

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 the 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 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.

Sections

Introduction

History and emergence of mpox

MPXV life cycle

Phylogeny, evolution and genetic adaptations

Natural reservoir

Transmission dynamics

Risk factors for mpox transmission and infection

Clinical characteristics

Prevention and control of mpox

Future directions and challenges

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Introduction

Mpox, formerly monkeypox, is a zoonotic viral disease historically found in Africa that has now spread globally¹. This prompted the WHO and the Africa CDC to declare Public Health Emergencies of International Concern (PHEICs) in 2022 and 2024 (refs. 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 Africa⁴, 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. Before 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 risk¹⁰. Newly identified viral clades, emerging transmission routes, links with HIV or 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, and current and future prevention and control strategies, including the landscape of therapeutics and vaccines.

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 Statens Serum Institute in Denmark¹³. Human mpox remained unknown until August 1970, when a 9-month-old boy in Basankusu, Democratic Republic of Congo (DRC; then Zaire), became the first documented human case¹⁴. This discovery occurred during the final phase of the global smallpox eradication programme, creating immediate concern. By 1971, three additional cases were reported in Liberia and Sierra Leone, confirming human susceptibility to the virus¹⁵. 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 years and under through zoonotic spillovers with minimal household transmission⁴.

In 2003, the first outbreak of mpox outside Africa occurred in the USA, showing the potential of the disease for global spread through the exotic pet trade¹⁶. Although the US outbreak was managed without deaths or human-to-human transmission, the virus continued to cause outbreaks in Africa⁴. In the DRC, mpox cases surged 20-fold from 2000 to 2016 compared with the 1980s^{4,17}, ascribed to decreased population immunity after cessation of smallpox vaccination¹⁸.

Mpox reemerged in Nigeria in 2017 after a 39-year hiatus^{19,20}. Molecular analysis suggests that the virus began circulating undetected in Rivers State, South-South, Nigeria, around 2014 (ref. 21). This resurgence was marked by an unusual cluster of cases in urban areas and among adults^{20,22,23}, with subsequent international transmission and sporadic cases in the UK, Israel, Singapore and the USA between 2018 and 2021 (ref. 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 23 July, 2022,

the WHO declared the outbreak a Public Health Emergency of International Concern. The unprecedented outbreak was caused by the same clade (clade IIb) responsible for the Nigerian outbreak and was spreading via sexual contact mostly among GBMSM²⁸. Although the PHEIC was declared over in May 2023, owing to significant decline in cases globally, mpox infections continued in endemic regions in Africa, especially in the DRC²⁹. In mid-2023, an unusual cluster of clade Ia mpox was reported among young adults, including GBMSM in Kenge Kwango Province, DRC³⁰. This represented the first detection of mpox among GBMSM in Africa and also the first documented transmission of clade I mpox via sexual contact³⁰. 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 settlements³⁰. 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 enhanced transmissibility and geographical expansion of the variant 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 (ref. 29). As of 27 July, 2025, clade Ib mpox has been reported in at least 33 countries, including 23 countries outside Eastern Africa³⁶. 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, whereas The Gambia documented its first case in July 2025.

This historical trajectory shows the progression of mpox from a rare zoonotic disease to a globally significant public health issue, emphasizing the interactions between pathogen ecology, human behaviour and waning cross-protective immunity following cessation of smallpox vaccination programmes. 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.

MPXV life cycle

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^{37,38} (Fig. 2a). Unlike most DNA viruses, Poxviridae, including MPXV, replicates entirely within the host cell cytoplasm using virus-encoded enzymes for DNA replication and mRNA synthesis³⁹ (Fig. 2b).

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 – utilizing envelope proteins such as A27 and H3, whereas 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.

