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# Understanding the Mpox outbreak: Advances in epidemiology, management and prevention (Review)

ABDULELLAH SAMER ALGHAMDI[1], BASHEER ALDAJANI[1], MOHAMMED ALI ALJASIM[1], ABDULLAH HANI ALOTAIBI[1], ALI TALEB ALSULTAN[1], ABDULLAH ABBAS ALHUSSAIN[1], ABDULAZIZ KHALIL ALSWEDAN[1], KAMALUDDIN H. MOTAWEI[2], MUHAMMAD IQBAL[3] and SHAHID BASHIR[4,5]

[1]College of Medicine, Imam Abdulrahman Bin Faisal University, 34221 Dammam, Kingdom of Saudi Arabia; [2]Department of Anatomy, College of Medicine, Imam Abdulrahman Bin Faisal University, 34221 Dammam, Kingdom of Saudi Arabia; [3]Department of Physiology, College of Medicine, King Saud University, 11362 Riyadh, Kingdom of Saudi Arabia; [4]Neuroscience Center, King Fahad Specialist Hospital Dammam, Dammam 32253, Kingdom of Saudi Arabia; [5]King Salman Center for Disability Research, Riyadh 11614, Kingdom of Saudi Arabia

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**Abstract.** Monkeypox (Mpox) is a zoonotic disease caused by the monkeypox virus (MPXV), a member of the *Poxviridae* family. Historically endemic to Central and West Africa, its spread beyond these regions in 2022 prompted the World Health Organization to declare it a public health emergency. Mpox is primarily transmitted through direct skin-to-skin contact with lesions, animal bites, or exposure to contaminated materials. The present review discusses the epidemiological, virological, immunological, clinical, diagnostic, and preventive aspects of Mpox infection. It highlights the two main viral clades (clade I and clade II), the role of APOBEC3-driven mutations, and factors contributing to the resurgence of outbreaks, such as environmental changes, increased urbanization, air travel, and the prevalence of HIV/AIDS. Clinical manifestations range from localized rash and systemic symptoms to severe complications like encephalitis and sepsis. Diagnostic approaches including PCR, whole-genome sequencing, and electron microscopy are explored, alongside preventive measures such as the JYNNEOS and ACAM2000 vaccines. Management primarily involves supportive care and antiviral therapy with tecovirimat, although recent clinical trials have raised concerns about its efficacy. Challenges in outbreak control include limited vaccine access, diagnostic resource gaps, stigma, particularly among high-risk populations, and the potential emergence of antiviral resistance. The present review emphasizes the importance of the One Health approach, recognizing the interconnectedness of human, animal, and environmental health sectors, to ensure a coordinated and effective response. Furthermore, it underscores the need for ongoing research into viral evolution, novel therapeutic development, enhanced diagnostic methods, and understanding long-term physical and psychosocial outcomes to strengthen global preparedness against Mpox outbreaks.

*Correspondence to:* Dr Shahid Bashir, Neuroscience Center, King Fahad Specialist Hospital Dammam, Dammam, Ammar Bin Thabit Street, Al Merikbat Neighbourhood, Dammam 32253, Kingdom of Saudi Arabia
E-mail: shahidbpk13@gmail.com

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**Contents**



## 1. Introduction

While the world was still recovering from the pandemic caused by the coronavirus disease 2019 (COVID-19), the emergence of a new monkeypox (Mpox) outbreak raised concerns among public health authorities about whether it posed an unprecedented threat to the general population (1,2). The present review aimed to provide a comprehensive overview of the virus; this may be critical at this time, due to the two Public Health Emergency of International Concern (PHEIC) declarations related to Mpox since 2022. The first declaration was announced on July 23, 2022, and was removed less than 1 year later on May 11, 2023 following the recommendation of the International Health Regulations (IHR) due to significant progress being made in controlling the outbreak worldwide (3,4). The second declaration was made on August 14, 2024 as advised by the IHR after reviewing recent data indicating an upsurge in Mpox infections with the potential to spread within Africa and beyond (5). The following day this became a reality with confirmation of a case of Mpox in Sweden (6). Another reason for the importance of the present review is the recent emphasis on One Health, an approach that considers the interconnectedness of people, animals and ecosystems. With the ongoing increase in the human population and their expansion into new areas, close contact with animals whether livestock or pets has increased. Additionally, the rise in international travel and trade has contributed to the spread of zoonotic diseases (7,8). This is particularly relevant for Mpox, as the virus affects both animals and humans, and transmission can occur between them (9).

