equitable access to countermeasures in high-burden African settings remains critically inadequate. Priorities include strengthened genomic surveillance in Africa, expanded access to JYNNEOS, and urgent clade Ib-specific effectiveness data.

Keywords: Mpox; Monkeypox; Virology; Infectious diseases; Vaccinology; Epidemiology

1. Introduction

Monkeypox (Mpox) is an infectious disease caused by the Mpox virus (MPXV), an enveloped double-stranded DNA virus belonging to the genus *Orthopoxvirus* within the family Poxviridae. First documented in humans in 1970 in the Democratic Republic of the Congo (DRC), the disease was historically recognized as a sporadic zoonosis causing self-limited outbreaks in forested regions of Central and West Africa. This characterization has been substantially revised over the past decade.¹ The global 2022 outbreak, which affected more than 87,000 individuals across over 100 countries and prompted the World Health Organization (WHO) to declare its first Mpox Public Health Emergencies of International Concern (PHEIC), exposed the capacity of MPXV to sustain efficient human-to-human transmission in new epidemiological networks.¹⁻³ The emergence of clade Ib in the DRC beginning in 2023 and its spread to neighboring countries in East Africa prompted a second WHO PHEIC in August 2024, which was subsequently lifted in 2025, although clade Ib transmission has continued at the time of writing in June 2026.⁴

These developments have occurred against a background of profound global inequity in surveillance, diagnostic infrastructure, vaccine access, and antiviral availability. While JYNNEOS was rapidly deployed in high-income countries during the 2022 outbreak, endemic and outbreak-affected countries in Africa faced constrained access throughout both emergencies.⁵ Similarly, whole genome sequencing (WGS) capacity required to characterize viral evolution and detect recombinant strains remains unevenly distributed, with most sequencing occurring in high-income settings.

This review synthesizes current evidence on MPXV

virology and genomics, transmission, epidemiology, pathogenesis, clinical features, diagnostics, therapeutics, vaccines, and public health responses, as of May 2026. The review aims to support clinicians, public health practitioners, and researchers across all settings, with particular attention to clinical and operational challenges in African epidemic contexts. Evidence quality and areas of ongoing uncertainty are identified throughout.

2. Literature search strategy

A comprehensive narrative search was conducted across MEDLINE (via PubMed), Embase, the Cochrane Library, WHO disease outbreak news and technical reports, Centers for Disease Control and Prevention (CDC) Health Advisory Network alerts, and the Africa CDC Mpox situation reports. Preprint repositories (medRxiv, bioRxiv) were searched for emerging data with significant public health relevance; preprint citations are indicated where used. The search terms included combinations of the following: “Mpox,” “monkeypox,” “monkeypox virus,” “MPXV,” “clade I,” “clade Ib,” “clade II,” “clade IIb,” “transmission,” “epidemiology,” “pathogenesis,” “diagnostics,” “tecovirimat,” “JYNNEOS,” “vaccine effectiveness,” and “genomic surveillance.” The time period covered is from database inception through May 2026. References were selected based on clinical or public health relevance, methodological quality, and recency, with peer-reviewed literature prioritized over preprints and secondary sources. Given the rapidly evolving nature of clade Ib epidemiology and recombinant strain biology, WHO and Africa CDC technical documents were included as primary sources for surveillance data where peer-reviewed literature was unavailable. The review also incorporates recent clinical and regulatory synthesis published by Rizk *et al.*³ as a reference for current management frameworks.

3. Virology and genomics

3.1. Viral classification and structure

Monkeypox virus is a double-stranded DNA virus with a genome of approximately 197 kbp. Like other orthopoxviruses, it encodes structural proteins, enzymes for cytoplasmic viral replication, and a suite of immunomodulatory proteins that facilitate immune evasion.¹ The virion exists in two infectious forms: the intracellular mature virion and the extracellular enveloped virion (EEV). The EEV form is responsible for cell-to-cell and systemic spread, and its envelope proteins are targets for both the humoral immune response and antiviral agents such as tecovirimat, which inhibits VP37, a protein essential for EEV wrapping.^{4,5} MPXV is genetically and antigenically related to variola virus, the causative agent of smallpox, and to vaccinia virus, the basis for smallpox and Mpox vaccines. This relatedness underlies the cross-protective immunity observed with vaccinia-based vaccines across *Orthopoxvirus* sp., though the degree of cross-protection is not uniform across all MPXV clades and immunological endpoints.⁴⁻⁶

3.2. Clade classification

Monkeypox virus has historically been classified into two major clades: clade I (formerly Congo Basin clade) and clade II (formerly West African clade). Refinements in genomic characterization have led to the recognition of subclades Ia and Ib within clade I, and IIa and IIb within clade II.^{2,6} These designations reflect phylogenetically

distinct lineages with differences in geographic origin, transmissibility, case fatality, and clinical presentation. Table 1 presents a comparative summary of the clades and subclades.⁶

3.3. Immunomodulatory genes and clade I virulence

Clade I MPXV encodes a larger set of immunomodulatory genes than clade II, including proteins that modulate tumor necrosis factor receptor signaling, interferon responses, and complement activation. While these differences likely contribute to the higher virulence and case fatality observed with clade I relative to clade II, it is important to note that the specific mechanistic contribution of individual immune evasion genes to enhanced clade I pathogenicity in humans has not yet been fully characterized in controlled experimental settings.^{6,7} Claims attributing specific virulence differences to particular gene products should be treated with appropriate caution until corroborated by mechanistic studies.

