REVIEW: Concurrent outbreaks of mpox in Africa – an update

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ABSTRACT

In this review, we examine the concurrent outbreaks of mpox in Africa, focusing on clade 1a, the newly emerged clade 1b, and clade 2b lineage A, and how they differ from the 2022 global outbreak caused by clade 2b lineage B.1. Historically, clades 1a and 2a have caused sporadic, limited outbreaks in Central and West Africa, respectively, primarily through zoonotic transmission. Clade 2b first caused an outbreak in Nigeria in 2017 and later spread globally via sexual contact in 2022. Recently, the WHO declared a global health emergency due to the newly identified clade 1b outbreak in eastern DRC, which has now expanded to several other countries and is spreading through direct and sexual contact in urban centers and refugee camps. Clades, route of exposure, infectious dose, and host immune response are the main factors influencing clinical presentation. For clade 1a and 2a, zoonotic transmission plays an important role, while for clade 1b and 2b, the spread is achieved through sustained human-to-human transmission without zoonotic exposure. For both clade 1a and 2a, lesions follow a generalized centrifugal distribution, while for clade 2b they are mainly localised to the anogenital area. For clade 1b, data is still emerging, but current cases show a mix of localized lesions and centrifugal distribution. Ty. Diagnostic challenges include false negative results for clade 1b with existing PCR assays and limited testing access in remote areas. Tecovirimat, the primary antiviral during the 2022 outbreak, has shown variable efficacy across clades, with reduced effectiveness against clade 1a. The MVA-BN vaccine has been shown to be up to 90% effective against clade 2b after two doses and is safe for children, though effectiveness drops to 20% when used as post-exposure prophylaxis. Given the evolving nature of the mpox virus, ongoing research and strong public health responses are critical to managing potential future outbreaks.

SEARCH STRATEGY

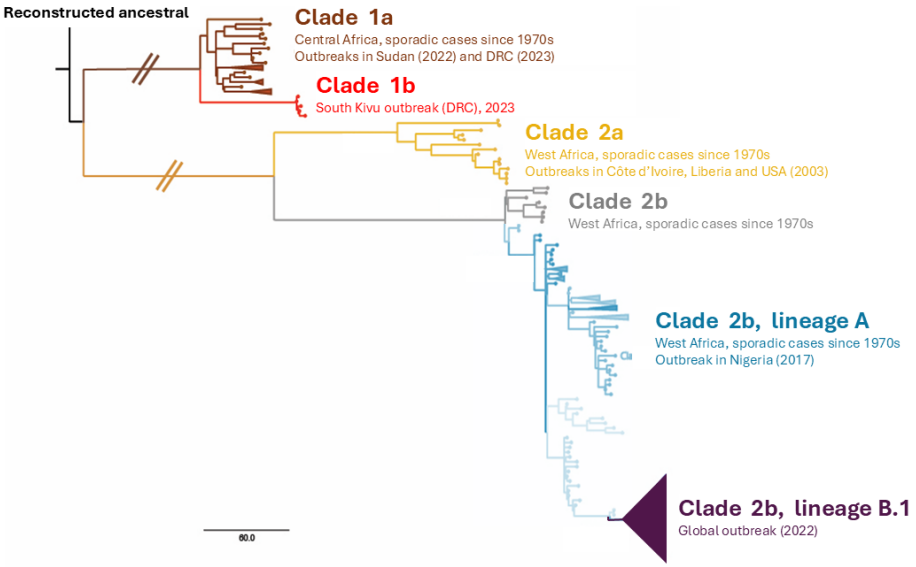
This review is aimed at updating the extensive description of the 2022 global clade 2b lineage B.1 monkeypox virus outbreak published in a The Lancet Seminar, placing particular attention to the new discoveries and insights on the outbreak reported in the Democratic Republic of Congo. We searched PubMed for peer-reviewed articles published in the past two years with any of the following terms: “mpox”, “monkeypox virus”, ”smallpox”, “vaccinia”, “orthopoxvirus”, “tecovirimat”, “cidofovir”, and “modified vaccinia Ankara”, in combination with the words “pathophysiology”, “animal model”, “immunology”, “sexually-transmitted infections“, “HIV”, “immunosuppression”, “global outbreak”, “risk factors”, “treatment”. Additionally, we searched the website of key institutions for recent releases and announcements regarding mpox, including the following: US Food and Drug Administration, World Health Organization, the US Centers for Disease Control and Prevention, the African Centre for Disease Control, and the European Centre for Disease Prevention and Control, the African Medicines Agency, and the Autorité Congolaise de Règlementation Pharmaceutique. We prioritized new information, regardless of language, that emerged after November 2022.