The present review aimed to present a thorough and comprehensive summary of Mpox, including its etiology, drivers of recent outbreaks, transmission epidemiology, geographic distribution, eradication efforts, predisposing factors, clinical presentation, diagnosis, management, vaccination, prevention, treatment, complications, future directions and importance of One Health approach for a coordinated response to outbreaks.

## 2. Monkeypox virus

Monkeypox virus (MPXV) is an enveloped, double-stranded DNA virus with a genome of ~190 kb (10). It belongs to the genus *Orthopoxvirus* in the *Poxviridae* family, which also includes vaccinia, cowpox, variola and various other animal-pathogen poxviruses (11,12). Poxviruses have a higher tolerance to extreme pH and temperature levels compared to other enveloped viruses and are highly resistant to drying, which contribute to their persistence in the environment (13). Viruses in the *Orthopoxvirus* genus are known to remain stable in the environment for extended periods of time (14). As a result, MPXV can survive on household surfaces for at least 15 days following contamination (15). While common disinfectants pose a risk to poxviruses, they are most resistant to organic disinfectants compared to other enveloped viruses, increasing their chances of survival and transmission (16).

*History of MPXV.* MPXV was initially isolated from monkeys in 1958 at the Statens Serum Institut in Copenhagen, Denmark, which is how its name was derived, although monkeys are not the true reservoir of the virus. Other natural hosts include dormice, tree squirrels, rope squirrels and Gambian pouched rats (17). The virus is incidentally transmitted to humans from these hosts, as is common with a number of zoonotic diseases, when they come into contact with infected animals. The first recorded human case of Mpox infection occurred in the Democratic Republic of the Congo (DRC) in 1970 (17). After sequencing MPXV, including archived samples from 1971, it has been observed that the virus has undergone a series of TC→TT and GA→AA mutations since then, as shown in the Mpox phylogenetic tree (18). This mutation pattern indicates that APOBEC3 deamination, which is characteristic of replication in humans, is a major source of genetic variation of these recent genomes (18). APOBEC3 enzymes have antiviral function, inactivating the virus by inducing changes in its genome via repeated rounds of C→T and G→A mutations on the positive strand during replication (18). While heavily mutated genomes are likely non-viable and unable to be transmitted further, moderately mutated genomes still retain their viability and continue to be transmitted to other susceptible hosts occasionally (18).

*Genetic clades.* Currently, there are two genetically distinct MPXV clades: Clade I, previously known as the Central African (Congo Basin) clade, and clade II, formerly called the West African clade (19). Clade II is further divided into subclades IIa and IIb (20). These two clades exhibit genetic differences in their viral genomes, which may account for variations in viral pathogenesis and clearance (21,22). Historically, clade I has been shown to be associated with more severe disease, higher mortality rates and is considered to be more transmissible (23,24). However, the current Mpox outbreak appears to be primarily caused by clade II (17). Recently, a new lineage of clade I was discovered in an ongoing outbreak in the DRC (5). Additionally, APOVBEC3-related mutations have been identified as a hallmark for human-to-human transmission of the virus. As a result, clade I has also been subdivided into two subclades Ia (previously known only as I), and Ib (the novel lineage discovered) (5,25).

In summary, recent Mpox outbreaks involve two main clades: Clade II linked to the recent outbreaks and a new sublineage of clade I. The present review also emphasizes a One Health approach to understanding its spread.