Review article

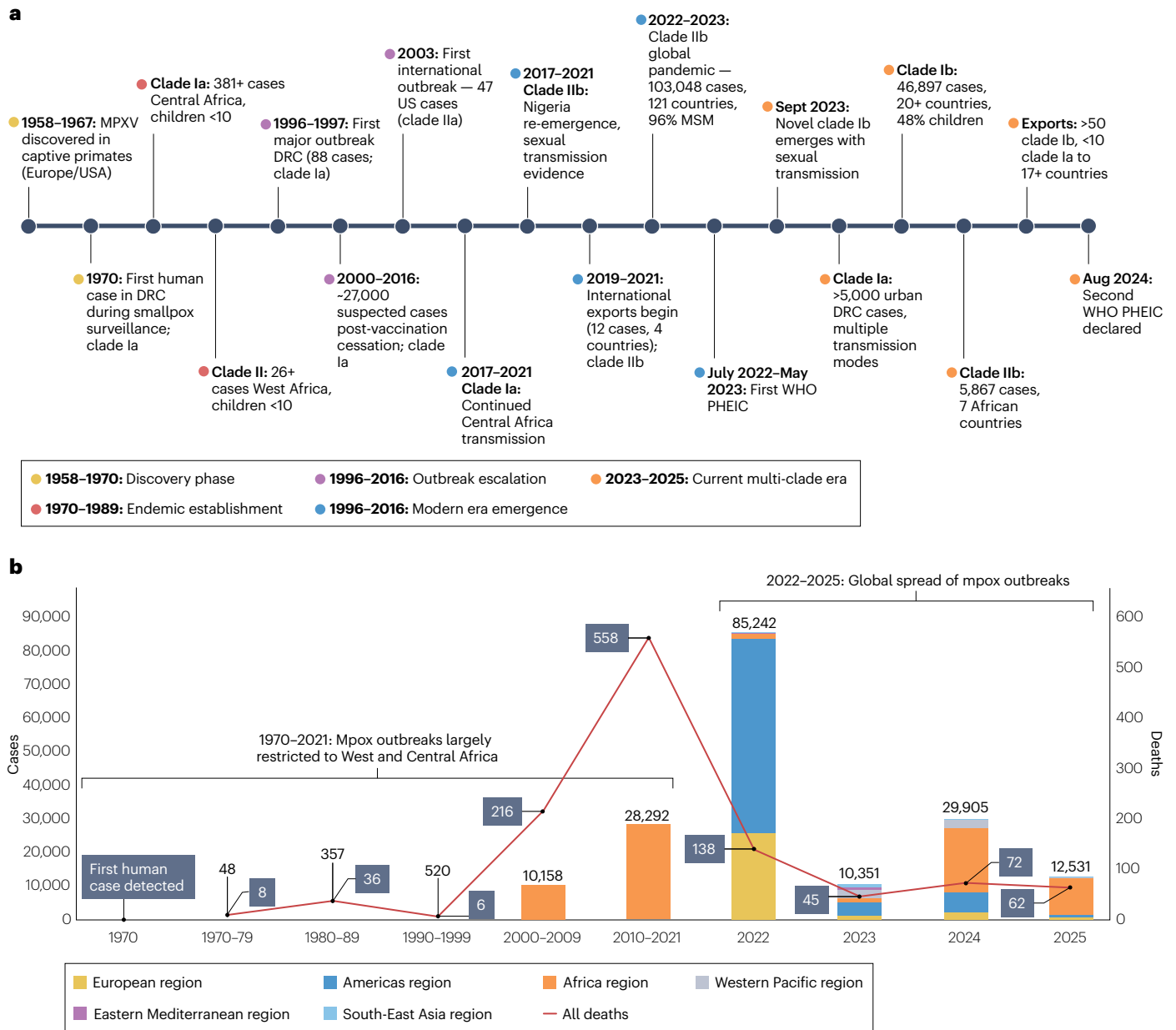


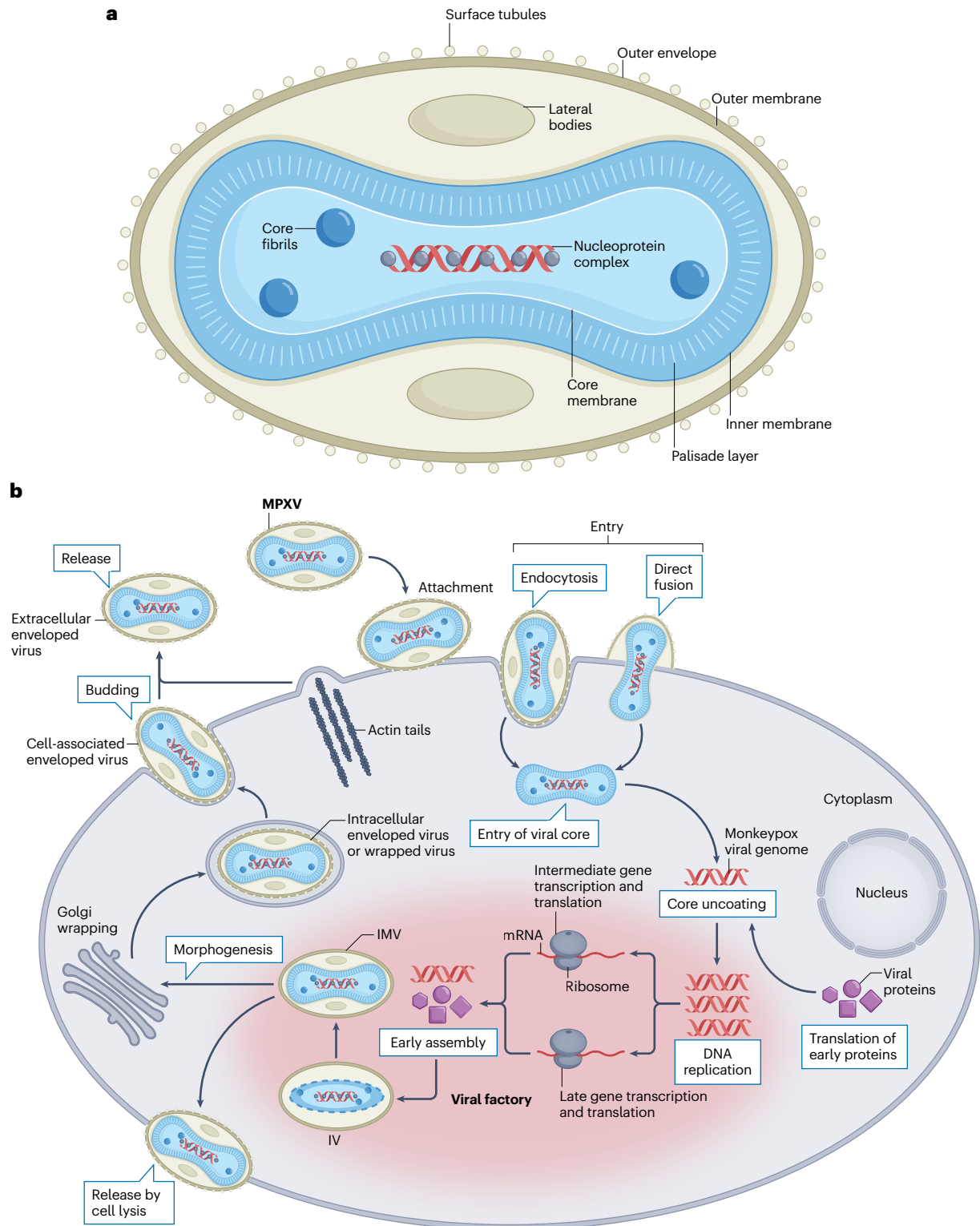
Fig. 1 | Global evolution and epidemiological shift of mpxv. a, A timeline of the global evolution of mpxv from its discovery to the present day (1958–2025). The timeline is divided into key eras: discovery (1958–1970), endemic establishment (1970–1989), outbreak escalation (1996–2016), modern era emergence (2017–2023), and the current multi-clade era (2023–2025), detailing major milestones and outbreaks within each period. **b**, The global spread of mpxv

outbreaks from 1970 to 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. DRC, Democratic Republic of Congo; MPXV, monkeypox virus; MSM, men who have sex with men; PHEIC, Public Health Emergency of International Concern.

Crucially, poxviruses package a complete transcriptional apparatus within the virion core, including a multisubunit 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 favour 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, wherein MPXV-encoded proteins – including



DNA polymerase, primase and helicase – carry out genome replication independently of the nuclear machinery of the host^{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

Fig. 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 (also known as core wall), 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, a central 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 programmes. Intermediate gene products include transcription factors required for late gene expression, whereas 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 (IVs) that mature into intracellular mature virions (IMVs). Some IMVs acquire additional membrane envelopes through Golgi wrapping to form intracellular enveloped virions or wrapped virions. These mature into cell-associated enveloped virions that can facilitate cell-to-cell spread via actin-based motility or be released as extracellular enveloped virions for systemic dissemination. IMVs can also exit through cell lysis.

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, also known as intracellular enveloped virions (IEVs). The IEVs facilitate localized cell-to-cell spread, allowing the virus to efficiently infect neighbouring uninfected cells. Conversely, cell-associated extracellular viruses are also formed and are characterized by their association with actin tails, promoting further localized spread. Extracellular enveloped viruses, which are released from infected cells, have 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 neighbouring uninfected cells, promoting direct cell-to-cell spread.

Throughout this cycle, MPXV uses a variety of immune evasion strategies^{45–47}. The virus encodes proteins that antagonize type I and II interferon signalling, 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.

Phylogeny, evolution and genetic adaptations

Phylogenetic classification

MPXV is classified into two major clades with substantial differences in virulence and transmissibility^{48,49} (Fig. 3a). Figure 3b,c outlines 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 Ib⁵⁰. 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 towards more efficient spread^{31,53}. Clade II (formerly West African clade), subdivided into clade 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 owing to genetic variations in terminal genome regions that encode immunomodulatory proteins and factors that determine host range, with specific genes such as *D14L*, *OPG195*, *B14R* and *B10R* having 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 with that of clade II viruses^{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.

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 profiles³¹.