INTRODUCTION

Epidemiological, animal, and molecular evidence suggest that two clades of monkeypox virus (MPXV) have existed in different regions of Africa in the past decades.[1] Clade 1, present primarily in Central Africa, has been associated with higher virulence in both animal and observational studies and in humans.[1,2] In contrast, clade 2, which affects countries in West Africa, lacks several genes present in clade 1 MPXV and is associated with less severe outcomes[2,3] (Figure 1).

Recently, phylogenetic analyses have revealed the presence of subtypes in both clade 1 and clade 2 . Clade 1a is the predominant strain in Central Africa, particularly in the northern and central regions of the Democratic Republic of the Congo (DRC). Clade 1b, discovered in 2023, was identified through genomic analysis of strains from previously non-endemic provinces in the eastern part of the DRC.[4] Clade 2a circulated in West Africa before a large outbreak in Nigeria in 2017, where Clade 2b became dominant. A global multi-country outbreak in 2022, which affected non-endemic areas, revealed the divergence of Clade 2b into two lineages: Clade 2b A, dominant in the 2017 Nigerian outbreak, and Clade 2b B.1, dominant during the global outbreak in 2022. Initial analyses of the 2022 outbreak strains revealed more mutations than expected,[5,6] suggesting that the virus might be adapting to humans more rapidly. The total nucleotide difference between the common ancestor of clades 1 and clade 2a genomes is of $2{\cdot}2x10^{-03}$ substitutions per site, while the corresponding value for clades 2a and 2b is approximately $0{\cdot}9x10^{-03}$.[7,8]

Figure 1. Global Phylogenetic (with geographic and temporal identification) of mpox Clades



MODE OF TRANSMISSION

Knowledge about the mode of transmission, viral shedding, and infectious period of MPXV varies significantly across viral clades and remains limited for some of them. The extremely low secondary attack rates (up to 0.9% in vaccinated individuals and 7.2 in unvaccinated) reported during outbreaks in West Africa in the 1980s and previous sequencing studies have suggested that clades 1a and 2a are primarily transmitted through zoonotic spillovers, with little or no human-to-human transmission.[9–11] In contrast, clades 1b and 2b have been linked to more significant outbreaks, providing clear evidence of human-to-human transmission. Even in these cases, the reproduction numbers reported indicate that MPXV is less transmissible than smallpox: the reported reproduction numbers (R_0) ranged 0·8 – 2·1 for MPXV and 4 – 6 for smallpox.[12]

The potential sites of viral shedding and entry routes also vary across clades. Direct contact is generally accepted as the primary route of MPXV transmission, which usually occurs when a person touches infectious materials (e.g., infected skin), or bushmeat, and subsequently touches their facial mucosa (i.e., eyes or mouth).[12–14] Contact with fomites has also been proposed as a potential transmission route, and analyses of virus stability on several surfaces found that viral particles remain stable for 1-to-2 days on porous and water-absorbent surfaces and up to 5 days on glass or stainless steel.[15] Alternatively, transmission can also occur through a breach in the recipient's skin or genitalia, providing a direct entry point for the pathogen.[16] Foodborne transmission (including bushmeat consumption) has been traditionally suspected, though this indirect route of transmission has not been fully confirmed.[14]

Clade 1a, found in patients infected in the DRC between 2007 and 2011, primarily due to zoonotic spillovers, was associated with early detection of high levels of viral DNA in the throat and blood, even before the rash appeared.[17] This could suggest viral entry through the oropharynx or respiratory tract, often presenting with initial symptoms like a sore throat, followed by viremia and disseminated skin lesions. The presence of viral DNA in these patients was highest and more prolonged in skin scabs, where it could be detected for up to 20 days, which could be a potential source of viral shedding and onward transmission.

Clade 1b (DRC, 2023), and clade 2b lineage A (Nigeria, 2017), both were assumed to spread through general direct contact, with an important component of sexual transmission but affecting all age ranges.[11,18] Conversely, clade 2b lineage B.1, responsible for the 2022 outbreak in non-endemic countries, was markedly associated with sexual contact. Transmission in these cases often required intimate contact, which could be facilitated by breaches in the skin or genital mucosa, leading to more localized infections at the entry point.[19] Whether the differences between Clade 1b and 2b A and Clade 2b B.1 are driven by the virus or primarily reflect the networks within which transmission took place remains unclear.

Airborne transmission has been suggested based on observation of animals in experimental settings,[20] the potential for airborne transmission of smallpox, and the stability of Orthopoxviruses in the environment.[21] The detection of MPXV in upper respiratory samples during the 2022 outbreak in non-endemic areas[19] and viable viral particles in hospital surfaces[22] has raised further concerns about the possibility of airborne transmission. Epidemiological data to date, including the absence of illness among neighbours[21] and no transmission among healthcare workers without face masks,[23] suggests that airborne spread is unlikely to be an important route of onward transmission. However, this statement should be taken cautiously due to limited evidence.

