Mpox emergence, epidemiology, biology, clinical features and control

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Abstract

Mpox, a zoonotic orthopoxvirus disease, has transitioned from a rare infection confined to African rainforests to a global public health threat. Originally identified in laboratory monkeys in 1958, the first human case was documented in 1970 in the Democratic Republic of Congo. Following the declaration of smallpox eradication in 1980 and the subsequent cessation of smallpox vaccination, mpox cases persisted at low levels before surging, ultimately leading to the declaration of two Public Health Emergencies of International Concern by WHO in 2022 and 2024, and the Africa CDC declaration of mpox as a Public Health Emergency of Continental Security in August 2024. Monkeypox virus (MPXV) comprises two major clades: clade I (formerly the Central African clade) subdivided into Ia and emerging Ib variants, and clade II (formerly the West African clade) also subdivided into IIa and the globally circulating IIb subclade. Recent outbreaks demonstrate enhanced human-to-human transmission, particularly through sexual networks, challenging traditional epidemiological patterns. Clinical presentation varies by clade and transmission route, ranging from classical centrifugal rash with high lesion counts to localized anogenital lesions. This Review outlines the emergency, epidemiology, biology, transmission dynamics, risk

factors, clinical characteristics, and prevention and control strategies of mpox, and identifies future priorities for addressing this ongoing global issue.

[H1] Introduction

Mpox, formerly Monkeypox, is a zoonotic viral disease historically found in Africa that has now spread globally.[1] This prompted the WHO and the Africa CDC to declare Public Health Emergencies of International Concern (PHEIC) in 2022 and 2024[2,3] , which were later terminated in September 2025 (WHO) and January 2026 (Africa CDC) following improved response capacity and a progressive decline in number of cases and deaths. Initially reported in humans in 1970 as a zoonotic disease largely affecting children in West and Central Africa[4], mpox is now associated with substantial transmission within sexual networks among younger adults globally.[5–7] The rapid evolution of the virus underscores the risk that local health threats can escalate into global public health emergencies. Prior to 2022, mpox received little attention, leaving gaps in knowledge about its epidemiology, transmission and natural history, as well as a lack of effective vaccines and therapeutics.[8,9] With the decline in cross-protective immunity from historic smallpox vaccination, over 75% of the global population is now at risk.[10] Newly identified viral clades, emerging transmission routes, links with HIV/AIDS and other sexually transmissible infections (STIs), and ongoing knowledge gaps complicate prevention and control efforts.[11,12] In this Review, we examine the emergence of mpox, its epidemiology, viral life cycle, transmission dynamics, risk factors, clinical characteristics, as well as current and future prevention and control strategies, including the landscape of therapeutics and vaccines.

[H1] History and emergence of mpox

Monkeypox virus (MPXV) was first identified in 1958 during outbreaks of a pox-like rash illness among laboratory monkeys imported from Singapore to Denmark's Statens Serum Institute.[13] Human mpox remained unknown until August 1970, when a 9-month-old boy in Basankusu, DRC (then Zaire) became the first documented human case.[14] This discovery occurred during the final phase of the global smallpox eradication program, creating immediate concern. By 1971, three additional cases were reported in Liberia and Sierra Leone, confirming human susceptibility to the virus.[15] From 1970 to the early 2000s, mpox cases in humans were mostly limited to rural rainforest areas of West and Central Africa, affecting mainly children aged 10 and under through zoonotic spillovers with minimal household transmission.[4]

In 2003, the first outbreak of mpox outside Africa occurred in the United States, showing the disease's potential for global spread through the exotic pet trade.[16] While the US outbreak was managed without deaths or human-to-human transmission, the virus continued to cause outbreaks in Africa.[4] In the DRC, mpox cases surged 20-fold from 2000 to 2016 compared to

the 1980s[4,17], ascribed to decreased population immunity after cessation of smallpox vaccination.[18]

Mpox reemerged in Nigeria in 2017 after a 39-year hiatus.[19,20] Molecular analysis suggests the virus began circulating undetected in Rivers State, South-South, Nigeria, around 2014.[21] This resurgence was marked by an unusual clusters of cases in urban areas and among adults[20,22,23], with subsequent international transmission and sporadic cases in the United Kingdom, Israel, Singapore, and the United States between 2018 and 2021.[24] The Nigeria outbreak from 2017 to 2019 also documented the first instances of sexual transmission of mpox[23,25] and its negative correlation with advanced HIV disease (AIDS).[22]

The global landscape changed drastically in May 2022 when unusual clusters of mpox were identified simultaneously in multiple non-endemic countries among gay, bisexual and other men who have sex with men (GBMSM) without direct links to Africa.[26,27] By July 23, 2022, the WHO declared the outbreak a Public Health Emergency of International Concern. The unprecedented outbreak, was caused by the same clade (IIb) responsible for the Nigerian outbreak, and was spreading via sexual contact mostly among GBMSM.[28] Whereas the PHEIC was declared over in May 2023, due to significant decline in cases globally, mpox infections continued in endemic regions in Africa, especially in the DRC.[29] In mid 2023, an unusual cluster of clade Ia mpox was reported among young adults, including GBMSM in Kenge Kwango Province, DRC.[30] This represented the first detection of mpox among GBMSM in Africa and also the first documented transmission of clade I mpox via sexual contact.[30] During the same period, clade Ia was also detected in Kinshasa, the capital of DRC, for the first time in history, spreading among adults and children in urban settlements.[30] By September 2023, a new mpox variant emerged in Eastern DRC that was named clade Ib and spread rapidly across bordering East African countries.[29,31–35] This variant transmitted more easily in urban sexual networks and among GBMSM, also spreading non-sexually in households, especially among children. This variant's enhanced transmissibility and geographical expansion prompted both the Africa CDC to declare a Public Health Emergency of Continental Security and the WHO to declare a Public Health Emergency of International Concern in August 2024.[29] As of July 27th, 2025, clade Ib mpox has been reported in at least 33 countries, including 23 countries outside Eastern African .[36] During this same period, the travel-related clade Ia has also been detected in three countries outside the Eastern Africa. Beginning in 2024, there has been a renewed emergence of clade IIb across several West African nations. Notably, Sierra Leone, Liberia, Ghana, and Guinea experienced significant increases in reported cases in 2025, while The Gambia documented its first case in July 2025.

This historical trajectory shows mpox's progression from a rare zoonotic disease to a globally significant public health issue, emphasizing the interactions between pathogen ecology, human behavior, and waning cross protective immunity following cessation of smallpox vaccination programs. Figure 1a outlines the epidemiological timelines of mpox outbreaks since the first animal outbreak in 1958. Figure 1b outlines the global spread of mpox outbreaks from 1970 to 2025.

[H1] MPXV life cycle

Monkeypox virus (MPXV) belongs to the *Orthopoxvirus* genus within the *Poxviridae* family, alongside variola virus (smallpox), vaccinia virus (VACV), and cowpox virus.[37,38] MPXV is a large (200–250 nm), brick-shaped, enveloped virus with a linear double-stranded DNA genome (~197 kb) encoding approximately 190–200 proteins (Figure 2a).[37,38] Unlike most DNA viruses, *Poxviridae*, including MPXV, replicates entirely within the host cell cytoplasm using virus-encoded enzymes for DNA replication and mRNA synthesis (Figure 2b). [39]

The life cycle of MPXV has primarily been elucidated through research involving related Orthopoxviruses, particularly VACV.[39–42] Infection begins when MPXV binds to host cell surface receptors — most notably glycosaminoglycans (GAGs) — utilizing envelope proteins such as A27 and H3, while D8 and A26 further contribute to host specificity and recognition.[43,44] The virus exploits multiple entry pathways: it may fuse directly with the host cell membrane to deliver the viral core into the cytoplasm, or it may be internalized through macropinocytosis or clathrin-mediated endocytosis.[39,40,42] In the latter case, acidification within the endosome is thought to prime the core for subsequent cytoplasmic activity, including the initiation of early gene transcription.