## 3. Drivers of recent outbreaks

*Mpox zoonotic transmission.* MPXV is mainly transmitted through three modes: animal-to-animal, animal-to-human, or human-to-human (26). While the natural reservoir remains unknown, current evidence suggests that *Funisciurus anerythrus,* a rodent, may serve as the natural reservoir for Mpox (27). The first case of Mpox outside Africa occurred in 2003, when giant rats infected prairie dogs through direct contact. These prairie dogs were later sold as household pets in the Midwestern USA, leading to the infection of 71 humans; this raised the attention of the international community to Mpox (28). It was later shown that animal-to-human transmission was achieved by touching an infected animal or receiving a bite or scratch (26,28). The recent outbreak in 2022 is mainly driven by human-to-human transmission, which occurs through skin-to-skin contact, intimate contact, body fluids, shared dishes and utensils, or respiratory droplets (29).

*Environmental changes.* Mpox usually spikes during the fall in the Central African Republic (CAR) due to heavy rainfall, which leads to flooding and deforestation of natural habitats, s, pushing animals closer to human settlements. This increases the risks of animal-to-human transmission as humans come into more frequent contact with natural reservoirs (30). Furthermore, a change in ecological balance, caused by the unsustainable hunting of rodent predators and other large species in regions such as Lobaye, CAR, leads to an increase in small mammals. As a result, there is a greater consumption of rodents in local diets, further contributing to the spread of the disease (31).

*Human factors*. Since the 2003 outbreak in the USA, the majority of reported cases outside of the African continent have been sporadic and related to travel. Between 2018-2021, there were 8 documented cases, all involving males who travelled from Nigeria (32). The study by Gao *et al* (33) analyzed the 2022 outbreak and found that population density plays a crucial role in the spread of the disease. Cities at most risk tend to have high population density, a large migration rate and numerous connection hubs, all of which facilitate the transmission of Mpox (33). Recently, air travel and the prevalence of HIV/AIDS have been predicted to be the main drivers of Mpox prevalence across various countries (34).

*Relation to one health*. One Health is described by the Centers for Disease Control and Prevention (CDC) as 'an approach that recognizes that the health of people is closely connected to the health of animals and our shared environment' (35). One Health is now more important than ever in the light of the accelerated rate of emerging novel zoonotic diseases. To address this, it emphasizes the prompt identification and rapid response to disease outbreaks to avoid future epidemics (36). To achieve this, a strategic framework should be established that involves professionals from human health, animal health, environmental agencies, and other sectors. This will facilitate communication, collaboration, and coordination across all disciplines (35).

As Mpox spreads between animals and humans, environmental factors, such as deforestation, air travel, population density and the prevalence of HIV/AIDS contribute to its transmission. Therefore, the One Health approach is crucial for ensuring a coordinated response to the Mpox outbreak.

## 4. Transmission

MPXV enters the host via breaches in the skin or mucosal surfaces. Zoonotic transmission occurs through direct contact with infected animals, including exposure to body fluids, bites, scratches, or the consumption of undercooked meat (37). Human-to-human spread primarily involves fomites, respiratory droplets, and contact with skin lesions (36,37). Some cases have been linked to sexual contact, particularly among bisexual and homosexual males (38,39), although the detection of MPXV nucleic acid in semen does not confirm infectivity (40). Rare perinatal and nosocomial transmissions have been documented (41-43), with no evidence supporting transmission via other human-derived substances (44).

Thus, monkey pox spreads through skin contact, animal bites, human lesions, droplets and sometimes-sexual contact, with rare perinatal and nosocomial cases.

## 5. Epidemiology

For any outbreak, a more rapid, safer and more accurate diagnosis is crucial, particularly in regions where the disease is prevalent. Early detection not only aids in containing the disease, but also helps in identifying its causes, ultimately preventing further spread.