The incubation period varies between studies, though is generally shorter for clade 2b (7 – 10 days post-exposure) than clades 1a and 1b (mean 5 – 13 days; range 4 – 21).[24]However, it is unclear if this is due to the intrinsic characteristics of the virus or the route of exposure (sexual contact providing more direct access to the skin and, therefore, resulting in a shorter incubation period). The transmission window has been more accurately investigated in clade 2b lineage B.1., responsible for the 2022 outbreak. The potential period of infectiousness varied across different body compartments, with the DNA virus remaining detectable in skin lesions for up to 25 days, while the oropharynx, rectum, and semen cleared the virus within 13 to 16 days.[19] A study in the DRC, conducted during a period of Clade 1a dominance, found higher and more persistent oropharyngeal viral loads compared to clade 2b B.1., with similar viral shedding load and time in skin lesions.[17] The higher basic reproductive number (R_0 ~2.5) observed during the MPXV 2b B.1 outbreak is likely attributable to a high number of contacts within affected networks rather than an intrinsic increase in the virus transmissibility (i.e., higher secondary attack rate).

EPIDEMIOLOGY AND DEMOGRAPHIC DIFFERENCES

Clade 1a primarily circulates in Central Africa, especially in northwestern DRC, southern Central African Republic, and northern Republic of Congo,[17,25,26] in rural and rainforest areas (Table 1). The virus is primarily transmitted through zoonotic spillover, typically occurring through close contact with infected animals, such as during hunting and handling of bushmeat, followed by limited human-to-human spread. Genetic analysis of 348 high-quality genomes collected between 2018 and 2022 revealed substantial genetic diversity within clade 1a, with different genomes associated with distinct epidemic events, suggesting multiple independent zoonotic introductions into human populations.[27]

Historically, mpox cases in Central Africa were infrequent from 1970 to the 2000s.[28] However, after 2010, the number of cases began to rise significantly.[29] This trend escalated throughout 2023, reaching 21,835 cumulative suspected cases and 716 deaths by September 2024 in DRC (Figure 2, A).[30] In this last outbreak, children under 15 years old accounted for 70% of cases and over 80% of deaths.[31] The most affected provinces in DRC were Équateur, Sud-Ubangi, Tshopo, and Tshuapa (Figure 2,B).[30] Although testing is limited, the positivity rate among tested individuals is high, ranging from 50% to 90%, depending on the reports.[31] The increasing numbers of clade 1a cases reported in the DRC differs from trends in other countries and may be linked to the cessation of smallpox vaccination,[29] enhanced surveillance, increased human-wildlife interactions due to hunting and farming deeper into forests, and movement of the animal reservoirs in more close proximity to humans. Population growth, urbanization, and greater mobility may also be contributing to more frequent, though localized, outbreaks. These factors may all be amplified by ongoing humanitarian crises in the region.

The outbreak caused by clade 1b in DRC began in September 2023 in the province of South Kivu, a region previously unaffected by mpox, except for isolated cases in 2011.[32] Genomic analysis of 47 genomes revealed that 22 genomes from Kamituga —a medium-sized town in South Kivu — were classified as belonging to the newly identified clade 1b.[27] By September 1, 2024, the number of confirmed mpox cases in the South Kivu province amounted to 2,969.[30] Sexual contact has been identified as a significant mode of transmission in this outbreak and likely contributing to the rapid spread in densely populated urban centres and across borders; 29% of individuals with confirmed mpox were sex workers.[4] However, children have also been

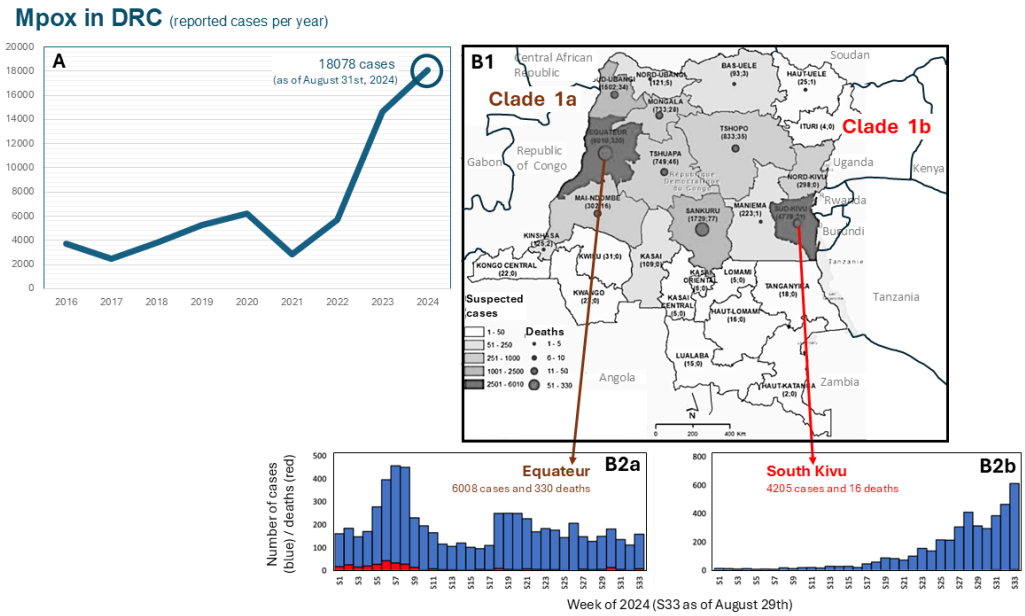
affected, and clade 1b has emerged in a refugee camp near Goma, with close contact suspected as the primary mode of transmission. The public health response in East DRC is difficult due to compromised healthcare infrastructure and the ongoing civil unrest, which makes it challenging to transport samples and obtain necessary reagents. The virus has since spread to neighbouring countries, including Rwanda, Uganda, Kenya, and Burundi.[33] In Burundi, 40% of cases are among children under 10 years old, further indicating spread within the community.[34]