3.4. APOBEC3-driven mutation and human adaptation

A key marker of sustained human-to-human transmission is the accumulation of C-to-T and G-to-A single-nucleotide substitutions at TC/GA dinucleotide motifs within the viral genome. These substitution patterns are the signature of apolipoprotein B mRNA editing enzyme, catalytic subunit 3 (APOBEC3), a family of cytidine deaminases that constitute part of the innate immune

Table 1. Comparative summary of monkeypox virus clades and subclades⁶

Clade/ Subclade	Geographic distribution	Dominant transmission routes	Case fatality (approximate)	Clinical features	Vaccine access/coverage
Clade Ia	Central Africa (DRC)	Animal reservoirs (rodents/primates); household contact; vertical transmission	Higher (~10%); children and immunocompromised disproportionately affected	Classical generalized rash; systemic features; higher complication rate	Limited vaccine access; smallpox-era immunity waning; wild-type; stable clade.
Clade Ib	DRC and neighboring countries; ongoing since 2023	Sustained human-to-human; sexual contact; household	Higher than clade IIb; ongoing outbreak	Classical features with extensive mucocutaneous involvement	Constrained; active scale-up in progress; APOBEC3 mutational signatures confirmed.
Clade IIa	West Africa (Nigeria, Cameroon)	Zoonotic spillover predominant; limited human-to-human	Low (under 1% in community settings)	Moderate illness; fewer complications than clade I	Limited outside endemic zones; stable reference clade.
Clade IIb	Global; 2022 outbreak in MSM networks	Sexual contact (especially MSM); close non-sexual contact; fomites	Low (under 0.2% in the 2022 outbreak)	Atypical; genital, perianal, oral lesions; fewer systemic features	Expanded; JYNNEOS deployed widely in high-income settings; most sequenced clade.

Abbreviations: APOBEC3: Apolipoprotein B mRNA editing enzyme catalytic subunit 3; DRC: Democratic Republic of the Congo; MSM: Men who have sex with men.

restriction machinery in human cells.⁸ When these mutations accumulate at rates exceeding those explainable by background replication error alone, they provide phylogenetic evidence of prolonged replication within human hosts rather than repeated independent zoonotic spillover events.⁸

The significance for public health is substantial: APOBEC3 mutational signatures were identified in the clade IIb lineage responsible for the 2022 global outbreak and have now been confirmed in clade Ib strains from the 2023 to 2026 DRC epidemic.^{9,10} These signatures indicate that clade Ib has been sustaining human-to-human transmission chains long enough for the human immune restriction machinery to imprint on the viral genome, representing a qualitative shift from historical zoonotic Mpox behavior. This, by itself, does not indicate accelerated mutation of functionally important virulence or immune evasion loci, but it supports the conclusion that zoonotic spillover alone does not explain the current epidemic trajectory.⁹

3.5. Recombinant strains

The detection of putative recombinant MPXV strains, arising from co-infection of a single host with two genetically distinct MPXV lineages, has been reported in surveillance data from the DRC.¹⁰ As of May 2026, characterization of these strains remains incomplete, and their phenotypic properties, including transmissibility, virulence, and vaccine or antiviral susceptibility, have not been experimentally established. These reports are

predominantly based on WGS data from surveillance programs and have not yet undergone full peer review in all cases. Accordingly, conclusions regarding their public health significance should be drawn cautiously, with ongoing surveillance and experimental validation required.

4. Epidemiology

4.1. Overview and historical context

Since the 1970s, Mpox has been endemic in DRC, with sporadic outbreaks reported across Central and West Africa. The interruption of universal smallpox vaccination following eradication in 1980 has progressively eroded herd immunity to orthopoxviruses in successive birth cohorts, an effect that appears to have contributed substantially to increased Mpox incidence and more efficient human-to-human transmission over time. Modeling studies have estimated that the proportion of individuals with prior smallpox vaccination-derived orthopoxvirus immunity has declined to under 30% in numerous African countries and under 20% in younger urban populations, removing a significant immunological barrier to sustained Mpox transmission.^{1,3}

Intense international travel, urbanization, changing sexual contact patterns, and the concentrated vulnerability of immunosuppressed populations (particularly those living with advanced human immunodeficiency virus [HIV] infection) have additionally shaped contemporary outbreak dynamics. [Table 2](#) summarizes major Mpox

Table 2. Summary of major monkeypox outbreaks, from 1970 to 2026^{11,12}

Year	Region	Clade	Transmission	Reported cases	CFR	Affected populations	Public health significance
1970	DRC	Clade I	Zoonotic	~1 (index case, child)	N/A	Children	First documented human case; endemic pattern established
1996–1997	DRC (Kasai)	Clade Ia	Household contact	500+	1–5%	Mixed	First large outbreak; person-to-person transmission confirmed
2003	USA	Clade IIa	Pet prairie dogs (imported rodents)	81	0%	Mixed; adults	First extra-African outbreak; zoonotic spillover in a non-endemic setting
2017–2019	Nigeria	Clade IIa/IIb	Zoonotic + sexual contact	200+	~3%	Young adults, MSM	Resurgence after 40-year absence; MSM transmission identified
2022	Global (100+ countries)	Clade IIb	Sexual contact (MSM networks); close contact	~87,000	<0.2%	MSM; adults	WHO PHEIC declared July 2022; atypical presentation; JYNNEOS deployed

(Cont'd...)