Crucially, poxviruses package a complete transcriptional apparatus within the virion core, including a multi-subunit DNA-dependent RNA polymerase, early transcription factors, and mRNA-capping enzymes. This enables early gene transcription to commence immediately upon cytoplasmic entry, while the viral genome remains encapsidated within the intact core. Early mRNAs are extruded through pores in the core and are translated in the surrounding cytoplasm. The products of early gene expression promote viral DNA replication, modulate host immune responses, and manipulate host cell functions to favor a productive infection. Complete uncoating of the core occurs only after early gene expression has initiated, releasing the viral genome for subsequent replication.

DNA replication occurs within specialized cytoplasmic structures termed viral factories, where MPXV-encoded proteins — including DNA polymerase, primase, and helicase — carry out genome replication independently of the host's nuclear machinery. [37,38] Following DNA replication, intermediate and late classes of genes are sequentially expressed. Intermediate gene products include transcription factors required for late gene expression as well as some structural proteins. Late gene products encompass the majority of virion structural and envelope proteins, as well as enzymes and early transcription factors that will be packaged into progeny virions to enable immediate transcription upon subsequent infection.[37,38]

During the assembly phase, viral components are packaged into immature virions that mature into intracellular mature virions (IMVs). Some of these IMVs can acquire additional envelopes from the trans-Golgi network or early endosomes, forming wrapped virions (WVs), also known as intracellular enveloped virions (IEVs). The IEVs facilitate localized cell-to-cell spread, allowing the virus to efficiently infect neighboring uninfected cells. Conversely, cell-associated extracellular viruses (CEVs) are also formed and are characterized by their association with actin tails, promoting further localized spread. Extracellular enveloped viruses (EEVs), which are released from infected cells, play a crucial role in the broader dissemination of the virus through body fluids, enabling it to spread more widely within and between hosts.

MPXV progeny can exit the host cell via two principal routes: mature virions can be released through cell lysis, leading to local tissue damage and inflammation, whereas wrapped virions

use actin-based and microtubule-driven motility to deliver particles to neighboring uninfected cells, promoting direct cell-to-cell spread.

Throughout this cycle, MPXV employs a variety of immune evasion strategies.[45–47] The virus encodes proteins that antagonize type I and II interferon signaling, inhibit apoptotic pathways to prolong cell viability, and downregulate MHC class I molecules, thereby diminishing the ability of infected cells to present viral antigens to cytotoxic T lymphocytes. This array of tactics ensures successful replication, dissemination, and persistence of the virus within the host, while simultaneously impeding effective immune clearance.

[H1] Phylogeny, evolution and genetic adaptations

[H2] Phylogenetic classification

MPXV is classified into two major clades with substantial differences in virulence and transmissibility (Figure 3a).[48,49] Figures 3b and 3c outline the global epidemiology of mpox clades and subclades. Clade I (formerly Congo Basin clade) predominantly circulates in Central Africa and is subdivided into clades Ia and Ib.[50] Clade I has historically been associated with higher virulence (case fatality rate (CFR) 2–10%), more severe disease, and less efficient human-to-human transmission (basic reproduction number (R_0) <1). [50–52] However, the emerging clade Ib (2023–2025) demonstrates enhanced transmissibility (R_0>1), suggesting viral evolution toward more efficient spread.[31,53] Clade II (formerly West African clade), subdivided into IIa and IIb, typically causes milder disease (CFR <1%).[49] The 2022–2023 global outbreak involved clade II acquiring additional mutations associated with novel transmission patterns through sexual networks, challenging previous assumptions about MPXV transmissibility.[51,54]

The differences in transmissibility and virulence between MPXV clades are primarily due to genetic variations in terminal genome regions that encode immunomodulatory proteins and factors that determine host range, with specific genes like D14L, OPG195, B14R, and B10R playing critical roles in determining these differences. [51,52,55] The immunomodulatory genes encode proteins that interfere with host immune responses, including inhibitors of cytokines, chemokines, and complement proteins. Clade I viruses possess more intact immunomodulatory genes, potentially explaining their enhanced virulence compared to clade II. [51,52,55] This phylogenetic classification is pivotal for understanding the epidemiological patterns observed in outbreaks, and for developing targeted public health responses to distinct viral lineages.

[H2] Evolution and adaptation

MPXV demonstrates a dynamic pattern of evolution, marked by the divergence of clade I and clade II, which are distinguished by over 900 single nucleotide polymorphisms (SNPs) according to phylogenetic analyses of historical and more recent isolates from the early 1970s up to the 2017 Nigeria outbreak.[54,56] Clade I, mostly circulating in Central Africa, exhibits higher virulence and retains a larger repertoire of immune evasion genes, such as C3 complement inhibitors and interferon antagonists. Importantly, clade Ib which emerged in September 2024 within Central Africa as a branch of clade I, shows further genetic divergence, gene truncations, and recombination events. Genetic data from the 2023–2025 outbreaks in Central Africa indicate that clade Ib is defined by a unique set of mutations, possibly contributing to changing epidemiology and clinical profiles.[31]

Clade II, which includes most of the viruses implicated in recent global outbreaks, has evolved into two principal subclades: IIa and IIb. Clade IIa is typically associated with localized outbreaks and milder disease, whereas clade IIb is the driving lineage behind outbreaks in Nigeria (2017), international exportations (2018–2021), and the widespread 2022–2023 multicounty epidemic. Genetic distances, measured as SNP accumulation, show approximately 50–60 SNP differences between the 2017 Nigerian clade IIb viruses and those from the 2022–2023 outbreaks, reflecting ongoing, rapid microevolution under serial human transmission.[54,56,57]

Within clade IIb, further diversification is observed, with sub-lineages now designated alphabetically as A through F. For example, sub-lineage A dominated early in the 2022 outbreak, whereas sub-lineages such as B and C emerged during the global expansion, each accumulating additional SNPs and signature changes in genes associated with viral entry, host adaptation, and modulating immune responses. The continued appearance of new sub-lineages — including up to F in some recent analyses — demonstrates not only mutation but also occasional gene loss and recombination, resulting in viruses with altered epidemiological traits.[54]

A defining feature of recent MPXV evolution, particularly for clade IIb strains, is the pervasive influence of host APOBEC3 cytidine deaminases. These enzymes introduce a mutational signature characterized by GA→AA and TC→TT transitions, a phenomenon associated with human-to-human transmission cycles. Analyses of genomes from the 2022–2023 outbreak have revealed over 40–50 additional APOBEC3-linked SNPs when compared with strains circulating in Nigeria in 2017.[54,57,58] Notably, studies from the DRC highlight an increasing proportion of genomes in both clade Ia (68%) and Ib (72%) displaying these APOBEC3-driven mutations, supporting the idea that prolonged human-to-human transmission is shaping viral evolution more than continued zoonotic spillover.[31,56,59]

Together, these genetic adaptations of MPXV — across clades, lineages, and sub-lineages — underscore its flexibility and the complex interplay between mutation, immune escape, host adaptation, and transmission mode. The rapid rise of new groups within clade I, and multiple sub-lineages within clade IIb (including A through F), signals the ongoing risk of further increases in transmissibility or shifts in disease presentation. Robust genomic surveillance and real-time molecular epidemiology will remain essential for understanding the direction and public health impact of this adaptive evolution.