Table 1. Epidemiology and transmission of Monkeypox Virus Clades

Category	**Clade 1a**	**Clade 1b**	**Clade 2a**	**Clade 2b, lineage A**	**Clade 2b, lineage B.1.**
Period	1970-2024	2024	2003	2017-2024	2022-2023
Geographical Distribution	Central Africa (West/Central DRC)	East DRC, regional spread	West Africa, some international	Nigerian outbreak 2017-2019	Global since 2022
Transmission Dynamics[9,12,28,35]	Zoonotic (70%), limited human spread	Human-to-human spread	Zoonotic (100%)	Zoonotic and widespread human-to-human	Sexual contact
Historical trends	Low until 2010, then rise	Emerged 2023, spreading	Small outbreaks	2017 Nigeria outbreak	2022 global outbreak
Demography	Mostly children	Mostly adults	Adults and children	Mostly adults	Mostly adult MSM
Genomics[4,8]	High diversity, multiple zoonotic introductions. Infrequent APOBEC3-type mutations (8% of all mutations)	Low diversity, limited spread. Significant mutations observed. Frequent APOBEC3-type mutations (55% of all mutations).	High diversity, multiple zoonotic introductions. Limited APOBEC3 activity (13% of all mutations).	Very frequent APOBEC3-type mutations (90.8% of mutations)	High diversity. Frequent APOBEC3 mutations (84.8% of observed mutations)

DRC: Democratic Republic of Congo. **MSM:** men who have sex with men

Figure 2. Incidence of mpox in the Democratic Republic of Congo.



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202 *Figure legend:* ***A)*** *Annual reported cases of mpox in the Democratic Republic of Congo (DRC)*
203 *from 2016 to 2024, with a notable increase in 2023.* ***B1)*** *Geographic distribution of mpox clades*
204 *in DRC (2024): clade 1, in Central and Northern DRC; clade 1b, concentrated in the South Kivu*
205 *region.* ***B2a)*** *Number of reported cases of Mpox in Equateur province in 2024 by*
206 *epidemiological week (clade 1a).* ***B2b)*** *Number of reported cases of Mpox cases in South Kivu in*
207 *2024 by epidemiological week: Initial cases in Kamituga (January 2024) were followed by rapid*
208 *expansion to other health zones, especially during May and June 2024. Comparison of case*
209 *numbers between South Kivu and other provinces, highlighting a high but stable number of*
210 *cases in other regions and a significant increase in South Kivu during 2024.*

211

212 Clade 2a, primarily found in West Africa, caused several isolated cases linked to zoonotic
213 transmission between 1970 and 2000 in countries including Cote d'Ivoire, Liberia, and Sierra
214 Leone.[32] In 2003, the U.S. experienced an outbreak of 71 cases across six states, traced back to
215 prairie dogs infected by animals imported from Ghana, with all human cases associated with
216 zoonotic transmission.[36–38]

217 Clade 2b lineage A.1 was identified during a large outbreak that occurred in Nigeria from 2017
218 to 2019, with over 300 confirmed cases.[11,18] This outbreak provided evidence of sustained
219 human-to-human transmission, although ongoing zoonotic transmission has also been
220 reported.[39] Sporadic cases of clade 2b have been reported in Western countries, often linked to
221 international travel.[40,41] In Nigeria, the ongoing human epidemic is currently driven by clade 2b
222 lineage A.2.3.