Clade II, which includes most of the viruses implicated in recent global outbreaks, has evolved into two principal subclades: clade 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,

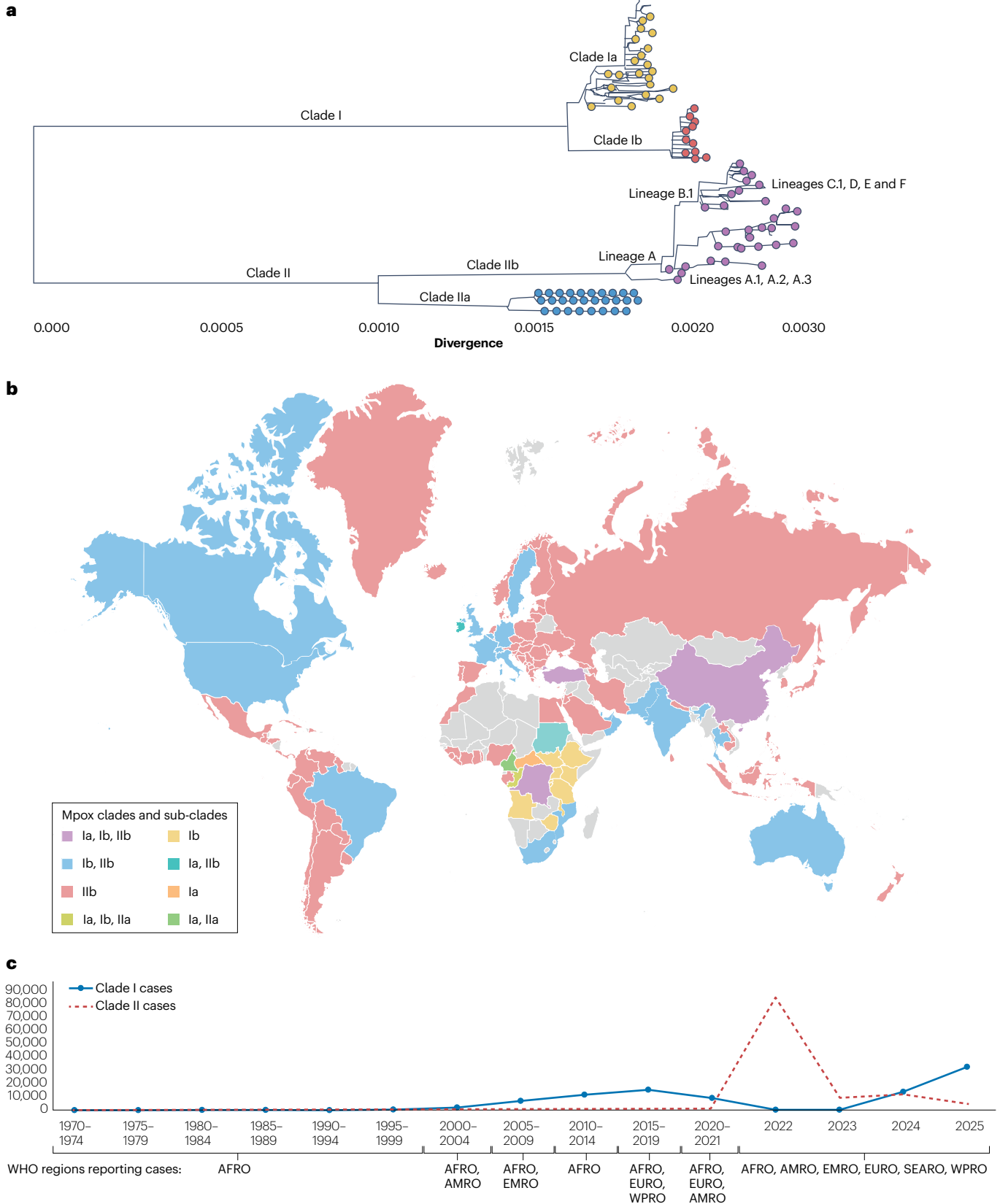


Fig. 3 | Phylogenetic tree and global distribution of mpox viral clades and subclades. a, Phylogenetic tree of monkeypox virus showing genetic divergence between major clades. Phylogenetic analysis of monkeypox virus (MPXV) genetic diversity showing major clades and lineages based on whole-genome sequencing 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 subclades. The map uses different colours 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**, Comparison of 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.

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 traits⁵⁴.

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 (refs. 54,57,58). Notably, studies from the DRC highlight an increasing proportion of genomes in both clade Ia (68%) and clade 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.

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 has revealed a pooled prevalence of MPXV at 16% in non-human primates, 8% in rodents, and 1% in shrews⁶⁰, 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 studies⁶¹. This finding,

alongside the epidemiological data from the 2003 US mpox outbreak¹⁶, 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 zoonotic origins of the disease 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 (ref. 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' 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 the definitive reservoir of MPXV, 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.