[H1] Natural reservoir

Despite decades of research, the definitive natural reservoir of MPXV remains inadequately characterized. A meta-analysis of 56 studies published up to 2022 revealed a pooled prevalence of MPXV at 16% in non-human primates, 8% in rodents, and 1% in shrews[60], indicating a significant presence within various animal populations. The first successful isolation of MPXV in wild animals occurred in 1985 from a wild rope squirrel in the DRC during disease ecology studies.[61] This finding, alongside the epidemiological data from the 2003 U.S. mpox outbreak,[16] provides strong evidence that rodents may serve as natural reservoirs for MPXV.

Notably, the second isolation of MPXV was reported in wild monkeys in Côte d'Ivoire (Ivory Coast),[62] although non-human primates are believed to act as incidental or secondary hosts for the virus. Consequently, the term 'monkeypox' reflects the initial discovery of MPXV in primates but has contributed to misconceptions regarding the disease's zoonotic

origins and its naming. In response to the global outbreak of mpox in 2022 and to mitigate stigmatization, the WHO adopted 'mpox' as a new designation in November 2022.[63] This name change aims to reduce barriers to testing and care while addressing the inaccurate association of the virus with Africa.

Despite this update, the term 'Monkeypox virus' (MPXV) continues to be used as the name for the causative agent of mpox — a misnomer that has become entrenched in the literature. The presence of MPXV in diverse animal species across Africa, particularly in areas endemic for mpox, suggests that the virus circulates within a complex ecological network involving multiple species. Several challenges hinder the identification of MPXV's definitive reservoir, including difficulties with animal sampling, variances in viral shedding, isolation techniques, and the evolving patterns of transmission from zoonotic sources to human-to-human spread.

[H1] Transmission dynamics

MPXV is transmitted through direct and indirect exposure to infectious viral particles from animals, humans, and the environment (Figure 4a). Animal to human spillover events occur through handling, skinning, butchering, preparing or consumption of infected animals, or from bites or scratches from infected animals. Suspected human to animal transmission of MPXV was reported during the 2022 global outbreak in domestic animals (two dogs), one each in France and a Brazil, but the transmission dynamics are more suggestive of environmental contamination. [64] A US study examining potential human to household pets transmission found viral DNA in some animals (17% of dogs and 11% of cats) but no evidence of live virus or antibody development, suggesting that while pets are exposed to the virus, actual infection appears uncommon and the health risks to pets and transmission risks from pets to others are likely minimal. [65]

Human-to-human transmission usually follows close physical contact through skin or sexual contact, respiratory droplets following prolonged face-to-face contact, and vertical transmission through transplacental or perinatal exposure. Skin-to-skin contact is the primarily mode of transmission observed since 2022 and could follow both sexual and non-sexual contact. Airborne transmission is possible as suggested by animal models[66,67], prior human outbreaks without close contact[68] and detection of MPXV in air samples.[67] However, this route appears to play a minor role in real-world transmission observed with 2022 clade 2b mpox compared to direct contact with lesions and bodily fluids.[67]

Mpox also spreads through contact with contaminated surfaces and objects (fomites) in healthcare, household, laboratory and tattoo or piercing settings.[69] Viral DNA has been detected on bed linens, clothing, bathroom surfaces, medical equipment, tattoo instruments, and animal cages, and the virus can remain viable for up to 15 days, particularly on porous materials.[69,70]

Excretion of infectious virus occurs in lesions (mucosal or dermal), salivary-respiratory secretions, and other bodily fluids, including semen. Entry into the host occurs through mucous membranes like the eyes, nose, mouth, and genitals, as well as via broken skin. The route of viral entry may also determine routes of virus spread and excretion, especially if the viral infection remains localized. Skin lesions are most infectious with highest viral loads, remaining contagious until fully healed (2–4 weeks).[71] Viable virus can persist in semen for up to 39 days (median), with some cases reaching 12 weeks. Anorectal secretions and

oropharyngeal fluids frequently contain infectious virus.[71] MPXV DNA has been detected in blood, urine, feces, and vaginal secretions, though with lower viral loads.[71,72] Presymptomatic transmission may be a component of mpox spread, or may also be a reflection of the emergence of initial lesions in mucosal or the ano-genitourinary system, and a lack of recognition of the lesions. Some studies model that 27–50% of paired cases result from transmission during a presymptomatic period[73], occurring 1–4 days before recalled symptom onset.[69 74]

Mpox's epidemiological parameters define its spread patterns across populations. The incubation periods may range from 1–40 days, with most cases falling between 3–17 days.[73,75–77] Studies have shown that the incubation period could be shortened by invasive exposure (scratch or bites from animals),[78] and direct inoculation (sexual or anogenital contact, and tattoos or piercings) when compared to non-invasive exposures. [79,80] Serial intervals average 8–15 days depending on context, whereas generation times span 6–18 days. The basic reproduction number (R_0) varies drastically by transmission network, from near-zero to above 7 in high-risk settings. Historically, clade I exhibits longer parameters than clade IIb: longer incubation periods (9.9 vs 7.6 days), extended serial intervals (10.1–18.4 vs 8.3 days), and slower generation times (11.3–17.2 vs 12.5 days).[75] This may reflect a different route of exposure and transmission. The 2022 outbreak maintained similar incubation periods to previous outbreaks but showed shortened serial intervals.[77] The emerging clade Ib combines clade I's slower parameters with concerning R_0 values above epidemic threshold (1.08–1.18), demonstrating enhanced human-to-human transmission, particularly in mining regions of DRC.[75] The high transmission rates characterizing both the 2022 clade IIb global outbreak and recent clade Ib spread in DRC and Eastern Africa likely reflect shared environmental and behavioral determinants — including urban density, intimate contact patterns, and network amplification — rather than clade-specific differences in viral transmissibility.

[H1] Risk factors for mpox transmission and infection

Mpox transmission risk varies by viral clade and exposure context. Zoonotic infection occurs primarily through contact with infected wildlife (rodents, primates), with hunters and animal handlers at significantly higher risk.[81] Secondary household attack rates range from 0.7% in clade IIb [28] to 8% in clade I [82], with risk highest among those sharing sleeping spaces or handling contaminated materials.[82] The 2022 global outbreak demonstrated efficient sexual transmission, with multiple partners, condomless sex, and sex venue attendance as significant risk factors.[79] The emerging clade Ib affects broader demographics (48% children, 34% men, 18% women)[32] and shows enhanced transmissibility in both sexual and non-sexual contexts, particularly in crowded refugee settings with $R^0>1$.[31,32]

A comprehensive 2023 systematic review and meta-analysis analyzing 31 studies encompassing 148,499 mpox cases identified hierarchical risk factors including animal contact (odds ratio (OR)=5.61, 95% confidence interval (CI): 2.03–15.56), HIV infection (OR=4.46, 95% CI: 2.82–7.07), close contact with infected individuals (OR=2.39, 95% CI: 1.75–3.27), MSM status (OR=2.18, 95% CI: 1.58–3.01), multiple sexual partners (OR=1.61, 95% CI: 1.24–2.09), other STIs (OR=1.76, 95% CI: 1.10–2.81), and unprotected sexual activity (OR=1.53, 95% CI: 1.03–2.28), while prior smallpox vaccination demonstrated significant protective effects (OR=0.24, 95% CI: 0.15–0.39).[83]

Mpox transmission is also fundamentally linked to environmental disruption in endemic African regions.[84–86] Deforestation and land-use changes increase human–animal contact at rainforest edges, facilitating zoonotic spillover from rodent or primate reservoirs. Bushmeat hunting, handling and consumption create direct transmission pathways. Seasonal rainfall patterns influence reservoir behavior and virus viability. Habitat fragmentation forces infected wildlife closer to human settlements, perpetuating transmission cycles.