223 A new variant Clade 2b lineage B.1. triggered a global epidemic that began in May 2022. This
224 lineage spread to 113 countries, affecting over 100,000 people and resulting in 152 deaths.[16,24]
225 Transmission was human-to-human, with rapid spread through dense human networks,
226 especially among populations with sexual contact with multiple partners, predominantly
227 affecting men who have sex with men (87%), with approximately 50% of cases occurring in
228 people living with HIV.[42] The global spread was further facilitated by international travel and
229 interconnected communities.[43,44] Several factors likely contributed to this unusually large
230 outbreak, including chance events like large festivals where many people gathered, the

structure of the sexual networks involved, and viral adaptation.[44] Clade 2b MPXV has a high frequency of APOBEC3-induced mutations, indicating extensive adaptive microevolution in humans.[8,45] Cases in the global outbreak dropped sharply after three months, likely due to a combination of public health and social measures such as changes in sexual behaviour, vaccination of individuals at higher risk, and immunity amongst those who acquired mpox. However, the virus continues to circulate in many countries. In some countries, such as South Africa, this has been associated with a high CFR (i.e., up to 15%), likely driven by infections in people with unmanaged or recently diagnosed HIV infection.[46] Whether differences in transmission patterns simply reflect entry of the virus into different networks or is also partly driven by viral mutations remains unclear.

CLINICAL PRESENTATION AND SEVERITY OF OUTCOMES

Mpox has traditionally caused a systemic illness that includes fevers and myalgias, with a characteristic rash that is important to differentiate from that of other vesicular eruptions (e.g., chickenpox, smallpox). The reported clinical presentation of the disease varies significantly between clades.[24] It is not entirely clear to what extent these differences are influenced by viral clade, the patient's immune status, the route of exposure, or the infectious dose.

Across all clades, systemic symptoms such as fever, fatigue, and headache are common, reflecting some degree of systemic inflammatory response (Table 2). Lymphadenopathy is a key feature of mpox, with clades 1a, 2a, and 2b lineage A, presenting with generalized lymphadenopathy,[17,18,39] whereas clade 2b lineage B.1 more frequently presents with localized lymphadenopathy near skin lesions.[16,47,48]

The type of rash and local or systemic complications also varied in different outbreaks (Table 2). In clade 1a cases from DRC, skin lesions are primarily concentrated on the head, arms, and legs, spreading in a centrifugal pattern;[10,17,28,49] more than 90% of patients presented with more than 100 lesions, and 70-80% typically experienced lymphadenopathy (Figure 3A). Severe complications, including secondary bacterial infections with sepsis (20%) and involvement of the respiratory (11%) or gastrointestinal tracts (8%), are common.[10,17] Ocular manifestations were also less frequently reported in the 2022 outbreak compared with previous outbreaks.[50]

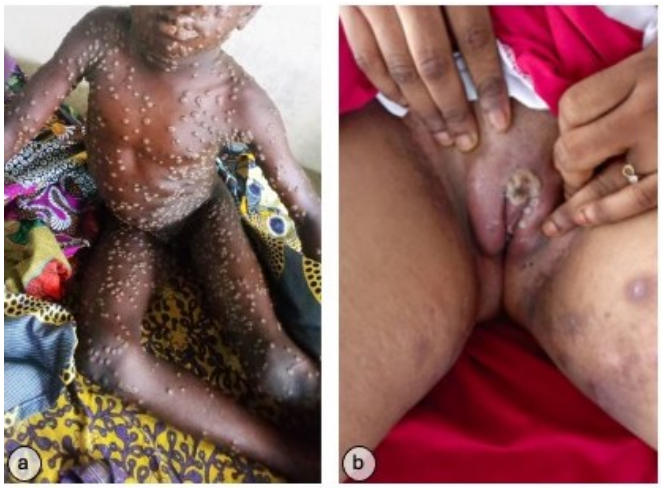
The clinical presentation of clade 2a MPXV infection was described in a few cases from West Africa; most of them were classified as mild or moderate, as opposed to cases linked to central Africa (clade 1), which were mostly classified as severe.[51] Clade 2a clinical presentation was more extensively described in the 2003 zoonotic outbreak in the U.S.[37] Patients presented with fever (85%), and generalized lesions mostly on the arms and legs (81%), and a small proportion had >100 lesions (20%) or a secondary complication (9%), mostly mild. Similarly, clade 2b lineage A also presents with generalized, though fewer in number lesions, and severe complications are reported to be less frequent.[11,18]

The clinical presentation of clade 2b lineage B.1. was described in detail during the 2022 outbreak.[16,27,47,48] Lesions are localized to specific areas, such as the genital, anal, and oral regions, reflecting transmission primarily through sexual contact. Sixty percent of cases present with less than 10 lesions, and very few have more than 100 lesions, with 50% experiencing lymphadenopathy. This clade generally does not lead to severe systemic complications, except for some rarely described events of vision loss, encephalitis, or myocarditis.[52,53] However, in individuals with advanced HIV (CD4 count <200 cells/μL), clade 2b can cause more severe outcomes, with some developing a fulminant condition, including necrotizing skin lesions (36%), lung nodules (15%), bowel obstruction (20%), or sepsis (28%).[54] Likewise, clinical reports

of the 2022 outbreak in Nigeria showed severe outcomes in patients co-infected HIV or varicella zoster virus.[55,56] Solid organ transplant recipients with clade 2b infection also experienced severe outcomes.[57]

In the recently described clade 1b, the median age of affected individuals is 22 years, with 50% being female and 30% being sex workers, though children are also affected.[4,27,49] Genital lesions were reported in 63% – 85% of cases. While 91% of patients were hospitalized, primarily for isolation, only 10% experienced severe respiratory issues. (Figure 3B) Clinical data are still emerging.