Transmission dynamics

MPXV is transmitted through direct and indirect exposure to infectious viral particles from animals, humans and the environment (Fig. 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 Brazil, but the transmission dynamics are more suggestive of environmental contamination⁶⁴. A US study examining potential transmission from humans to household pets has found viral DNA in some animals (17% of dogs and 11% of cats) but no evidence of live virus or antibody development, suggesting that although pets are exposed to the virus, actual infection appears uncommon and the health risks to pets and transmission risks from pets to others are probably minimal⁶⁵.

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 primary mode of transmission observed since 2022 and could follow

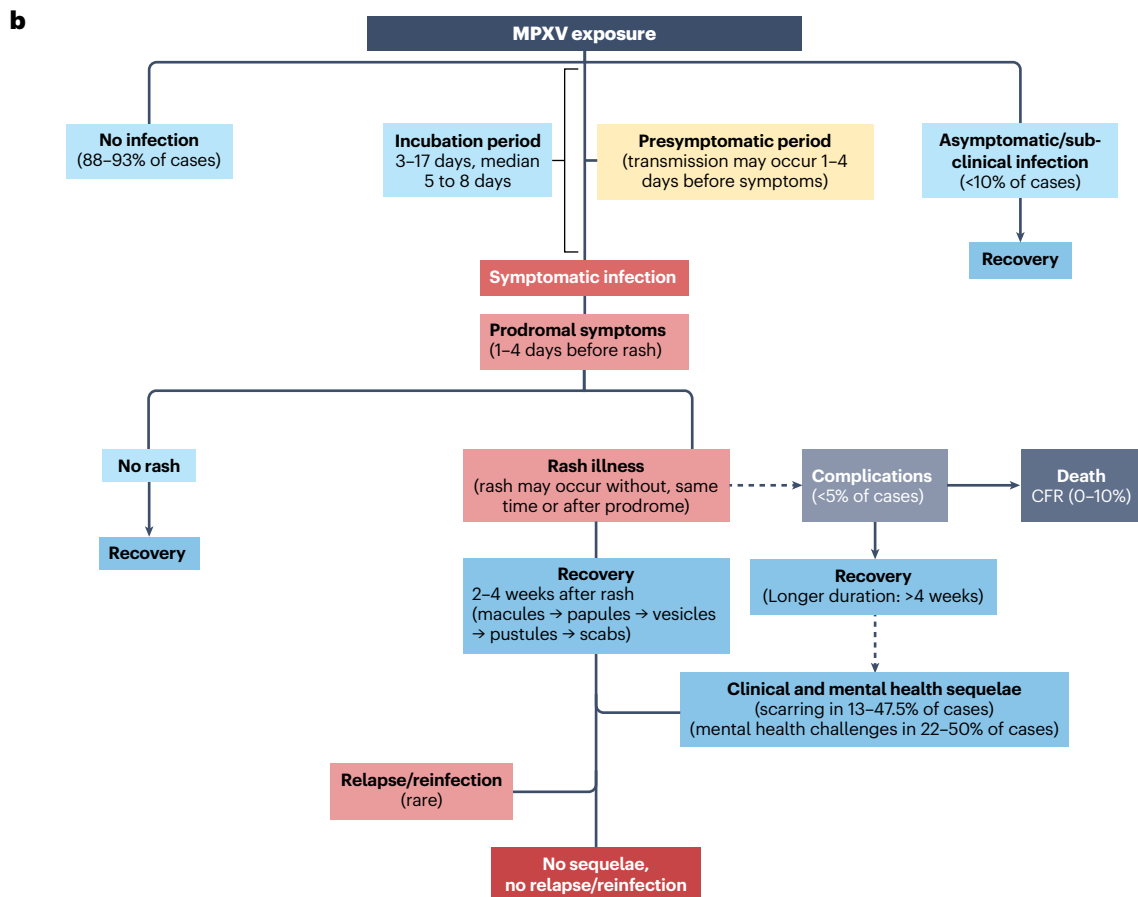
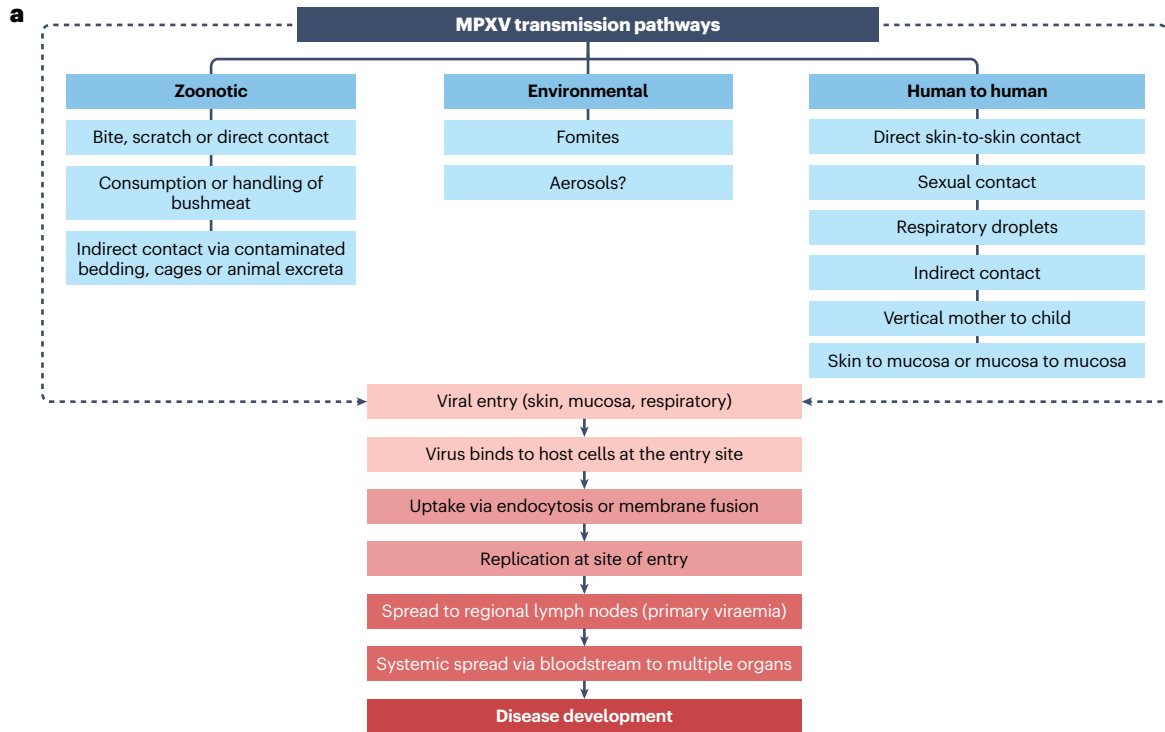