Beyond environmental drivers, socioeconomic determinants play a central role in shaping mpox transmission dynamics in endemic regions by influencing patterns of exposure, transmission, and outbreak control.[32,83,85,87,88] Poverty and food insecurity increase reliance on bushmeat hunting and consumption, elevating the risk of zoonotic spillover.[85] Weak healthcare systems in resource-limited settings delay case detection, diagnosis, and isolation, undermining effective containment.[88] Population displacement related to conflict and rapid urbanization further intensify transmission by creating overcrowded living conditions and altering contact networks.[87] Limited access to clean water, sanitation, and hygiene infrastructure facilitates pathogen persistence, while low health literacy can delay symptom recognition and healthcare-seeking behaviour.[85] Together, these interacting socioeconomic and environmental factors create conditions that can enable both sustained human-to-human transmission and recurrent spillover events.

[H1] Clinical characteristics

[H2] Natural history of mpox

Following exposure to MPXV, an incubation period ranges from 3 to 17 days (average 5–8 days), after which individuals may develop asymptomatic (detectable by serology or PCR of mucosal swabs) or symptomatic disease (Figure 4b). Symptomatic disease ranges from mild or paucisymptomatic to severe (WHO classification based on mobility, rash count, and systemic involvement).[89,90] Classical mpox begins with constitutional symptoms (fever, malaise, headaches) and lymphadenopathy, followed 1–3 days later by a skin or mucosal rash progressively evolving from macules to papules, vesicles, pustules, crusting, and healing over 2–4 weeks.[91–93] During the 2022 outbreak, systemic symptoms frequently occurred concurrently with or after rash onset.[28] Healed lesions may result in scarring or pigmentation changes typically resolving within 3–12 months.[94] Reinfection has been reported in a healthcare worker in Nigeria prior to the 2022 global outbreak[95] and among GBMSM during the 2022 outbreak.[96,97] Cases of reinfection are associated with milder symptoms, and shorter duration of illness.

[H2] Clinical features across mpox outbreaks

Mpox presents with distinct clinical patterns across different outbreaks, influenced by virus clade, transmission routes, and host factors (Table 1). Initial animal outbreaks (1958–1968) first documented the characteristic vesiculopustular rash, though human cases were not documented. Historical clade I outbreaks in DRC presented with severe disease characterized by high lesion counts (mean, 370), prominent lymphadenopathy, and respiratory involvement, with case fatality rates of 4–12% .[4,91,92] By contrast, historical clade II outbreaks

386 featured moderate systemic symptoms and lower mortality (1–3.6%).[20,90] The 2003 U.S.
387 clade IIa outbreak uniquely showed local inoculation sites with satellite lesions but no
388 fatalities.[16] Recent outbreaks exhibit evolving patterns: the 2022–2023 global clade IIb
389 outbreak demonstrated predominantly anogenital lesions with lower prodromal symptom
390 frequency and mortality (<0.1%),[28,98] whereas the 2023–2025 clade Ib outbreak shows mixed
391 presentations with variable severity (CFR 0.7% overall, 4% in infants)[33,99]

392 [H2] Complications, sequelae and outcomes of mpox

393 In immunocompetent individuals, mpox typically resolves spontaneously within 2–4 weeks,
394 though complete lesion healing may be prolonged, particularly with ulceration and mucosal
395 involvement. Virus clearance patterns vary by site, with persistent detection of nucleic acid
396 occasionally observed in oropharyngeal samples.[71,100]

397 Complications vary by population demographics and anatomical exposure sites. Secondary
398 bacterial infections affect 15–30% of cases, particularly with confluent or necrotizing lesions
399 in resource-limited settings.[91,101,102] Ocular complications range from conjunctivitis (10–
400 15%), keratitis (2–4%), to vision loss (1–3%), particularly when corneal infection occurs.[103]
401 Severe complications, though infrequent, include sepsis (1–3%), parotitis (0.5–1%), proctitis
402 (14–36% in sexually transmitted cases), rectal perforation (<0.5%), epiglottitis (<0.5%),
403 lymphadenopathy causing airway compromise (0.5–1%), and neurological involvement like
404 meningitis and encephalitis (<0.5%). [22,28,91,98,102,104]

405 Long-term sequelae include scarring (13–48%), skin discoloration (18–32%), and
406 psychosocial consequences (24–50%)[22,105–107] . Case fatality rates differ by clade: 4–12% for
407 clade I versus <0.1% for clade II, with recent data showing improved outcomes: 1.7–4% for
408 clade Ia and 0.7% for clade Ib (4% in infants) with adequate care.[31–33,52,55,99] Groups at
409 increased risk include infants, severely immunocompromised individuals, and pregnant
410 women, with pregnancy-related complications including miscarriage, fetal loss, and
411 congenital or neonatal mpox.[108,109]

412 [H1] Prevention and control of mpox

413 [H2] Supportive care

414 Management primarily focuses on symptom control through comprehensive supportive
415 measures. Pain management with appropriate analgesics remains foundational, with WHO
416 guidelines recommending a stepwise approach from acetaminophen or non-steroidal anti-
417 inflammatory drugs (NSAIDs) to opioids for severe pain.[110] Antibiotics should be reserved
418 for treating secondary or concurrent bacterial infections within local and institutional
419 evidence-based antimicrobial stewardship guidelines. Adequate fluid replacement therapy
420 prevents complications from dehydration, particularly when accompanied by prolonged fever
421 or dysphagia. Topical care for skin lesions includes keeping lesions clean and dry, with
422 petroleum jelly application to prevent adhesion to clothing and saline soaks for painful
423 genital or oral lesions. Psychological support addressing stigma, isolation concerns, and
424 disease anxiety should be integrated into care plans.[110]

[H2] Specific therapeutics

Antivirals and immunotherapy are currently being explored in the treatment of mpox (Table 2) tecovirimat (TPOXX) inhibits the viral F13 protein (also known as VP37), preventing viral envelope formation and extracellular virion release.[111] Despite promising preclinical studies and animal data showing dramatic survival improvements in lethal MPXV models[112,113], two recent randomized controlled trials — PALM-007 for clade I and STOMP for clade II — found no significant reduction in time to lesion resolution.[114,115] Nevertheless, tecovirimat often remains recommended for severe disease, immunocompromised individuals, and pediatric cases. Cidofovir and its oral prodrug brincidofovir inhibit viral DNA polymerase but there is limited clinical data, and cidofovir can cause nephrotoxicity.[111] Brincidofovir can cause hepatotoxicity, limiting its widespread use, although participants are being recruited to a clinical trial in the DRC. [111] Vaccinia Immune Globulin Intravenous (VIGIV) has been used in severe cases, particularly for ocular involvement and in immunocompromised individuals, though efficacy evidence is limited to case series.[116]

[H2] Emerging treatments for mpox

Emerging therapies include NIOCH-14, an experimental compound with promising anti-orthopoxvirus activity demonstrated in animal models. The active metabolite of NIOCH-14 is ST-246 (tecoviromat) and may be a candidate for further clinical testing. Other potential treatments explored in preclinical studies include ribavirin and 3-deazaneplanocin A, both of which have shown effectiveness in reducing poxvirus replication.[117] Nanotechnology-based therapies, such as silver nanoparticles (AgNPs), are under investigation for their antiviral effects and ability to enhance drug delivery.[117] Human monoclonal antibodies targeting the conserved A35 protein of MPXV demonstrate potent therapeutic efficacy in preclinical models and correlate with improved clinical outcomes in patients, representing a promising new class of mpox treatments.[94] With few available treatments for mpox, ongoing clinical trials are essential to improve efficacy, create new therapies, and address emerging variants and drug resistance.