Figure 3. Comparison of Disseminated and Genital Mpox Presentations in clades 1a and 1b



A) A child with disseminated mpox lesions associated with clade 1a, showing widespread umbilicated vesicles on the torso and limbs. B) A female patient with genital mpox lesions associated with clade 1b, characterized by vulvar coalescent whitish vesicles with umbilicated center.

Table 2. Clinical presentation and complications of Monkeypox Virus Clades*

Feature	Clade 1a	Clade 1b	Clade 2a	Clade 2b lineage A	Clade 2b lineage B.1.
Population features					
Age	10% adults	85% adults in DRC, 60% in Burundi.	73% adults	70% adults	80-99% adults
Mean age	14 years	22 years	--	26–32 years	37–41 years
Male/Female	M: 50-64% F: 26-50%	M: 48% F:52%	M:53% F:47%	M: 53–78% F: 22-47%	M: 97–100% F:0-3%
Smallpox vaccination in childhood	2%	Unknown	Unknown	20%	11–18%
Exposure to animal products	100%	0%	100%	No	No
Living with HIV	0.5%	7%	unknown	ND	36–67%
Systemic symptoms					
Fever	44-50%	60%	85%	45-90%	54-72%
Fatigue or myalgia	85%	--	71%	73-85%	24-81%

Headache	24%	--	65%	48-79%	25-53%
Sore-throat or cough	78%	--	50%	ND	ND
Lymphadenopathy	51-98% (submaxillary, cervical)	42%	71%	57–87% (cervical, 50%)	60% (inguinal)
Clinical features of the rash					
Severe Rash (>100 lesions)	93%	unknown	20%	20–42%	0–4%
Distribution	Generalized (100%)		Generalized (75%)	Generalized	Localised
Primary site of lesions	Face	Oral (40%), genital (80%)	Arms	Site of animal contact	Anogenital (70-87%)
Face	100%	--	62%	96–98%	20–39%
Arms and Legs	100%	--	81%	81–91%	50–60%
Palms and soles	70-81%	--	28%		
Trunk	70-100%	--	56%	80–93%	25–57%
Genitalia	27%	--		67–68%	55–61%
Perianal	ND	--		ND	34–44%
Oropharyngeal	28-52%	--		38%	14–43%
Severe Complications					
Secondary bacterial infection	19%	--	6·3%	19%	3-4%
Respiratory	11% (abnormal lung sounds)	--	6·3% retropharyngeal abscess	12% bronchopneumonia	0%
Rectal (proctitis)	0%	--	--	ND	11-25%
Gastrointestinal	7-8%	--	--	ND	ND
Ocular	4-6%	--	6·3%	0.4%	1%
Neurological	0·4-6%	--	--	0.4%	0%
Hospital admission	6%	--	24%	26%	1–13%
Fatality rate	1–12%	0·6%	0%	3·6%	<0·1%

*Data were retrieved from published retrospective cohorts[3,10,11,16–18,28,37,47,48]

The case fatality rate (CFR) has been higher in clade 1 compared to clade 2. During the 2023 outbreak in the DRC (clade 1a), the estimated overall CFR was 4%, rising to 11% in children under five years old.[49] In earlier studies, the CFR reported for Central Africa ranged from 4% to 12%, with deaths generally occurring in the second week of illness.[10,28,58] The 2017 Nigeria outbreak (clade 2b lineage A) resulted in a fatality rate of 3·6%, which was likely magnified due to several deaths occurring in immunocompromised persons with HIV.[11,59] Based on the adverse outcomes reported, other groups, such as pregnant women, are likely at higher risk of death, though the CFR is less well established than associations with age and HIV.[60] In contrast, there were no deaths in the 2003 outbreak in the U.S. (clade 2a).[38,61] During the multi-country 2022 outbreak (clade 2b lineage B.1.) only a few deaths have been reported.[62] Most of these cases have been reported in immunocompromised persons with advanced HIV (CFR 15%, CD4 counts <200 cells/μL).[54,57,63]

The higher severity of clade 1 compared to clade 2 has also been observed in pregnancy. Although data from the 2022 outbreak are limited for this population group because it affected mostly men, no deaths or vertical transmission was reported among pregnant women infected with MPXV.[60,64] Conversely, MPXV infections among pregnant women occurred in outbreaks dominated by clade 1 resulted in stillbirth or miscarriage in 75% of the cases.[60,65] The CFR among pregnant women has not been fully established.