Table 2. (Continued)

Year	Region	Clade	Transmission	Reported cases	CFR	Affected populations	Public health significance
2023–2024	DRC	Clade Ia and Ib	Household; sexual networks; vertical	>20,000 (DRC alone)	5–10%	Children, adults, sex workers	Second WHO PHEIC (2024); clade Ib emergence; spread to East Africa
2024–2026	Multiple (Africa + sporadic global)	Clade Ib; recombinant strains detected	Sexual contact; household; travel-related	Ongoing; global surveillance is active	Ongoing	Adults; MSM; sex workers	Second PHEIC lifted; clade Ib circulation continues; recombinant strains under investigation

Abbreviations: CFR: Case fatality rate; DRC: Democratic Republic of the Congo; MSM: Men who have sex with men; N/A: Not applicable; PHEICs: Public Health Emergencies of International Concern; WHO: World Health Organization.

outbreaks by year, region, clade, and public health significance.

4.2. The 2022 global outbreak (clade IIb)

From May to November 2022, Mpox caused by clade IIb spread rapidly through sexual networks, predominantly affecting gay, bisexual, and other men who have sex with men (MSM) in Europe, North America, and Latin America. WHO declared a PHEIC in July 2022. The outbreak was characterized by atypical clinical presentations with genital and perianal lesions frequently preceding or replacing the classical generalized rash, low mortality (under 0.2% in high-income settings), and rapid JYNNEOS vaccine deployment.¹³ The PHEIC was lifted in May 2023 as case counts declined following behavior change and vaccination.^{13,14}

It is important to note that while sexual contact in MSM networks was the dominant transmission route in the 2022 outbreak, Mpox is not classified as a sexually transmitted infection in the strict sense. Transmission can occur through any form of close, prolonged skin-to-skin contact, respiratory droplets, fomites, zoonotic exposure, and vertically from mother to fetus. Framing that overemphasizes the sexual transmission route risks misrepresentation of the risk landscape and may contribute to stigmatizing narratives that impede public health response.^{12–15}

4.3. Clade Ib emergence and the second PHEIC (2023 to 2026)

A novel subclade, clade Ib, was identified in the DRC in late 2023. Unlike prior clade I outbreaks, which were predominantly driven by household contact, zoonotic spillover, and pediatric transmission in rural forested communities, clade Ib demonstrated efficient transmission

in sex work networks in the eastern DRC before spreading to household contacts and children.^{1,5} The outbreak expanded into neighboring countries in East Africa, leading the WHO to declare a second PHEIC in August 2024. This PHEIC was subsequently lifted; however, clade Ib transmission continues as of 2026.⁷ Sporadic travel-associated clade Ib cases have been detected outside Africa, and local transmission events have been confirmed in at least one non-African setting, underscoring the risk of further international spread.

4.4. Regional and population-specific considerations

The epidemiology of Mpox differs substantially across regions and requires context-specific interpretation. In Central Africa, particularly the DRC and the Republic of the Congo, clade Ia disease is predominantly zoonotic with household amplification and disproportionately affects children in forested communities.¹⁵ In East Africa (eastern DRC, Burundi, Rwanda, Uganda, Kenya), clade Ib is driving an outbreak centered initially in sex work networks with substantial pediatric and household spillover. In West Africa (Nigeria, Cameroon), clade IIa disease presents sporadically, predominantly through zoonotic exposure with limited sustained human-to-human transmission. In Europe and North America, clade IIb disease persists at low endemic levels, predominantly in MSM networks with incomplete vaccination coverage. In Asia and Oceania, sporadic travel-associated cases continue to occur across multiple clades.¹⁵

These distinctions matter for clinical practice, outbreak response, risk communication, and resource allocation. Generalizing findings from high-income settings, such as low case fatality and atypical presentation, to endemic or epidemic African settings where access to care, diagnostics, and antivirals differs markedly is inappropriate and risks underestimating disease burden and severity.

5. Animal reservoirs and transmission

5.1. Zoonotic reservoirs

The animal reservoir of MPXV has not been definitively established despite decades of investigation. Rodents, particularly squirrels of the genera *Funisciurus* and *Heliosciurus* and the African rope squirrel (*Funisciurus anerythrus*), are the most frequently implicated zoonotic reservoir species on the basis of seroprevalence surveys, detection of MPXV-compatible poxvirus antigen, and epidemiological case-contact data. Non-human primates, including sooty mangabeys, can be infected with MPXV and develop disease, but are more likely incidental hosts than reservoir species.¹⁶ The 2003 United States outbreak was directly linked to imported Gambian pouched rats (*Cricetomys gambianus*).¹⁷

The precise mechanisms by which MPXV persists endemically in wildlife populations, including the role of different rodent species as reservoirs versus dead-end hosts, the seasonality of zoonotic spillover, and the ecological drivers of increased spillover risk in human-encroached forest environments, remain incompletely understood. Filling these gaps is a research priority with direct implications for predicting outbreak risk and designing environmental interventions.^{16,17}