[H2] Vaccination

Modified vaccinia ankara (MVA) (JYNNEOS/IMVANEX/IMVAMUNE) is a non-replicating vaccine administered in two doses, 28 days apart.[118] Real-world effectiveness estimates range from 35–86% after one dose and 66–90% after two doses[118], with breakthrough infections typically presenting as milder disease.[119] Intradermal administration (one-fifth dose) demonstrates comparable immunogenicity to standard subcutaneous administration, extending limited supplies.[118] LC16m8 (KM Biologics) is a minimally replicating vaccine administered as a single dose. A recent human and animal study suggest favorable clinical efficacy and safety profile,[120] with effectiveness evaluation ongoing in DRC outbreaks.[121] ACAM2000, a fully replicating second-generation vaccine, offers good immunogenicity but carries increased risk of adverse effects, including myopericarditis (1 in 175 cases) and progressive vaccinia in immunocompromised individuals.[121–123] mRNA vaccines represent a promising next-generation platform for mpox prevention by leveraging synthetic messenger RNA encoding specific viral antigens, instructing host cells to produce viral proteins and elicit immune responses.[124]

[H2] Public health measures

Effective control strategies include enhanced surveillance with PCR testing of suspicious lesions, case isolation during infectious periods (typically 2–4 weeks until all lesions have crusted), comprehensive contact tracing with monitoring for 21 days, and ring vaccination of close contacts within 4 days of exposure (optimally) or up to 14 days to reduce disease severity.[125] Risk communication targeting affected communities should address transmission routes, symptoms, testing availability, vaccine hesitancy and stigma reduction. During the global outbreak, effective risk communication, leading to behavior change, was considered the main driver and a crucial element in the decline of mpox epidemic in many countries.[126–128] International coordination for outbreak response through surveillance data sharing, vaccine and therapeutic access, and the use of standardized case definitions enhances global preparedness. Targeted prevention strategies for high-risk populations should consider regional transmission patterns and cultural contexts.

[H1] Future directions and challenges

The transformation of mpox from a neglected zoonotic disease to a global health threat underscores the dynamic nature of emerging infectious diseases. Recent outbreaks, particularly of the severe clade I variant in Central Africa and the emergence of clade Ib in Europe and North America, highlight how quickly local pathogens can adapt and cross borders. This evolving epidemiological landscape raises substantial concerns about the global endemicity of mpox. As long as viral transmission continues and the global population remains susceptible due to waning protective immunity, the potential for the re-emergence of new threats linked to mpox is a pressing reality.

The declaration of mpox as a public health emergency by the WHO and the Africa CDC has led to increased investments in surveillance, diagnosis, vaccination, and public health responses.[129] However, these gains may not be sustainable without strong local ownership, ongoing support, and international solidarity, particularly in resource-constrained African regions with weak health systems.

Persistent inequalities in access to vaccines remain a critical barrier to mpox control in Africa.[88] Despite bearing the highest burden of disease, African countries received less than 2% of the global mpox vaccine supply during the 2022–2024 period. Several factors contribute to this disparity: (1) limited global vaccine manufacturing capacity concentrated in high-income countries; (2) procurement challenges including high costs and competing global demand; (3) inadequate cold-chain infrastructure for vaccine storage and distribution; (4) regulatory delays in vaccine approval in some African nations; and (5) insufficient funding for vaccine purchase and deployment programs. The Africa CDC's Continental Mpox Response Plan 2.0 has prioritized vaccine access equity, advocating for dose-sharing agreements, regional vaccine stockpiles, technology transfer for local manufacturing, and innovative delivery strategies such as intradermal fractional dosing to extend limited supplies. However, translating these strategies into actual vaccine availability requires sustained international commitment and resource mobilization.

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To effectively combat mpox, especially in Africa, critical research and programmatic shifts are urgently needed (Box 1). A comprehensive approach should prioritize evaluating transmission dynamics, particularly asymptomatic spread and sexual transmission. Understanding these factors will enhance knowledge of disease outcomes and inform the efficacy of treatments and vaccines.

The continued evolution of MPXV necessitates real-time genomic surveillance to detect emerging variants. Programmatically, integrating mpox prevention and care with established HIV and STI and sexual health programs is crucial, given the overlapping epidemics and transmission routes. This leverages existing infrastructure and improves care for coinfected individuals.

Strengthening public health responses also requires the integration of a One Health approach that encompasses human, animal, and environmental health surveillance to mitigate zoonotic spillover. Strategies should focus on building local manufacturing capacity for diagnostics and vaccines, implementing targeted awareness campaigns to address stigma within communities, and ensuring equitable access to medical countermeasures through global collaboration and dedicated funding.

The true burden of mpox is often underestimated due to inadequate diagnostics and surveillance tools, which underscores the need for developing affordable and field-ready solutions. Additionally, longitudinal studies are essential to comprehend transmission dynamics and the ecology of disease reservoirs and hosts in endemic regions.

Despite the WHO's declaration that the PHEIC has ended, endemic infections and sporadic outbreaks continue, particularly across Africa.[129] Without sustained political commitment and investment in public health infrastructure, mpox will continue to pose a substantial threat to global health. As long as vaccination coverage remains limited, and disparities in public health responses persist between wealthy and poorer nations, the risk of mpox evolving into a more significant global health challenge will remain.

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Author contributions

All authors researched data for the article. All authors contributed substantially to discussion of the content. D.O. wrote the article. All authors reviewed and/or edited the manuscript before submission.

Competing interests

The authors declare no competing interests.

Peer review information

Nature Reviews Microbiology thanks Nicaise Ndembi and the other, anonymous, reviewers for their contribution to the peer review of this work.

Display Items

Table 1: Clinical characteristics and outcome of mpox across various animal and human outbreaks (1958–2025)

Outbreak type	Primary clinical features	Case fatality rate	Refs.
Animal outbreaks (1958–1968)	Fever, rhinitis, lymphadenopathy (mandibular, inguinal), vesiculopustular rash progressing from macules to papules, vesicles, pustules, and crusts over 2–3 weeks. Lesions concentrated on face, limbs, palms, soles, and tail. Severe conjunctivitis, respiratory distress, and prostration in fatal cases. Asymptomatic infections estimated at 10–20% in exposed primates based on serological surveys.	Mortality rates of 30–60% in captive primates	[60,130–132]
Historical clade I (DRC)	Febrile prodrome (1–4 days), centrifugal rash distribution, high lesion counts (mean, 370), prominent lymphadenopathy. Early-onset fever, headache, myalgia, severe malaise, chills, profound prostration. All lesions progress synchronously through stages.	4–12% historically	[89,91,92,133]
Clade IIa U.S. outbreak (2003)[16,101,134,135]	Lesions often at animal exposure site, mixed lesion stages simultaneously. Fever, chills, lymphadenopathy, headache, sweats, persistent fatigue.	0% (no deaths reported)	[16,101,134,135]
Clade IIb Nigeria (2017–2018)	Vesiculopustular rash, fever, pruritus, regional lymphadenopathy, body aches, sore throat. Typical lesion count: 30–150. Genital lesions prominent (68%), including in children. Higher prevalence of secondary bacterial infections (22%).	3.6% (predominantly in people living with HIV)	[19,20,22,23]
Clade IIb Global (2022–2023)	Lower prevalence of prodromal symptoms, site-specific lesions (genital, perianal, oral), lower lesion counts (median 8, range 1–214). Proctitis (25% of MSM), pharyngitis, fever, myalgia.	<0.1% overall (higher in advanced HIV)	[28,74,79]
Clade Ia (2023–2024)	Classical presentation with fever, myalgia, headache, oral rash, genital rash, mostly preceding centrifugal skin rash.	1.7-4% with adequate supportive care	[136,137]
Clade Ib (2023–2025)	Both localized (genital) and generalized presentations observed. Fever, lymphadenopathy, headache, myalgia. Initial rash facial in children, genital in adults.	0.7% overall (4% in children <1 year)	[31–35,75]