Whether the observed differences in severity of outcomes and CFR of clade 1 and clade 2 MPXV are primarily driven by differences in the virus, population characteristics (e.g., age, and

co-morbidities) or access to timely diagnosis and supportive care is not yet fully understood. For example, in the 2022 global outbreak, reported CFRs varied depending on the prevalence of untreated, advanced HIV amongst the affected populations.[24] Further study is required to better delineate the role of viral, host and health system factors in explaining observed differences.

People with prior mpox infection or previous vaccination tend to have milder symptoms. In a report of 37 cases of reinfection or post-vaccination infection, symptoms were less severe than in the 2022 global outbreak. Reinfections had a shorter disease course with less mucosal involvement, while post-vaccination cases showed few lesions, minimal mucosal disease, and low analgesia needs.[66]

DIAGNOSTICS

Mpox diagnosis primarily relies on the detection of viral DNA through real-time polymerase chain reaction (rt-PCR), allowing for the detection of the virus in various specimen types, including swabs from skin lesions, oropharyngeal, genital, and anal regions. Accurate diagnosis is highly dependent on proper sample collection, storage, and transport. Self-collected swabs have emerged as a practical option in some settings.[67] Of note, in many settings, diagnosis is made via clinical assessment alone due to inadequate access to diagnostic testing. Clinical diagnosis may be less reliable in children due to the wide range of other causes of fever-rash illnesses in this age group.

rt-PCR assays recommended by the CDC have been proposed, which can distinguish MPXV from other orthopoxviruses, but also between clade 1 and clade 2.[68] These include primers for generic MPXV detection (G2R_G), as well as clade1 (C3L) and clade 2 (G2R_WA) specific detection.[69] However, clade 1b is associated with specific diagnostic challenges, as it can be missed by certain PCR assays due to deletion of the C3L gene, leading to false negatives.[70] To ensure accuracy, it is crucial to use PCR tests with multiple targets, including very conserved regions, and to employ kits specifically validated for detecting clade 1b. Identification of clades is vital for precise diagnosis and epidemiological monitoring. When possible, direct sequencing may be used to confirm clade identity and the development of multiplex assays that can detect multiple clades simultaneously should be prioritized.

In the DRC, a robust network of GeneXpert machines is available, providing valuable diagnostic capacity. However, the current GeneXpert MPX/OPX assay is designed to detect non-variola Orthopoxvirus and MPXV clade 2. While the first target is useful for the DRC, the second one has no utility in areas where only clade 1 circulates. In these settings, MPXV clade 1 infection is being indirectly inferred when clade 2 results are negative.[71] This shortcoming underscores the need for updating and expanding the diagnostic toolkit to ensure comprehensive detection of all relevant clades.

Rapid antigen tests are available, but they often show very low sensitivity.[72] The use of polyclonal antibodies in these tests is recommended to enhance their performance since monoclonal antibodies may lose effectiveness due to mutations. In addition to these antigen tests, molecular diagnostic options are advancing: the WHO recently approved the Alinity m MPXV assay by Abbott Molecular Inc. for emergency use, marking the first commercial molecular assay for mpox. More independent evaluations are needed to better understand the utility of rapid antigen and molecular tests for mpox.

THERAPEUTICS

Mpox treatment primarily involves supportive care to manage symptoms and complications, such as pain relief, hydration, and treating secondary infections. No drugs are specifically approved for mpox, but antivirals like tecovirimat, cidofovir, and brincidofovir have shown some evidence for efficacy in preclinical studies and are available under compassionate use protocols, particularly for severe cases.[73]

Tecovirimat, widely used during the 2022 outbreak, acts by inhibiting the function of envelope proteins required for the production of extracellular virus.[74] In some countries (e.g., the UK and European Union) tecovirimat is approved for the treatment of mpox, while in the U.S., it is an investigational agent that needs to be accessed through either the CDC's Expanded Access-Investigational New Drug (EA-IND) protocol or the open-label arm of the STOMP trial.[74] In highly immunocompromised patients, combination therapy has been used. Case reports have shown that mpox patients living with HIV with very low CD4 counts (<200 cells/μL) and uncontrolled HIV loads can have a prolonged course of disease and high mortality, even with treatment.[75] The use of tecovirimat is being further evaluated in six ongoing placebo-controlled randomized controlled trials (RCTs), most of which are expected to be completed by 2025. Early results from an RCT in the DRC did not demonstrate clear benefits of tecovirimat for treatment of patients with mpox clade 1 infections.[76] The overall mortality rate of the trial was lower than expected (1·7%), likely due to the enhanced care provided, emphasizing the importance of high-quality supportive care in managing mpox.