5.2. Animal-to-human transmission

Zoonotic transmission to humans occurs through direct contact with infected animals (handling, butchering, bites, scratches), consumption of undercooked bushmeat, and possibly through respiratory exposure in confined settings. The risk is highest in communities with close contact with forest wildlife, including hunters, bushmeat traders, and households in forested rural zones. Occupational exposure in laboratory workers and animal care personnel handling non-human primates or infected rodents also constitutes a recognized risk.¹²

5.3. Human-to-human transmission

Human-to-human transmission of MPXV occurs through multiple routes, and the relative contribution of each route varies substantially across outbreaks, populations, and settings. The principal modes include direct contact with infectious skin lesions, crusts, or mucosal surfaces; respiratory droplets and possibly short-range aerosols during close, prolonged face-to-face contact; contact with virus-contaminated fomites (bedding, clothing, utensils); sexual contact involving skin-to-skin genital, perianal, or oral contact with lesions; and vertical transmission from mother to fetus during pregnancy or peripartum exposure.¹⁸

In the 2022 clade IIb outbreak, sexual contact was the dominant transmission route in affected MSM networks, with epidemiological and virological evidence supporting this pathway.^{9,10} In Central African clade Ia outbreaks, household contact without sexual activity, including exposure to respiratory secretions and fomites in shared sleeping areas, has been the principal driver. In the clade Ib outbreak, both sexual contact in commercial sex networks and household transmission have been documented. In pediatric populations across all clade I settings, household close contact and vertical transmission are the predominant routes, and sexual contact should not be assumed as the transmission pathway in pediatric cases.

6. Pathogenesis and host immune response

6.1. Overview of infection and disease progression

Following inoculation at a mucosal surface, skin break, or respiratory mucosa, MPXV initially replicates at the site of entry and in regional lymph nodes before seeding a primary viremia.^{1–10} Subsequent amplification in reticuloendothelial organs (spleen, liver, lymph nodes) produces a secondary viremia that disseminates the virus to the skin and other organs. Histopathologically, the characteristic skin lesion represents viral replication within epidermal keratinocytes, along with the associated inflammatory and immune response in the dermis.

6.2. Innate immune response

Infection with MPXV activates pattern recognition receptors, including Toll-like receptors (TLR2, TLR4) and cytoplasmic DNA sensors (cGAS-STING pathway). Viral recognition triggers type I and type III interferon responses, which limit early viral replication and activate natural killer cells and macrophages.¹⁹ MPXV encodes multiple interferon antagonist proteins, including the B18R interferon-binding protein homolog, that partially counteract these responses. The viral immunomodulatory gene repertoire is more extensive in clade I than clade II, consistent with, though not fully explaining, the higher clinical severity of clade I disease.¹⁹

6.3. Adaptive immune response

Both humoral and cellular adaptive immunity are important in controlling MPXV infection. Antibodies directed against surface proteins of the mature virion and the EEV (particularly L1, A27, B5, and A33 homologs) are detectable by the first week of illness and appear to contribute to viral clearance and protection against reinfection. However, the available evidence suggests that humoral immunity alone is insufficient to control acute severe disease in immunocompromised individuals, and

that CD4⁺ and CD8⁺ T-cell responses are critical for viral clearance and recovery.¹⁹

CD8⁺ cytotoxic T lymphocytes (CTL) recognize MPXV peptides presented by MHC class I molecules and eliminate infected cells. CD4⁺ T cells provide helper function for both antibody production and CTL expansion. In individuals with advanced HIV infection, particularly those with CD4 counts below 200 cells per μL , deficiencies in CD4⁺ T-cell numbers and function compromise both the direct cellular response and the quality of humoral responses, contributing to the severe, prolonged, and atypical Mpox presentations observed in this population.^{15,19}

6.4. Monkeypox in people with human immunodeficiency virus infection

Advanced HIV infection significantly modifies the clinical course of Mpox. At low CD4 counts (particularly below 200 cells per μL), Mpox presents atypically with necrotic, non-healing lesions, prolonged or relapsing disease course, absent or absent-and-reappearing rash, visceral involvement (pneumonitis, encephalitis), and higher mortality. Uncontrolled HIV replication compounds this vulnerability by further depleting and functionally impairing CD4⁺ T cells.²⁰

Individuals with high CD4 counts on effective antiretroviral therapy (ART) who have suppressed HIV viremia appear to mount adequate immune responses and generally experience disease courses comparable to HIV-negative individuals, though individual variation exists. Access to ART is therefore not merely a treatment priority but a critical determinant of Mpox severity and outcomes in co-infected individuals. In high-burden African settings, where HIV prevalence is elevated and ART coverage remains incomplete in many communities, Mpox-HIV co-infection presents a substantial clinical challenge.^{13,20}

7. Clinical features

7.1. Classical presentation

The classical Mpox presentation, most commonly seen with clade I disease and in non-sexually transmitted clade II infection, begins with a prodromal illness characterized by fever, headache, myalgia, lymphadenopathy, and fatigue lasting two to four days. Lymphadenopathy, particularly cervical, submandibular, and inguinal, is a distinctive clinical feature that helps differentiate Mpox from chickenpox.^{8–12} This is followed by synchronous centrifugal spread of a skin rash beginning on the face before involving the trunk and extremities, including the palms and soles. Lesions evolve through well-defined stages: macule, papule, vesicle, pustule, and crust. All lesions in a given patient tend to progress through these

stages synchronously. The illness typically resolves within two to four weeks in immunocompetent hosts.