914

915 Table 2: Overview of vaccine and therapeutics for mpox treatment and prevention

Name	Type	Target or mechanism	Clinical evidence and approval	Indications	Limitations and safety
Tecovirimat (TPOXX)	Antiviral	Inhibits invitro F13 (also known as VP37) protein; blocks virion formation	Approved for smallpox; Emergency use for mpox; RCTs (PALM-007/STOMP)	Severe/progressive mpox, immunocompromised, children	No clear clinical benefit in time to lesion resolution in RCTs; generally, well tolerated
Cidofovir	Antiviral	DNA polymerase inhibitor	FDA approved (for human cytomegalovirus); off-label for mpox	Severe/progressive mpox	Nephrotoxicity, intravenous only
Brincidofovir	Antiviral (oral prodrug)	DNA polymerase inhibitor	FDA for smallpox; limited mpox data	Severe/progressive mpox	Hepatotoxicity, limited clinical utility
Vaccinia immune globulin intravenous (VIGIV)	Passive immunotherapy	Neutralizes poxviruses, supports viral clearance	FDA/CDC for vaccinia complications, used in severe mpox/ocular disease	Severe/progressive/ocular mpox in immunocompromised	Limited efficacy evidence, intravenous infusion
Modified vaccinia ankara (MVA-BN, JYNNEOS, IMVANEX IMVAMUNE)	Vaccine (3rd gen, non-replicating)	induces Orthopoxvirus-specific immunity	Licensed and WHO-prequalified; real-world effectiveness (35–90%)	Pre- and post-exposure prophylaxis (PEP) in high-risk groups	Mild local/systemic side effects, safe in immunocompromised, potential short-lived immunity
LC16m8	Vaccine (attenuated, minimally replicating)	Induces *Orthopoxvirus* immunity	Licensed in Japan; DRC evaluation ongoing	Potential PEP in endemic settings	Safety in immunocompromised needs assessment
ACAM2000	Vaccine (Second generaiton, replicating)	Induces immunity via live Vaccinia virus	Licensed; used previously for smallpox	High-risk occupational settings	Myopericarditis risk, contraindicated in immunocompromised

916 FDA, Food and Drug Administration; CDC, Centers for Disease Control and Prevention

Figure legends

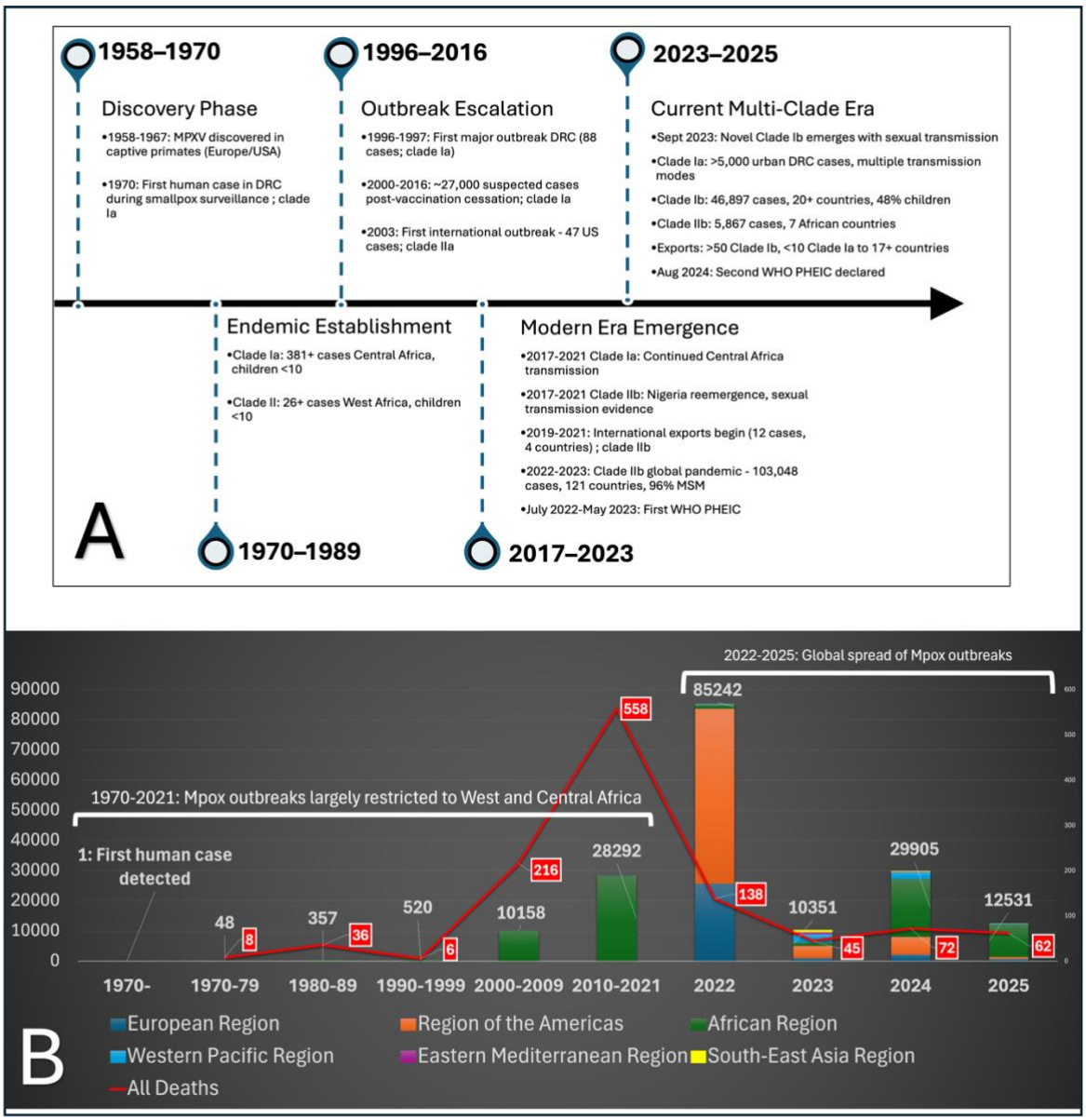

Figure 1: Global evolution and epidemiological shift of mpox. a| A timeline of the global evolution of mpox from its discovery to the present day (1958–2025). The timeline is divided into key eras: discovery (1958–1970), endemic establishment (1970–1989), outbreak escalation (1996–2016), modern era emergence (2017–2023), and the current multi-clade era (2023–2025), detailing major milestones and outbreaks within each period. b| The global spread of mpox outbreaks from 1970–2025, showing the number of cases per period by WHO region. The chart illustrates that outbreaks were largely confined to Africa until the 2022–2025 period, which marks a dramatic global surge in cases, particularly in the Region of the Americas and European Region.