*Background*. MPXV is the infectious agent that causes Mpox, often known as monkeypox. MPXV is classified into two recognized clades: Clade I, formerly known as the Congo Basin clade, and clade II, formerly known as the West Africa clade. Clade II is further divided into two subclades, clade IIa and clade IIb. One of the two clades of MPXV causes the illness. Mpox can be transmitted from animals to humans through contact with live animals or contaminated bush meat. It can also spread between individuals through close contact with lesions, bodily fluids, respiratory droplets or contaminated objects (45). Sexual interaction between homosexual males who are part of large sexual networks has for the first time been a driving and sustained factor in the spread of MPXV (46).

In 1958, MPXV was identified in Denmark in monkeys housed for scientific research. The first human case of Mpox was recorded in 1970 in a 9-month-old child in the DRC. Following the eradication of smallpox in 1980 and the global discontinuation of smallpox vaccinations, Mpox gradually spread across Central, East and West Africa due to the viruses belonging to the same genus. Since then, the prevalence of Mpox has been intermittently reported in Central and East Africa (clade I the more severe form) and West Africa (Clade II which triggered worldwide outbreak) (9,47).

In summary, MPXV has two clades: Clade I, which causes severe cases in central and east Africa, and clade II, linked to the global outbreak. It spreads from animals via bushmeat or contact between individuals, with sexual transmission among males now being a significant causal factor.

### *Geographic distribution*

*Outbreaks in the USA*. The first recorded human case of Mpox outside Africa occurred in the USA in 2003 (48). During the 2003 USA outbreak, six states (Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin) reported 47 confirmed cases and 10 probable cases (49). In the global outbreak that reached the USA between 2022-2023, nearly 32,000 cases of Mpox and >58 related deaths were reported. The USA accounted for approximately one-third of all cases worldwide (50).

As of September 28, 2024, >2,500 cases of Mpox Clade II have been reported in the USA, up to January 1, 2024. Due to the efforts of the CDC to combat the spread, the overall case count is increasing at a very slow rate, while the number of new cases continues to decline. Thankfully, as of January 10, 2024, no cases of clade I Mpox, the more severe type, have been reported in the USA. Clade II Mpox is still circulating at low levels, with no significant changes observed over the past 6 months. The majority of cases in the USA have occurred in individuals who were either unvaccinated or had received only one dose of the JYNNEOS vaccine. Two doses of JYNNEOS are recommended to provide maximum protection (51,52).

The cumulative number of Mpox cases in Region of the Americas from January 1, 2022, through June 30, 2024 has reached ~62,900, with 141 related deaths. Cases have been declining each month. The countries with the highest case counts include the USA, Brazil, Colombia, Mexico and Peru (53).

According to a recent CDC update from February 12, 2025, the first USA case of clade Ib Mpox (the severe version in Africa) was verified in California in November, 2024 after the patient travelled to an infected location. On January 14, 2025, a traveler from a nation where Mpox transmission was ongoing was proven to have contracted clade Ib Mpox in Georgia, the second in the USA. New Hampshire reported the third clade Ib Mpox case in the USA on February 7, 2025. In New York, on February 12, 2025, the fourth case of clade Ib Mpox in the USA was reported (54).

There have been no reports of the further spread of Mpox; the four cases are distinct occurrences that are not connected. Furthermore, the CDC determined that the clade I Mpox outbreak posed a low risk to the general American community as well as to some American populations. Furthermore, clade II Mpox is still circulating at low levels (54).

Owing to the CDC and the efforts of other organizations to combat the spread of Mpox in the USA, the number of new clade II cases has been extremely low, averaging between 1 and three 3 per day, from the beginning of 2025 to February 23, 2025, which was the time of the writing of the present review (55).