7.2. Modified presentation in the 2022 clade IIb outbreak

The 2022 outbreak introduced clinical presentations that diverged substantially from the classical pattern. Lesions were frequently localized to the genital, perianal, and oral mucosa, reflecting the predominant sexual transmission route. Systemic prodrome was often absent or mild. Lesions at different stages of evolution (asynchronous) were observed in several patients. Proctitis, urethritis, and tonsillar lesions were reported as isolated presentations in some cases without generalized rash.⁹

These atypical presentations carry important diagnostic implications. Localized genital, perianal, or oral ulcerative or vesiculopustular lesions may be mistaken for herpes simplex virus infection, syphilis, lymphogranuloma venereum, varicella zoster virus infection, chancroid, or other bacterial sexually transmitted infections. Clinical awareness of Mpox in the differential diagnosis of these presentations, particularly in MSM or individuals with recent high-risk exposure, is essential to avoid diagnostic delay.

7.3. Complications and severe disease

Complications of Mpox include secondary bacterial superinfection of skin lesions (the most common complication), scarring, ocular involvement with possible visual impairment, oral or laryngeal involvement causing dysphagia or airway compromise, bronchopneumonia, encephalitis, and, in the most severe cases, multi-organ failure. Children, pregnant women, and immunocompromised individuals are at greatest risk of severe disease. Neonatal infection resulting from vertical or peripartum transmission carries high morbidity and mortality.¹⁶

In individuals with advanced HIV infection, the clinical presentation is frequently atypical and severe, as described in Section 6.4, with necrotic lesions, visceral dissemination, and significantly elevated mortality compared to HIV-negative individuals.¹³

8. Diagnostics

8.1. Specimen selection and sampling considerations

Laboratory confirmation of Mpox relies on detecting MPXV DNA via polymerase chain reaction (PCR). Lesion swabs are the preferred specimen type because the viral load in skin lesions, particularly in the pustular and vesicular stages, is substantially higher than in blood,

nasopharyngeal, or oropharyngeal specimens.¹⁶ Paired swabs from multiple lesion sites, particularly of opened vesicles or pustules, maximize diagnostic sensitivity. Lesion crust specimens are also acceptable. Sampling quality, lesion stage at the time of sampling, and anatomical site all materially affect diagnostic yield. Lesions in very early (macular) or late (crusting/healing) stages yield lower viral loads. In atypical presentations with predominantly mucosal lesions, sampling from the affected mucosal site (rectal, oral, urethral) is preferred.¹⁶

Blood samples have lower sensitivity for MPXV PCR and are more useful for monitoring viremia in severe or systemic disease. Nasopharyngeal specimens may be considered in patients with prominent respiratory symptoms, but are generally not the first-choice specimen.

8.2. Molecular diagnostic platforms

Several commercial and laboratory-developed PCR assays have been validated for MPXV detection. Assays targeting the *F3L* or *E9L* genes, conserved across orthopoxviruses, may not distinguish MPXV from other orthopoxviruses; assays targeting species-specific loci are preferred for confirmed Mpox diagnosis. Orthopoxvirus PCR can serve as an initial screening test in settings where MPXV-specific reagents are unavailable, followed by confirmatory Mpox-specific PCR. Rapid antigen tests and rapid nucleic acid tests with point-of-care capability are under development and have been deployed in some outbreak-affected African settings with limited laboratory infrastructure.¹⁶

8.3. Whole genome sequencing for subclade and recombinant strain characterization

Whole genome sequencing is required for definitive subclade characterization, identification of recombinant strains, and molecular epidemiological tracking of transmission chains. Next-generation sequencing platforms enable comprehensive MPXV genomic characterization, including detection of APOBEC3 mutational signatures and identification of variants at immune evasion or drug resistance loci.^{14,16}

Critically, WGS capacity is not uniformly distributed. The majority of Mpox sequencing in the current outbreak is being performed in high-income country reference laboratories, with data submitted to public repositories (Global Initiative on Sharing All Influenza Data and GenBank of the National Center for Biotechnology Information). This creates a structural lag in genomic surveillance in high-burden African settings, where samples must often be transported to international reference centers for sequencing. Delays in genomic data sharing compound this inequity. Investment in in-country

sequencing capacity in DRC, Nigeria, and other high-incidence settings is a research and public health infrastructure priority.^{16,17}

9. Treatment and clinical management

9.1. Supportive care

Supportive care remains the primary and most evidence-supported treatment for Mpox in immunocompetent individuals with mild to moderate disease.^{1–4} This includes wound care to prevent secondary bacterial superinfection and scarring, adequate hydration and nutritional support, analgesic management of pain (which can be significant, particularly with genital or perianal lesions), antimicrobial therapy for documented secondary bacterial infection, and ophthalmic consultation for corneal involvement. Careful wound care technique, including avoiding premature crust removal, minimizes scarring and reduces transmission risk.