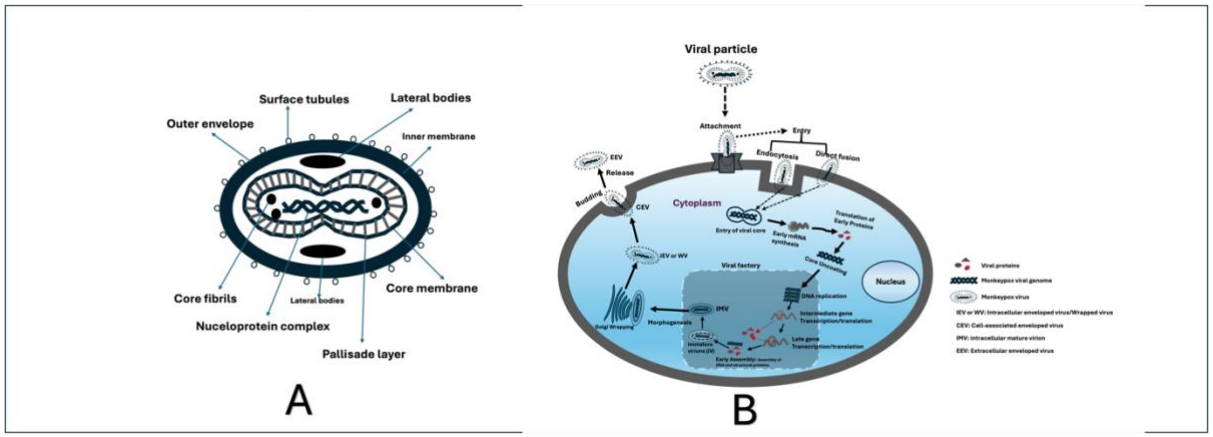

Figure 2: Virion structure and viral life cycle. a| Structural organization of the monkeypox virus (MPXV) virion. The mature infectious particle displays the characteristic brick-shaped morphology of orthopoxviruses with approximate dimensions of 200–250 nm. The viral structure consists of multiple concentric layers: outer envelope, a lipid bilayer derived from host cell membranes containing viral glycoproteins; surface tubules, proteinaceous structures projecting from the outer surface involved in host cell attachment and entry; lateral bodies, electron-dense protein masses of unknown function flanking the viral core; inner membrane, an additional lipid bilayer surrounding the nucleoprotein complex; palisade layer, a protein layer beneath the inner membrane; core membrane, the innermost membrane enclosing the viral genome; core fibrils, DNA-protein complexes containing the linear double-stranded DNA genome (~197 kb) associated with viral enzymes and transcription factors; nucleoprotein complex, acentral structure containing the viral genetic material and associated proteins required for early viral replication. This complex architecture enables the virus to survive in the extracellular environment and facilitates efficient infection of susceptible host cells. b| The life cycle of MPXV. MPXV enters host cells through two main pathways: endocytosis (left) or direct membrane fusion (right), delivering the intact viral core into the cytoplasm. Early mRNA synthesis occurs immediately within the intact core using pre-packaged viral RNA polymerase and transcription factors. Early mRNAs are extruded through core pores and translated in the cytoplasm to produce early proteins that facilitate viral DNA replication and manipulate host cell functions. Core uncoating follows early protein synthesis, releasing the viral genome into the cytoplasm. DNA replication occurs within specialized cytoplasmic structures called viral factories, which also house sequential intermediate and late gene expression programs. Intermediate gene products include transcription factors required for late gene expression, while late gene products encompass structural proteins, envelope components, and early transcription factors that are packaged into progeny virions. Viral assembly begins with the formation of immature virions (IV) that mature into intracellular mature virions (IMV). Some IMVs acquire additional membrane envelopes through Golgi wrapping to form intracellular enveloped virions (IEV) or wrapped virions (WV). These mature into cell-associated enveloped virions (CEV) that can facilitate cell-to-cell spread via actin-based motility or be released as extracellular enveloped virions (EEV) for systemic dissemination. IMVs can also exit through cell lysis.

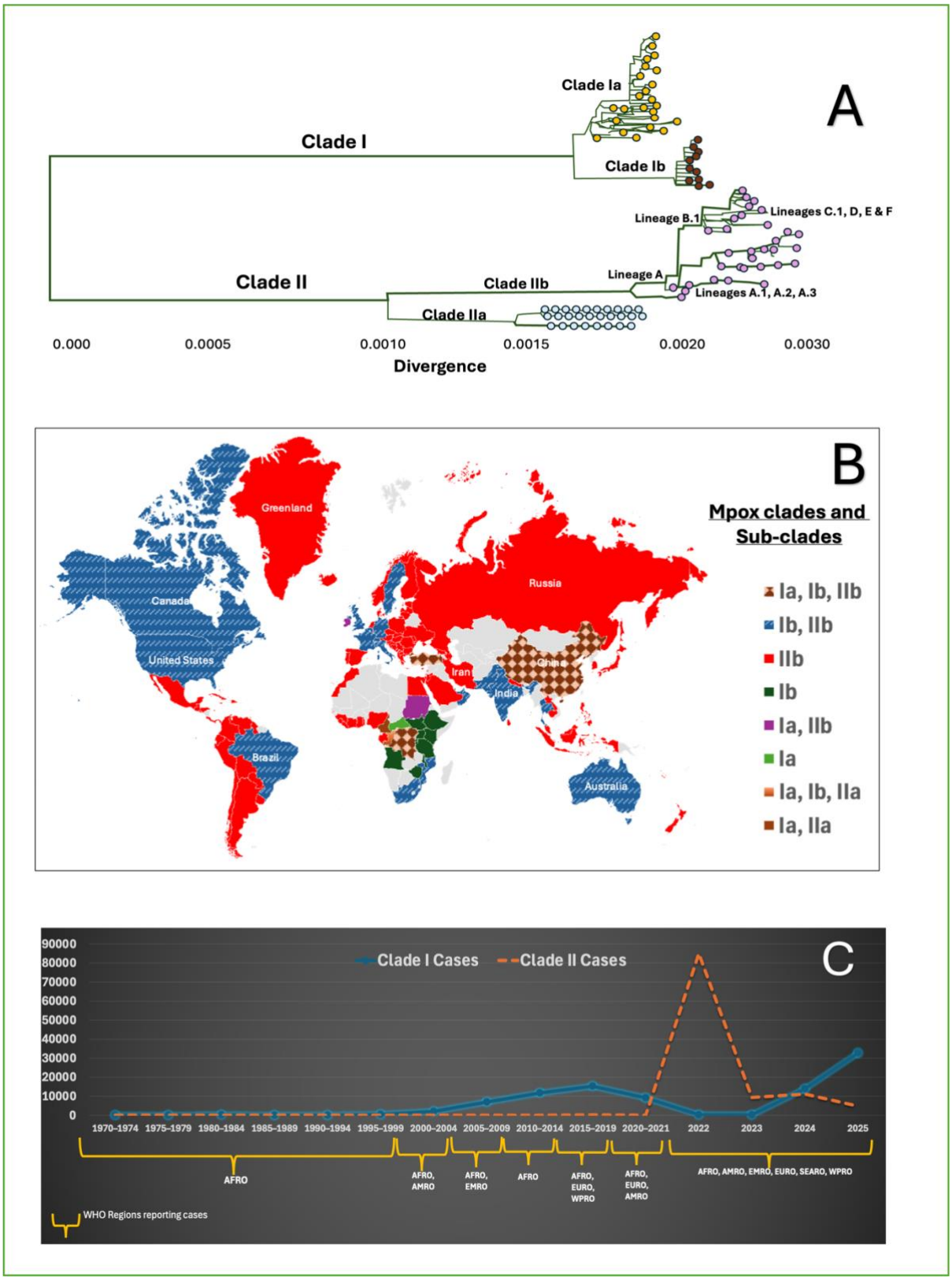

Figure 3: Phylogenetic tree and global distribution of mpox viral clades and subclades. a| Phylogenetic tree of monkeypox virus showing genetic divergence between major clades. Phylogenetic analysis of monkeypox virus (MPXV) genetic diversity showing major clades and lineages based on whole genome sequencing data. The phylogenetic tree demonstrates genetic divergence (x-axis) between viral isolates, with branch lengths proportional to evolutionary distance. Clade I (Central African): higher virulence, subdivided into clade Ia

(historical isolates) and clade Ib (emerging variant with enhanced human transmission, 2023–2024). Clade II (West African): milder disease, subdivided into clade IIa (historical) and clade IIb (caused 2022–2023 global outbreak). Multiple lineages within clade IIb (A, A.1-A.3, B.1, C.1, D, E, F) reflect international spread patterns during the global outbreak. b| Global distribution of MPXV clades and sub-clades. The map uses different colors and patterns to indicate which viral clades (Ia, Ib, IIa, IIb) have been detected in various countries, illustrating the worldwide spread and regional circulation of different genetic groups of the virus. c| A line graph comparing the reported number of clade I and clade II mpox cases over time (1970–2025). The graph illustrates the historical dominance of clade I, with data from the Democratic Republic of Congo (DRC) including both suspected and confirmed cases before 2022. From 2022 onwards, data for the DRC reflects confirmed cases only. The chart highlights a significant spike in clade II cases during the 2022 global pandemic and a subsequent resurgence of both clades.