*Europe outbreak*. Mpox clade IIb caused a global outbreak in 2022, originating in Europe. Sexual contact was the primary method of the human-to-human transmission of the disease (56). In the European region, between January 1, 2022 and June 30, 2024, ~27,500 Mpox cases and 10 related deaths were reported, with cases decline each month. The countries with the highest case numbers include Germany, UK, France and Spain (53). A total of 11 MPXV clade Ib cases have been documented in the EU/EEA since August 2024, according to a recent update from the European Center for Disease Prevention and Control (ECOC) on February 14, 2025, indicating that Mpox clade Ib has also reached Europe. The first imported case of Mpox caused by MPXV clade Ib in EU/EEA nations was reported by Sweden on August 15, 2024. Germany recorded 7 cases (1 case in October, 5 cases in December 2024, and 1 case in January 2025), Belgium reported 2 cases in December 2024, and France reported 1 case in January 2025. All individuals had mild disease (57,58).

Belgium and Germany reported confirmed secondary transmission events; 3 individuals (two of whom were children) were household contacts of an index case in Germany who had previously visited a nation that was affected. Of note, 1 child in Belgium was a household contact of an index case who had previously visited a nation that was impacted. China and the UK have also reported confirmed secondary transmission of Mpox caused by MPXV clade I outside of Africa (57,58). Additionally, the China CDC reports that it has only confirmed 4 cases of clade Ib, all of which were linked to travel and close contact. All these patients had mild symptoms, such as rash, and were treated appropriately. A few cities established a collaborative prevention and control mechanism to conduct epidemiological investigation, case diagnosis, and treatment following the discovery of the outbreak (59).

As of February 12, 2025, a total of 23,882 confirmed cases of Mpox had been reported from 29 EU/EEA nations since the outbreak began: As per the European Centre For Disease Prevention And Control (ECDC), these were reported as follows, starting from the highest to lowest: Spain, 8,513 cases; France, 4,392 cases; Germany, 4,136 cases; The Netherlands, 1,442 cases; Portugal, 1,212 cases; Italy, 1,109 cases; Belgium, 856 cases; Austria, 366 cases; Sweden, 326 cases; Ireland, 279 cases; Poland, 233 cases; Denmark, 216 cases; Greece, 138 cases; Norway, 121 cases; Czech Republic, 100 cases; Hungary, 85 cases; Luxembourg, 62 cases; Romania, 49 cases; Slovenia, 47 cases; Malta, 44 cases; Finland, 43 cases; Croatia, 37 cases; Slovakia, 19 cases; Iceland, 17 cases; Bulgaria, 11 cases; Estonia, 11 cases; Cyprus, 6 cases; Latvia, 6 cases; and Lithuania, 6 cases. Furthermore, related deaths were reported as follows: Spain, 3; Belgium, 2; Portugal, 2; Austria, 1; and Czech Republic, 1 (57,58).

Moreover, as of January 14, 2025, a total of 23,682 confirmed cases of Mpox were recorded from 29 EU/EEA countries since the outbreak began (57,58). Additionally, the recent update from ECDC ‘week 7 and 8’ states that since the last update on January 14, 2025, and as of February 12, 2025, 124 Mpox cases were reported from 18 EU/EEA countries. Starting from the highest to lowest, ECDC reported these as follows: Germany, 42 cases; Sweden, 15 cases; The Netherlands, 11 cases; Ireland, 9 cases; Italy, 9 cases; Czech Republic, 6 cases; France, 6 cases; Poland, 6 cases; Greece, 4 cases; Denmark, 3 cases; Portugal, 3 cases; Spain, 3 cases; Croatia, 2 cases; Belgium, 1 cases; Bulgaria, 1 case; Malta, 1 case; Romania, 1 case; and Slovakia, 1 case. Moreover, since January 14, 2025, no new countries have reported confirmed cases (57,58). MPXV clade II is still in circulation worldwide and it is primarily observed in adult homosexual males outside of Africa (57,58).

*Africa outbreak*. As of July 28, 2024, 15 African Union Member States (AUMS), namely Benin, Burundi, Cameroon, CAR, Congo, DRC, Egypt, Ghana, Liberia, Morocco, Mozambique, Nigeria, Rwanda, Sudan and South Africa, had reported a total of 37,583 cases and 1,451 related deaths [case fatality rate (CFR), 3.9%]. A total of seven AUMS reported 14,957 cases and 739 related deaths (CFR, 4.9%) in 2023 alone. Compared to 2022, there was a 78.5% increase in the number of new cases (60,61).