Fig. 4 | MPXV transmission pathways and natural history. **a**, The figure illustrates the multiple routes by which monkeypox virus (MPXV) can be transmitted to humans and the subsequent steps in viral pathogenesis. Upper panel: transmission pathways are categorized into three main routes: zoonotic transmission through direct animal contact (bites, scratches), consumption or handling of infected bushmeat, or indirect contact via contaminated animal materials; environmental transmission through exposure to contaminated fomites or aerosolized particles; and human-to-human transmission via direct skin-to-skin contact, sexual contact, respiratory droplets, vertical transmission from mother to child (through skin to skin, respiratory droplets or possibly blood), or indirect contact with contaminated materials. Skin to mucosa or mucosa to mucosa is mainly through sexual contact. Lower panel: following viral entry through the 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 wherein primary viraemia 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. After initial exposure, individuals may experience the following: no infection – successful immune clearance without establishment of infection; 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, although 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. CFR, case fatality rate.

both sexual and non-sexual contact. Airborne transmission is possible as suggested by animal models^{66,67}, prior human outbreaks without close contact⁶⁸, and detection of MPXV in air samples⁶⁷. However, this route appears to have a minor role in real-world transmission observed with 2022 clade IIb mpox compared with direct contact with lesions and bodily fluids⁶⁷.

Mpox also spreads through contact with contaminated surfaces and objects (fomites) in health-care, household, laboratory, and tattoo or piercing settings⁶⁹. 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 such as those in 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 the 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 virus⁷¹. MPXV DNA has been detected in blood, urine, faeces and vaginal secretions, although 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 determine through simulation that 27–50% of paired cases result from transmission during a presymptomatic period⁷³, occurring 1–4 days before recalled symptom onset^{69,74}.

The epidemiological parameters of mpox define its spread patterns across populations. The incubation periods may range from 1 to 40 days, with most cases falling between 3 and 17 days (refs. 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 with 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 versus 7.6 days), extended serial intervals (10.1–18.4 versus 8.3 days), and slower generation times (11.3–17.2 versus 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 intervals⁷⁷. The emerging clade Ib combines the slower parameters of clade I with concerning R_0 values above epidemic threshold (1.08–1.18), demonstrating enhanced human-to-human transmission, particularly in mining regions of DRC⁷⁵. The high transmission rates characterizing both the 2022 clade IIb global outbreak and recent clade Ib spread in DRC and Eastern Africa probably reflect shared environmental and behavioural determinants – including urban density, intimate contact patterns and network amplification – rather than clade-specific differences in viral transmissibility.