9.2. Tecovirimat

Tecovirimat (TPOXX, ST-246) inhibits VP37, a protein required for MPXV EEV wrapping, thereby limiting viral dissemination. Preclinical data in non-human primate models demonstrated strong efficacy.^{1,2} Based on these data and the animal rule, tecovirimat received Food and Drug Administration (FDA) approval for smallpox and was available under expanded access provisions for Mpox.

The PALM007 randomized controlled trial, conducted in the DRC during the current clade I outbreak, reported no statistically significant difference between tecovirimat and placebo for the primary endpoint of lesion resolution time or for secondary endpoints, including mortality in the enrolled population.^{2,3} This trial represents the most rigorous clinical evaluation of tecovirimat for Mpox to date and substantially modifies the clinical confidence previously placed in this agent. Important caveats include the predominantly clade Ia disease studied in PALM007, the challenge of blinding in the trial context, and the limited data on immunocompromised patients, for whom tecovirimat continues to be recommended by many expert groups based on mechanistic rationale despite the absence of controlled efficacy data.

For clade Ib disease specifically, no randomized controlled trial data exist as of May 2026.²¹ Clinical use of tecovirimat for clade Ib continues under compassionate access frameworks, and its effectiveness in this context remains uncertain. The tension between urgent clinical need and incomplete efficacy evidence is a recurring challenge in outbreak therapeutics and should be explicitly acknowledged in clinical decision-making and in patient communication.

9.3. Antiviral resistance

With expanded tecovirimat use across two PHEICs, resistance-associated mutations in the VP37 target gene have been identified in patients receiving prolonged or repeated courses, particularly those with immunosuppression-driven viral persistence. Specific mutations at the *E6L* (encoding VP37) locus have been associated with reduced tecovirimat susceptibility *in vitro*.^{2,17} Routine resistance testing is not currently available in most high-burden settings. The development of phenotypic and genotypic resistance surveillance systems, integrated into genomic surveillance programs where possible, is a clinical and public health priority.

9.4. Other antivirals

Cidofovir and its lipid conjugate, brincidofovir, inhibit the MPXV DNA polymerase (A22R homolog) and have

demonstrated efficacy in animal models. Human Mpox-specific clinical data are limited. Cidofovir is associated with significant nephrotoxicity and requires pre-hydration and probenecid co-administration. Brincidofovir is better tolerated when given orally but has been associated with hepatotoxicity in some clinical settings. Both agents are generally reserved for cases where tecovirimat is unavailable, contraindicated, or where resistance is suspected.²²

Vaccinia immune globulin (VIG) provides passive transfer of anti-orthopoxvirus antibodies and has been used historically for severe complications of smallpox vaccination. For Mpox, evidence is primarily anecdotal; VIG may be considered as an adjunct in severe disease in immunocompromised patients, particularly where tecovirimat is unavailable or failing.¹ Table 3 summarizes available therapeutic agents and their evidence profiles.

Table 3. Summary of therapeutic agents for Mpox^{2,17,23}

Agent	Mechanism	Indication	Evidence base	Resistance/safety	Route	Regulatory status
Tecovirimat	VP37 envelope wrapping inhibitor	Severe Mpox; immunocompromised patients; compassionate use in outbreak settings	Preclinical: effective. Clinical (PALM007 RCT, clade I): no significant reduction in viral clearance or clinical endpoints vs placebo. Data remain immature for clade Ib.	VP37 resistance mutations reported (<i>E6L/A8R</i> loci) with prolonged or repeated use; surveillance systems needed	Oral/IV; well tolerated; headache, nausea most common	Regulatory approval (FDA/EMA for smallpox); expanded access for Mpox through compassionate/IND frameworks; clade-specific efficacy unresolved
Cidofovir/brincidofovir	DNA polymerase inhibitor (UL30 homolog)	Alternative or adjunct when tecovirimat is unavailable or resistance is suspected	Limited human Mpox data; animal model efficacy established	Nephrotoxicity (cidofovir); GI toxicity (brincidofovir); requires prehydration for IV cidofovir	IV (cidofovir); oral (brincidofovir)	Not formally approved for Mpox; used under emergency/compassionate frameworks
IVIG (VIG)	Passive antibody transfer	Severe complications; progressive vaccinia; immunocompromised; adjunct in tecovirimat failures	Largely anecdotal; no controlled Mpox-specific trials	Risk of hypersensitivity, volume overload	IV infusion	CDC strategic stockpile; formal Mpox indication not established; used off-label
Supportive care	Symptom management; wound care; infection prevention	All patients; primary treatment for mild-to-moderate disease	Strong consensus; prevents secondary bacterial infection and scarring	Wound care risks if improper technique is used	Topical, oral analgesics, IV fluids where needed	Standard of care; universally recommended

Abbreviations: CDC: Centers for Disease Control and Prevention; EMA: European Medicines Agency; FDA: Food and Drug Administration; GI: Gastrointestinal; IND: Investigational new drug; IV: Intravenous; IVIG: Intravenous immunoglobulin; Mpox: Monkeypox; RCT: Randomized controlled trial; VIG: Vaccinia immune globulin.