Since the beginning of 2022 and as of July 28, 2024, the following 10 AUMS had reported a total of 14,250 cases (confirmed cases, 2,745; suspected cases, 11,505) and 456 related deaths (CFR, 3.2%) from Mpox: Burundi (8 cases; 0 deaths), Cameroon (35 cases; 2 deaths), CAR (213 cases; 0 deaths), Congo (146 cases; 1 death), DRC (13,791 cases; 450 deaths), Ghana (4 cases; 0 deaths), Liberia (5 cases; 0 deaths), Nigeria (24 cases; 0 deaths), Rwanda (2 cases; 0 deaths) and South Africa (22 cases; 3 deaths). Compared to the same period in 2023, this indicates a 160 and 19% increase in cases and deaths, respectively, in 2024. Of note, 97% of all recorded deaths this year and 96.3% of all cases are related to the DRC. Furthermore, Chad has reported 24 suspected cases in 2024, but no confirmed cases (60,61). The spike of Mpox cases in the DRC, along with a growing number of cases in other African nations prompted the WHO to declare a Public Health Emergency of International Concern on August 14, 2024. This announcement followed the Africa Centers for Disease Control and Prevention's (Africa CDC) August 13 designation of a Public Health Emergency of Continental Security (62).

The subclass of clade I Mpox known as ‘clade Ib’ is currently circulating throughout Africa, particularly the DRC, and it has also spread to other nations, such as Sweden and

Thailand. As a result, both clad Ia and clad Ib are circulating in the DRC, and the numbers of cases continue to increase daily (62).

According to a new WHO report no. 47 released on February 13, 2025, between January 1, 2024, and February 2, 2025, there were 21,113 confirmed Mpox cases in Africa and 70 confirmed deaths, with the majority of cases and deaths occurring in the DRC, Burundi, and Uganda (63,64). In Africa, there were 3,482 confirmed cases and 7 confirmed deaths between December 23, 2024, and January 2, 2025, in the same top three countries DRC, Burundi and Uganda (63,64).

*DRC*. During the smallpox outbreak, the first case of Mpox was identified in a 9-month-old infant at Basakusu Hospital in Equateur Province, Zaire (65,66). Between 1981 and 1986, 338 cases of Mpox (with 67% confirmed by viral culture) were found in the DRC due to an aggressive surveillance program by the WHO. Epidemiological data indicated that Mpox was a rare disease with a limited chance of person-to-person transmission and it was believed that the infection could not persist in humans (67,68). Between 1986 and 1995, only 13 instances of Mpox were recorded (67,69). However, between 1995 and 1996, >500 suspected cases of Mpox were reported, although only a few were confirmed through laboratory testing (67,70). Since 2005, the DRC has experienced multiple Mpox outbreaks, with >1,000 cases recorded annually between 2005 and 2018 (71,72). From November, 2005 and November, 2007, 760 cases were confirmed (73).

In 2013, the national surveillance system reported 104 suspected human cases of Mpox and 10 related deaths (a case fatality rate of 9.6%) from the Bokungu Health Zone, with a sharp increase in cases between January 1 and September 13, 2020 (74). A total of 4,594 probable cases of Mpox, including 171 deaths (case fatality ratio, 3.7%), were recorded across 127 health zones in 17 of the 26 provinces of the DRC (75).

In 2019, 3,794 suspected cases and 73 fatalities (CFR, 1.9%) were recorded, while in 2018, 2,850 suspected cases (CFR, 2.1%) were reported (75). Between January 1 and November 12, 2023, 156 health zones from 22 out of 26 provinces in the DRC reported 12,569 suspected Mpox cases, including 581 suspected Mpox fatalities (CFF, 4.6%) (76). As of May 26, 2024, the DRC had recorded 7,851 cases of Mpox, with 384 fatalities (CFR: 4.9%) reported in 177 of the 519 (34%) health zones across 22 out of the 26 provinces (85%) (77). The DRC continues to have a significant Mpox burden, with both clade I MPXV subclades in circulation, according to WHO report no.47, which was released on February 13, 2025. The situation in the nation is still alarming, with numerous regions experiencing persistent transmission, even if several provinces report stable trends in cases (63).