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 wild life (rodents, primates), with hunters and animal handlers being at significantly higher risk⁸¹. Secondary household attack rates range from 0.7% in clade IIb²⁸ to 8% in clade I⁸², with risk being highest among those sharing sleeping spaces or handling contaminated materials⁸². The 2022 global outbreak demonstrated efficient sexual transmission, with multiple partners, condomless sex and sex venue attendance as significant risk factors⁷⁹. 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 $R_0 > 1$ (refs. 31,32).

A comprehensive 2023 systematic review and meta-analysis analysing 31 studies encompassing 148,499 mpox cases has 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), whereas prior smallpox vaccination demonstrated significant protective effects (OR = 0.24, 95% CI: 0.15–0.39)⁸³.

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 the 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 US 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 people with 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	30,136
Clade Ib (2023–2025)	Both localized (genital) and generalized presentations observed Fever, lymphadenopathy, headache, myalgia Initial rash is facial in children, genital in adults	0.7% overall (4% in children <1 year old)	31–35,75

DRC, Democratic Republic of Congo; MSM, men who have sex with men.

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 behaviour and virus viability. Habitat fragmentation forces infected wild life closer to human settlements, perpetuating transmission cycles.

Beyond environmental drivers, socioeconomic determinants have 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 spillover⁸⁵. Weak health-care systems in resource-limited settings delay case detection, diagnosis and isolation, undermining effective containment⁸⁸. Population displacement related to conflict and rapid urbanization further intensifies transmission by creating overcrowded living conditions and altering contact networks⁸⁷. Limited access to clean water, sanitation and hygiene infrastructure facilitates pathogen persistence, whereas low health literacy can delay symptom recognition and health-care-seeking behaviour⁸⁵. Together, these interacting socioeconomic and environmental factors create conditions that can enable both sustained human-to-human transmission and recurrent spillover events.

Clinical characteristics

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 (Fig. 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 (refs. 91–93). During the 2022 outbreak, systemic symptoms frequently occurred concurrently with or after rash onset²⁸. Healed lesions may result in scarring or pigmentation changes typically resolving within 3–12 months (ref. 94). Reinfection has been reported in a health-care worker in Nigeria before the 2022 global outbreak⁹⁵ and among GBMSM during the 2022 outbreak^{96,97}. Cases of reinfection are associated with milder symptoms and shorter duration of illness.

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). The characteristic vesiculopustular rash was first documented during the initial animal outbreaks (1958–1968), although 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 featured moderate systemic symptoms and lower mortality (1–3.6%)^{20,90}. The 2003 US clade IIa outbreak uniquely showed local inoculation sites with satellite lesions but no fatalities¹⁶. Recent outbreaks exhibit evolving patterns: the 2022–2023 global clade IIb outbreak demonstrated predominantly anogenital lesions with lower prodromal

symptom frequency and mortality (<0.1%)^{28,98}, whereas the 2023–2025 clade Ib outbreak showed mixed presentations with variable severity (CFR 0.7% overall, 4% in infants)^{33,99}.

Complications, sequelae and outcomes of mpox

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

Complications vary by population demographics and anatomical exposure sites. Secondary bacterial infections affect 15–30% of cases, particularly with confluent or necrotizing lesions in resource-limited settings^{91,101,102}. Ocular complications range from conjunctivitis (10–15%), keratitis (2–4%), to vision loss (1–3%), particularly when corneal infection occurs¹⁰³. Severe complications, although infrequent, include sepsis (1–3%), parotitis (0.5–1%), proctitis (14–36% in sexually transmitted cases), rectal perforation (<0.5%), epiglottitis (<0.5%), lymphadenopathy causing airway compromise (0.5–1%), and neurological involvement such as meningitis and encephalitis (<0.5%)^{22,28,91,98,102,104}.

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

Prevention and control of mpox

Supportive care

Management primarily focuses on symptom control through comprehensive supportive measures. Pain management with appropriate analgesics remains foundational, with WHO guidelines recommending a stepwise approach from acetaminophen or non-steroidal anti-inflammatory drugs to opioids for severe pain¹¹⁰. Antibiotics should be reserved for treating secondary or concurrent bacterial infections within local and institutional evidence-based antimicrobial stewardship guidelines. Adequate fluid replacement therapy prevents complications from dehydration, particularly when accompanied by prolonged fever or dysphagia. Topical care for skin lesions includes keeping lesions clean and dry, with petroleum jelly application to prevent adhesion to clothing and saline soaks for painful genital or oral lesions. Psychological support addressing stigma, isolation concerns and disease anxiety should be integrated into care plans¹¹⁰.