10. Vaccinology

10.1. Current vaccines

Three vaccines are relevant to Mpox prevention: JYNNEOS (also known as Imvamune or Imvanex), ACAM2000, and LC16m8. Each differs in its platform, safety profile, regulatory status, and evidence base for Mpox protection.²⁴ Table 4 provides a comparative summary.

10.2. JYNNEOS effectiveness: clade IIb and clade Ib

JYNNEOS demonstrated approximately 82% pre-exposure effectiveness in the 2022 clade IIb outbreak based on retrospective and observational studies from the United States, United Kingdom, and European settings. Post-exposure prophylaxis (PEP) data suggest effectiveness when the vaccine is administered within four days of exposure.^{1,5,24} Ring vaccination strategies using PEP contributed to outbreak control in several European contexts.

For clade Ib disease, direct clinical effectiveness data from prospective studies or controlled trials are not available as of May 2026. Cross-protective immunity is biologically plausible based on orthopoxvirus antigenic relatedness and the shared immunodominant protein targets among MPXV clades.^{1,2,17} However, it would be inappropriate to assume full protection from clade IIb effectiveness estimates for a biologically and epidemiologically distinct

clade until supporting direct data are generated. This distinction should be communicated clearly in clinical guidance and vaccination program communications.

10.3. Equity and access

The contrast in vaccine access between high-income countries and Africa during both PHEICs represents one of the most consequential equity failures in recent global health history.¹⁵ During the 2022 outbreak, JYNNEOS was deployed at scale in Western Europe and North America, including pre-exposure vaccination campaigns among MSM, while endemic African countries had minimal or no access to the vaccine. During the second PHEIC driven by clade Ib in Africa, supply constraints, procurement barriers, and limited cold chain capacity continued to restrict access.^{12,18} This inequity in vaccine access is not a peripheral concern; it is a central failure that directly contributed to elevated mortality and prolonged transmission in the highest-burden setting.

Addressing this requires structural reform at the international level in vaccine procurement, technology transfer, and the application of existing mechanisms for access facilitation (including the Gavi-COVID-19 Vaccines Global Access infrastructure and the African Union vaccine procurement platform) to Mpox countermeasures. Domestic vaccine manufacturing capacity in Africa is a medium- to long-term strategic priority for pandemic preparedness more broadly.

Table 4. Comparative summary of vaccines for Mpox prevention^{1–3,24}

Vaccine	Platform	Dosing	Effectiveness evidence	Safety/contraindications	Regulatory status
JYNNEOS (MVA-BN)	Modified vaccinia Ankara; non-replicating	Two-dose SC/ID; 28 days apart; ID halving dose in supply-constrained settings	Clade IIb: ~82% effectiveness (pre-exposure, 2022 data); Clade Ib: plausible cross-protection based on shared orthopoxvirus antigens; direct effectiveness data limited.	Pregnancy, immunosuppression: not contraindicated; preferred in these groups; mild injection site reactions.	Licensed (FDA/EMA) for smallpox and Mpox; deployed in the 2022 global outbreak; constrained supply in Africa
ACAM2000	Live replicating vaccinia (NY board of health strain)	Single dose; bifurcated needle scarification	Immunological cross-protection against MPXV established; no Mpox-specific RCT data; anticipated effectiveness based on orthopoxvirus cross-reactivity.	Contraindicated in pregnancy, immunosuppression, eczema, and cardiac disease; progressive vaccinia, myopericarditis, and autoinoculation risks.	FDA-licensed for smallpox; Mpox use under expanded access, predominantly in the US strategic stockpile
LC16m8	Attenuated replicating vaccinia (Lister strain derivative)	Single dose; scarification	Effective in smallpox eradication program; limited Mpox-specific effectiveness data; pediatric safety profile favorable.	Lower adverse event rate than ACAM2000; replication attenuated; mild local reactions.	Japan-licensed; limited availability outside Japan; stockpile for national use

Abbreviations: EMA: European Medicines Agency; FDA: Food and Drug Administration; ID: Intradermal; Mpox: Monkeypox; MPXV: Monkeypox virus; MVA-BN: Modified Vaccinia Ankara–Bavarian Nordic; NY: New York; RCT: Randomized controlled trial; SC: Subcutaneous.

11. Public health response

11.1. Surveillance and case detection

Effective Mpox surveillance depends on clinical awareness among healthcare providers, accessible diagnostic capacity, functional reporting systems, and integration of community health workers and traditional care providers into notification networks. In high-burden African settings, significant under-reporting occurs due to healthcare access barriers, misclassification of Mpox lesions as other common skin conditions, stigma surrounding the disease associated with sexual transmission, and limited laboratory diagnostic capacity outside tertiary hospitals.²⁵

Syndromic surveillance, combined with community-based case finding through trained community health workers, has been deployed in some DRC provinces and has improved detection sensitivity. WHO and Africa CDC have supported mobile diagnostic capacity in affected zones. These approaches require sustained financial investment beyond emergency funding cycles.

11.2. Genomic surveillance

The detection of clade Ib and recombinant MPXV strains underscores the critical role of genomic surveillance in tracking viral evolution.^{7,17,20} Genomic surveillance enables the identification of novel lineages, the detection of resistance mutations, the characterization of transmission chains, and the early warning of variants with potentially altered biological properties. As discussed in **Section 8.3**, sequencing capacity is concentrated in high-income countries, creating systematic gaps in the surveillance data from Africa, where the most consequential viral evolution is currently occurring.