The majority of the sequenced samples from October 1, 2023, to February 2, 2025, were derived from the South Kivu and Kinshasa provinces. During this time, confirmed cases of Mpox have been recorded in every region in the nation; however, samples from four provinces, namely Ituri, Kasai Oriental, Lomami and Haut-Lomami have not undergone sequencing (63).

Since September, 2024, the reported number of weekly suspected cases has remained relatively consistent within the range of 2,000 to 3,000 cases, despite a noticeable upward tendency over the majority of 2024, according to the analysis of the epidemic trend of reported suspected Mpox cases. Despite this, the burden of >2,000 new suspected Mpox cases reported each week remains overwhelming (63).

Compared to clade IIb infections, clade I Mpox infections are more severe and fatal (76,78). Clade I Mpox has a CFR of 1.4% to >10%, while clade II Mpox has a CFR of 0.1 to 3.6% (78-81). Notably, children have been the primary victims of the clade I outbreak in DRC, with 67% of cases and 78% of fatalities occurring in those <15 years of age (82).

In contrast to the haplogroup IIb outbreak that largely affected the MSM community in the USA and worldwide, this epidemiological pattern indicates that paths other than sexual contact are more common. Experts believe that several transmission factors, including zoonotic, domestic, and sexual, are responsible for the outbreak, given the size of the DRC outbreak, its demographics and the genetic variety of the cases (78,81).

Since MPXV can be transmitted to humans through close, prolonged contact with infected individuals or through contact with infected wildlife, epidemiologists in the DRC have also documented heterosexual transmission, particularly among sex workers and their associates. The global clade II MPXV outbreak was primarily transmitted through sexual contact between homosexuals, bisexuals, or other men who have sex with men (MSM) (78,81).

It is evident that CFR varies noticeably among African nations, Western nations (such as the USA and Europe) and other nations (global outbreak). The primary reason for this is the difference between the two Mpox strains (clade I and clade II) in terms of mortality and contagiousness (81-84).

Clade I causes a higher mortality rate, is more severe, and has a low infectivity, which explains why CFR is high in African nations. By contrast, clade II, particularly clade IIb, is less severe and has a low mortality rate. However, it has a low CFR due to its high infectivity. Furthermore, as the West (the USA and Europe) had the greatest number of cases, clade II was the source of a worldwide outbreak (81-84).

Moreover, clade II was regarded as a global emergency despite having a lower mortality rate (and CFR) (83). The virus can spread through close contact, contact with infected wildlife or infected individuals, respiratory droplets, short-range aerosols, or contact with contaminated objects. However, the most significant way that the virus spreads is through sexual contact among homosexuals, bisexuals and other MSM, including in the USA and Europe. This places these groups at risk of becoming infected with the virus and spreading it throughout the community. The virus also poses a risk to children, individuals with compromised immune systems, including those with HIV, particularly those who have uncontrolled disease course which cause them to have low immunity (e.g. not on medications) and pregnant women (81,83,84).

The virus was also feared due to its wide complications. A bacterial infection of the skin can result in abscesses or severe skin damage, among other consequences that may affect individuals afflicted with Mpox virus. Pneumonia, corneal infections that result in blindness, pain or difficulty swallowing, vomiting and diarrhea that lead to malnourishment or dehydration, and infections of the blood (sepsis), brain (encephalitis), heart (myocarditis), rectum (proctitis), genital organs (balanitis), or urinary passages (urethritis) are additional complications. In certain situations, Mpox can be lethal (83).