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 release¹¹¹. 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 – have found no significant reduction in time to lesion resolution^{114,115}. Nevertheless, tecovirimat often remains recommended for severe disease, individuals with compromised immune system, and paediatric cases. Cidofovir and its oral prodrug

Table 2 | 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 and STOMP)	Severe or progressive mpox, individuals with compromised immune system, 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 or progressive mpox	Nephrotoxicity, intravenous only
Brincidofovir	Antiviral (oral prodrug)	DNA polymerase inhibitor	FDA for smallpox; limited mpox data	Severe or progressive mpox	Hepatotoxicity, limited clinical utility
Vaccinia immune globulin intravenous (VIGIV)	Passive immunotherapy	Neutralizes poxviruses, supports viral clearance	Approved by FDA and CDC for vaccinia complications, used in severe mpox or ocular disease	Severe, progressive or ocular mpox in individuals with compromised immune system	Limited efficacy evidence, intravenous infusion
Modified vaccinia ankara (MVA-BN, JYNNEOS, IMVANEX, IMVAMUNE)	Vaccine (third generation, non-replicating)	Induces <i>Orthopoxvirus</i> -specific immunity	Licensed and WHO-prequalified; real-world effectiveness (35–90%)	PEP in high-risk groups	Mild local or systemic side effects, safe in individuals with compromised immune system, potential short-lived immunity
LC16m8	Vaccine (attenuated, minimally replicating)	Induces <i>Orthopoxvirus</i> -specific immunity	Licensed in Japan; DRC evaluation ongoing	Potential PEP in endemic settings	Safety in individuals with compromised immune system needs assessment
ACAM2000	Vaccine (second generation, replicating)	Induces immunity via live vaccinia virus	Licensed; used previously for smallpox	High-risk occupational settings	Myopericarditis risk, contraindicated in individuals with compromised immune system

CDC, Centers for Disease Control and Prevention; DRC, Democratic Republic of Congo; FDA, Food and Drug Administration; PEP, pre-exposure and post-exposure prophylaxis; RCT, randomized controlled trial.

brincidofovir inhibit viral DNA polymerase, but there is limited clinical data, and cidofovir can cause nephrotoxicity¹¹¹. Brincidofovir can cause hepatotoxicity, limiting its widespread use, although participants are being recruited to a clinical trial in the DRC¹¹¹. Vaccinia immune globulin intravenous (VIGIV) has been used in severe cases, particularly for ocular involvement and in individuals with compromised immune system, although efficacy evidence is limited to case series¹¹⁶.

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 (tecovirostat) 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 replication¹¹⁷. Nanotechnology-based therapies, such as silver nanoparticles, are under investigation for their antiviral effects and ability to enhance drug delivery¹¹⁷. 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 treatments⁹⁴. With few available treatments for mpox, ongoing clinical trials are essential to improve efficacy, create new therapies, and address emerging variants and drug resistance.

Vaccination

Modified vaccinia ankara (MVA) (JYNNEOS/IMVANEX/IMVAMUNE) is a non-replicating vaccine administered in two doses, 28 days apart¹¹⁸. Real-world effectiveness estimates range from 35% to 86% after one dose and 66% to 90% after two doses¹¹⁸, with breakthrough infections typically presenting as milder disease¹¹⁹. Intradermal administration (one-fifth dose) demonstrates comparable immunogenicity to standard subcutaneous administration, extending limited supplies¹¹⁸. LC16m8 (KM Biologics) is a minimally replicating vaccine administered as a single dose. A recent human and animal study suggest favourable clinical efficacy and safety profile¹²⁰, with effectiveness evaluation ongoing in DRC outbreaks¹²¹. 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 individuals with compromised immune system^{121–123}. mRNA vaccines represent a promising next-generation platform for mpox prevention by leveraging synthetic mRNA encoding specific viral antigens, instructing host cells to produce viral proteins and elicit immune responses¹²⁴.

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 severity¹²⁵. 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 behaviour 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.

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 owing to waning protective immunity, the potential for the re-emergence of new threats linked to mpox is a pressing reality.

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 owing 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 behaviour of the virus 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 individuals with compromised immune system.

Integrate and localize the public health response

Mpox control cannot succeed in a silo. Integrating surveillance and care into established HIV and sexually transmissible infection (STI) programmes offers a pragmatic path to reach key populations and reduce stigma. Ultimately, success hinges on Africa-led research to ensure that 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 that countermeasures provide equitable protection for all.

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 responses¹²⁹. 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 Africa⁸⁸. 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 programmes. The Continental Mpox Response Plan 2.0 of Africa CDC 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^{87,129}.

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 programmes is crucial, given the overlapping epidemics and transmission routes. This leverages existing infrastructure and improves care for coinfecting 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 owing 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 declaration of WHO that the PHEIC has ended, endemic infections and sporadic outbreaks continue, particularly across Africa¹²⁹. 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 and contributed substantially to the discussion of the content. D.O. wrote the article. All authors reviewed and/or edited the manuscript before submission.

Competing interests

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