Brincidofovir, though less commonly used than tecovirimat, remains a potentially viable option,[77] especially when tecovirimat is ineffective or unavailable. It acts by interfering with viral lipid metabolism, and it is typically considered for patients who do not respond to tecovirimat, experience disease progression, or have contraindications. Pre-clinical research on antivirals against mpox is ongoing, and the number of mpox-related patents has increased rapidly in the past few years.[73,78]

VACCINES

All available vaccines are currently based on attenuated vaccinia-virus strains rather than MPXV itself. The first-generation monkeypox vaccine, Dryvax, was effective in reducing transmission in an African study by lowering the secondary attack rate among household contacts.[10] However, it was withdrawn due to outdated manufacturing methods. Currently, the available vaccines are ACAM2000 and LC16m8, both replicating vaccines derived from an attenuated viral isolate, and Bavarian Nordic's Modified Vaccinia Ankara (MVA-BN), a replication-deficient vaccine. A number of novel vaccines, including mRNA candidates, are in development, but none are sufficiently advanced for widespread deployment at this time.

The MVA-BN vaccine has shown effectiveness in preventing clade 2b mpox based on observational studies, though no RCTs have been conducted. A case-control study across 12 U.S. jurisdictions estimated the vaccine effectiveness at 75·2% after one dose and 85·9% after two doses,[79] and that the vaccine is effective across various administration routes (subcutaneous, intradermal, and heterologous) and provides substantial protection, even among immunocompromised individuals, albeit with slightly lower effectiveness in this group. Another U.S.-based study reported adjusted vaccine effectiveness of 35·8% for one dose and 66% for two doses.[80] MVA-BN vaccine effectiveness for post-exposure prophylaxis is much lower at only 20% (95%CI -24% – 65%).[81]

Safety data indicate that the vaccine is well-tolerated in children, with most adverse events being mild and self-limiting.[82] In a large-scale safety monitoring study involving nearly 1 million doses of MVA-BN administered in the U.S., the vaccine was well-tolerated across all ages, including children, with no serious adverse events in those under 18, confirming its safety in children.[82] Another study on children further validated its safety and reactogenicity.[83] Data on the efficacy of MVA-BN in the context of clade 1 MPXV is currently limited. However, given its proven efficacy in adults against clade 2 MPXV, and favourable safety profile in children, the vaccine is likely to be a mainstay of control efforts in the current outbreak in DRC.

The LC16m8 vaccine, based on a live attenuated strain of vaccinia, was licensed in Japan in 1975 without age restrictions after the last smallpox cases were reported in Japan. In August 2022, its use was expanded to include the prevention of mpox. There are no direct studies on its effectiveness against smallpox. Animal studies showed that LC16m8 provided strong protection in mice, rabbits, and monkeys against lethal challenges with the MPXV.[84] In immunogenicity studies, seroconversion was elicited in 90·2% [95% CI, 81·2% – 99·3%]) vaccinia-naive participants and 60·0% [95% CI, 52·3% – 67·7%]) of previously vaccinated participants. No severe adverse events were observed.[85]

There is limited data to inform the optimal vaccine roll-out strategy. Given the extent of the current outbreak, widespread vaccination for the population at risk is likely recommended. Identification of critical populations (such as health care workers and infants) who most urgently require vaccination is an important priority. Given the likelihood of a limited vaccine supply, evaluation of strategies such as delaying the second dose of vaccine to facilitate more rapid roll-out should be strongly considered.

BROADER PUBLIC HEALTH RESPONSE

Along with biomedical interventions, such as vaccines and therapeutics, a number of other elements are critical for the control of mpox. Although not specifically tested in the mpox context, isolation and contact-tracing strategies, both in the community and healthcare settings, have proven essential to minimise the risk of onward transmission in viral outbreaks.[86,87] Although critical, such measures require education and adequate facilities and staffing and can be, therefore, challenging to implement, especially as the number of cases requiring isolation and contact tracing increases.

The development of appropriate messaging and involvement of communities themselves in the outbreak response is a critical and often overlooked component. Such issues are especially marked in the current mpox outbreak where the visible nature of the illness and its transmission, at least in part through sexual contact, can both be associated with significant stigma. However, as demonstrated in previous ebola outbreaks, sustained community engagement and education are vital to ensure the success of control measures.

CONCLUSIONS

Recent years have witnessed large-scale outbreaks of both clade 1 and clade 2 of MPXV, with different transmission patterns and clinical characteristics between viral variants. There is an urgent need to evaluate and deploy public health measures to control the simultaneous outbreaks now occurring worldwide. Sustained term investment in outbreak preparedness and increasing access to mpox vaccination in Africa are urgently required to provide lasting

protection to affected and at-risk populations. Future research should also investigate the contribution of viral characteristics and external factors (e.g., population characteristics and access to healthcare resources) to the different outcomes observed between viral variants.

Contributors

All authors planned, wrote, and revised the manuscript. OM wrote the first draft and led the work.

Declaration of interests

The authors declared no conflicts of interest.

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