International support for in-country genomic surveillance infrastructure, including portable sequencing platforms, trained local bioinformaticians, and secure data sharing agreements, is a public health priority that cannot be deferred to inter-epidemic periods.

11.3. Risk communication and community engagement

Risk communication for Mpox is complicated by the dual transmission dynamics of the disease, involving both sexual contact in some networks and non-sexual household and zoonotic exposure in others. Messaging that overemphasizes the sexual transmission route risks stigmatizing affected communities, including MSM, commercial sex workers, and their contacts, and may reduce care-seeking behavior and diagnostic disclosure. Conversely, failure to clearly communicate transmission risks within specific high-risk networks can delay targeted

prevention.²⁵

Effective risk communication must be community-specific, culturally sensitive, evidence-based, and developed with the meaningful participation of affected communities. This is particularly important in settings where Mpox is associated with sexual behavior networks, where stigma can represent a direct barrier to testing, treatment, and contact tracing. Stigma-sensitive approaches developed for HIV programming provide useful models for Mpox risk communication, and partnerships with community-based organizations and peer health networks are essential components of an effective response.

11.4. Infection prevention and control

Standard contact and droplet precautions are recommended for suspected or confirmed Mpox cases in healthcare settings, with particular attention to the use of personal protective equipment during lesion examination, dressing changes, and aerosol-generating procedures. Healthcare workers caring for Mpox patients should be offered pre-exposure vaccination with JYNNEOS, where available.^{1–5} Patients should be isolated for the duration of the infectious period, from prodrome until all lesion crusts have separated and healed skin is present.

For household contacts of confirmed cases, contact tracing, risk stratification, and offer of post-exposure vaccination are recommended. The infectious period typically spans two to four weeks; household and close contacts should be monitored for 21 days after the last known exposure.^{5–8}

12. Priority research gaps

Despite the substantial body of literature generated by two consecutive global emergencies, important evidence gaps remain that constrain optimal clinical and public health decision-making. The following are considered priority research areas:

- Clade-specific vaccine effectiveness: Prospective evaluation of JYNNEOS effectiveness against clade Ib disease in endemic and outbreak-affected African settings is urgently required. Immunological correlates of protection against clade Ib should be characterized.
- Tecovirimat efficacy by clade and immune status: Randomized or well-controlled data on tecovirimat efficacy for clade Ib disease and for immunocompromised patients (particularly those with HIV) across all clades are lacking.
- Antiviral resistance surveillance: Systematic genotypic and phenotypic surveillance for tecovirimat resistance mutations in patients receiving this agent requires implementation, particularly in high-burden settings.

- Zoonotic reservoir identification: Definitive characterization of the primary animal reservoir species, seasonal drivers of spillover risk, and ecological interventions to reduce spillover are needed.
- Immunological correlates of protection: Understanding what immune responses (antibody titer, T-cell function, or combined endpoints) confer protection against disease and reinfection is essential for vaccine development and serological surveillance.
- Predictors of severe disease and death: Prospective cohort data identifying clinical, immunological, and virological predictors of severe Mpox and mortality across different clades and settings are required to guide triage and treatment.
- Recombinant strain characterization: Experimental characterization of the transmissibility, virulence, and countermeasure susceptibility of recombinant MPXV strains identified by genomic surveillance is needed.
- Self-limiting behavior and re-emergence cycles: A better understanding of the conditions under which Mpox transmission chains terminate spontaneously between outbreaks, and the triggers for re-emergence, would substantially improve outbreak prediction.
- Equity and access research: Operational research on barriers to vaccine uptake, diagnostic access, and care engagement in low-resource and stigmatized settings is required to optimize equitable access.

13. Conclusion

Monkeypox has evolved from a geographically circumscribed zoonotic disease into a global public health challenge characterized by sustained human-to-human transmission, viral evolution under human immune pressure, and deeply unequal access to the tools needed to prevent, diagnose, and treat it. The evidence reviewed here supports four priority messages.

First, continued viral evolution through APOBEC3-driven mutation, clade diversification, and the emergence of recombinant strains requires sustained investment in genomic surveillance, particularly in Africa, where the most active evolution is occurring and surveillance infrastructure is most constrained.

Second, equitable access to diagnostics, vaccines, and antivirals is not merely an ethical imperative; it is an epidemiological necessity. The concentration of surveillance, sequencing, and vaccine access in high-income settings, while the highest disease burden falls on African populations, is a structural failure that undermines global outbreak control.

Third, the evidence for tecovirimat, the most widely used antiviral for Mpox, is insufficient to support its routine

use without ongoing critical evaluation. The PALM007 results require recalibrating treatment frameworks, with particular attention to which patient populations, clades, and clinical scenarios may still benefit from antiviral therapy.

Fourth, the distinction between clade IIB effectiveness data for JYNNEOS and the absence of clade Ib effectiveness data must be maintained in clinical guidance. Biologically plausible cross-protection cannot substitute for direct evidence when shaping vaccination policy for an emerging epidemic.

Coordinated investment in surveillance, equitable access to countermeasures, stigma-sensitive risk communication, and targeted research to fill identified evidence gaps offers the most realistic pathway to sustainable global Mpox control.

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