AFRO, WHO Regional Office for Africa; AMRO, WHO Regional Office for the Americas; EMRO, WHO Regional Office for the Eastern Mediterranean; EURO, WHO Regional Office for Europe; WPRO, WHO Regional Office for the Western Pacific; SEARO, WHO Regional Office for South-East Asia

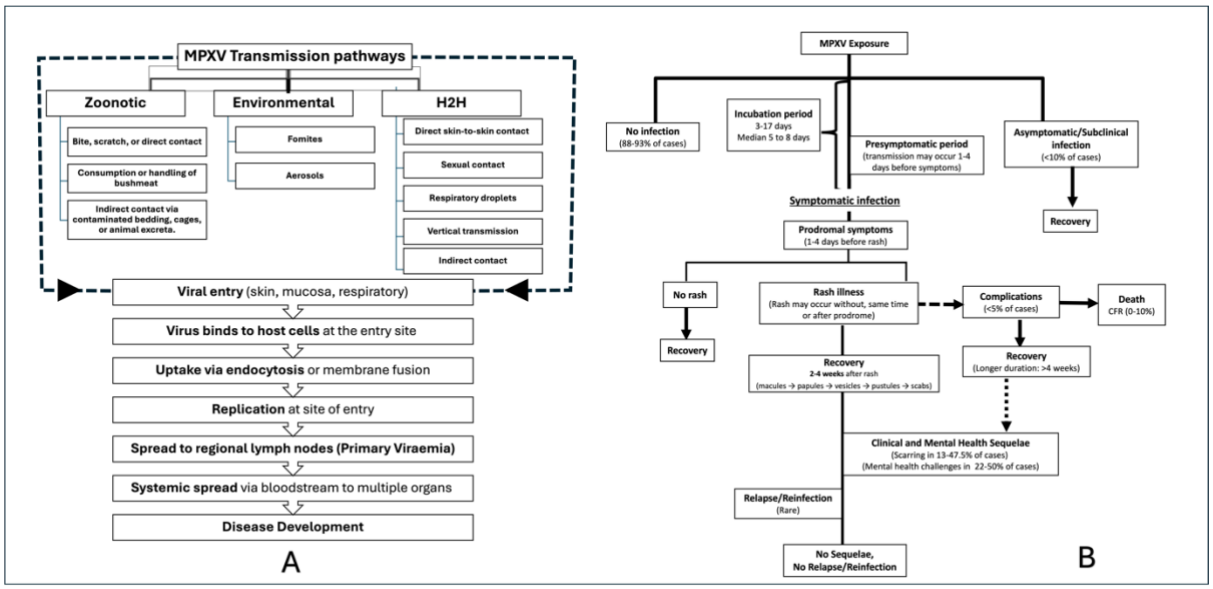

Figure 4. MPXV transmission pathways and natural history. a| The figure illustrates the multiple routes by which monkeypox virus (MPXV) can be transmitted to humans and the subsequent steps in viral pathogenesis. Upper panel: transmission pathways are categorized into three main routes: (1) zoonotic transmission through direct animal contact (bites, scratches), consumption or handling of infected bushmeat, or indirect contact via contaminated animal materials; (2) environmental transmission through exposure to contaminated fomites or aerosolized particles; and (3) human-to-human transmission via direct skin-to-skin contact, sexual contact, respiratory droplets, vertical transmission from mother to child, or indirect contact with contaminated materials. Lower panel: following viral entry through skin, mucosa, or respiratory tract, the virus binds to host cells at the entry site and gains access via endocytosis or membrane fusion. Local viral replication occurs at the entry site, followed by spread to regional lymph nodes where primary viremia develops.

Systemic dissemination via the bloodstream leads to multi-organ involvement and the characteristic clinical manifestations of mpox disease. The dashed border line emphasizes that all transmission pathways ultimately converge on the same pathogenic process once viral entry is established. b| Natural history and clinical outcomes following MPXV exposure. This flowchart illustrates the spectrum of possible outcomes after MPXV exposure. Following initial exposure, individuals may experience: (1) no infection, successful immune clearance without establishment of infection; (2) presymptomatic infection, viral replication occurs but clinical symptoms have not yet developed; or asymptomatic infection, viral infection occurs without overt clinical manifestations throughout the course of illness. Presymptomatic infection progresses to symptomatic infection, which can manifest as either a febrile prodrome (systemic symptoms including fever, malaise, and lymphadenopathy) or a rash with or without prodromal symptoms (characteristic skin lesions that may occur with or without preceding systemic symptoms). The febrile prodrome may resolve without rash development or progress to the characteristic skin or mucosal rash. The rash illness could be localized or generalized. From the rash stage, patients typically progress to recovery, though complications may develop that can lead to death. Following recovery, patients may experience long-term sequelae (persistent effects) and, in some cases, relapse or reinfection may occur. Asymptomatic infections can also lead directly to recovery. The diagram emphasizes that mpox presents with a diverse clinical spectrum, from completely asymptomatic cases to severe disease with fatal outcomes.

Box 1: A global agenda for mpox control

To counter the evolving threat of mpox, a forward-looking agenda must address fundamental scientific gaps and structural inequities. The following priorities represent critical areas for investment and action.

Illuminate the true burden of disease

The scale of mpox in Africa is severely underestimated due to underreporting and diagnostic limitations. Strengthening surveillance is paramount. This requires deploying a new generation of cost-effective, easy-to-use diagnostics to enable robust data collection, even in remote settings.

Advance foundational research tools

Progress is constrained by an outdated toolkit. We need animal models that reflect human transmission routes, such as mucosal exposure, to properly evaluate clade-specific virulence. Furthermore, developing sophisticated immunological assays to distinguish natural from vaccine-induced immunity is essential for understanding population-level protection and reinfection risks.

Unravel viral and clinical complexity

Key aspects of the virus's behavior remain obscure. Research must focus on quantifying asymptomatic transmission, clarifying the role of viral persistence in genital reservoirs, and

defining the long-term sequelae in diverse populations, including children and the immunocompromised.

Integrate and localize the public health response

Mpox control cannot succeed in a silo. Integrating surveillance and care into established HIV/STI programs offers a pragmatic path to reach key populations and reduce stigma. Ultimately, success hinges on Africa-led research to ensure solutions are contextually relevant and sustainable.

Validate countermeasure efficacy in endemic settings

Real-world effectiveness data for vaccines and therapies against different clades — particularly the virulent clade I in Africa — are critically lacking. Prioritizing clinical trials in these settings is the only way to ensure countermeasures provide equitable protection for all.

ToC blurb

In this Review, Ogoina et al. examine the emergence of mpox and its epidemiology, the viral life cycle, transmission dynamics, risk factors, and clinical characteristics. They also explore current and future prevention and control strategies, including the therapeutic and vaccine landscape, as well as the urgent need for integrated surveillance, equitable access to countermeasures, and Africa-led research to address the ongoing multi-clade threat.