*Global outbreak*. Mpox has been reported to the WHO from 123 Member States in all 6 WHO regions since January 1, 2022. As of August 31, 2024, the WHO has received reports of 106,310 laboratory-confirmed cases, 0 suspected cases and 234 fatalities (85).

Apart from the CAR, DRC, Kenya, Republic of Congo, Rwanda, Sudan and Uganda, which all have clade I cases, the epidemic is primarily caused by clade II, the less severe variety. However, Cameron, Sweden and Thailand are the three nations where there have been some recorded Mpox cases of clade I, making them both clade I and clade II (86). The WHO report no. 47 on February 13, 2025 reported 124,753 confirmed Mpox cases and 272 confirmed related deaths; not a single death by clade I was reported outside of Africa, and 128 reporting countries of the disease (58).

Only MPXV clade I travel-associated cases and/or occasional cases with epidemiological connections to travel-associated cases have been documented outside of Africa. There have been no reports of MPXV clade I-related mortality or transmission to a wider community outside of Africa (57,58).

Clade Ib MPXV has been detected in 13 countries as follows: USA (2 cases), Canada (1 case), France (1 case), India (1 case), Oman (1 case), Pakistan (1 case), Sweden (1 case), United Arab Emirates (1 case), Thailand (4 cases), Germany (7 cases), Thailand (4 cases), Belgium (2 cases), and UK and Northern Ireland (9 cases). There have been no documented clade Ib MPXV-related fatalities in these nations (63).

In summary, the recent Mpox outbreak resulted in almost 32,000 cases and 58 related deaths in the USA, mostly clade II, with a few travel-related cases of clade Ib. Europe reported 27,500 cases and 10 related deaths, mainly via sexual transmission. In Africa, particularly the DRC, severe clade I infections led to higher fatalities. Globally, >124,000 cases were confirmed, with clade II being the predominant strain.

*Endemic areas*

*Central and West Africa*. Between 1970 and 1980, 59 cases of human Mpox were reported in West Africa and Central Africa after it was identified as a human disease, with a mortality rate of 17% in children under the age of 10. All these incidents involved individuals who had come into contact with small forest animals in the rainforests of West and Central Africa such as rodents, squirrels and monkeys (82).

According to a population-based surveillance study, Mpox infection rates in the DRC increased 20-fold between 2005 and 2007 compared to the 1980s. During this period, 760 laboratory-confirmed cases of human Mpox were reported. Individuals with a history of smallpox immunization had a 5-fold reduced risk of becoming infected with Mpox compared to those who were unvaccinated, highlighting concerns about the rise in human Mpox cases due to the lack of prior smallpox vaccination. Higher infection risks were also associated with residing in wooded areas, being male and being <15 years of age (82). Several African nations, including Benin, Cameroon, CAR, DRC, Gabon, Ghana (identified only in animals in Ghana), Ivory Coast, Liberia, Nigeria, Sierra Leone, and South Sudan were all identified by the WHO in 2022 as having an endemic Mpox prevalence. Between January and May, 2022, the DRC reported 1,284 suspected Mpox cases and 58 related deaths (82).

Table I. The numbers of cases and deaths in the KSA compared to some of the most affected countries as of January 26, 2023 (87).

| Countries | Cases | Deaths[a] |
|---|---|---|
| USA | 30,097 | 27 |
| Spain | 7,514 | 3 |
| France | 4,114 | 0 |
| UK | 3,735 | 0 |
| Germany | 3,689 | 0 |
| Brazil | 10,690 | 15 |
| Nigeria | 775 | 7 |
| DRC | 348 | 0 |
| KSA | 8 | 0 |

[a]It is important to note the low mortality rate. DRC, the Democratic Republic of the Congo; KSA, Kingdom of Saudi Arabia.

*Nigeria*. After almost 40 years with no confirmed cases, there has been an increase in Mpox infections in Nigeria since 2017. Some cases from this outbreak have been reported among travelers returning to non-endemic nations (82).

In brief, between 1970 and 1980, 59 Mpox cases were reported in Africa, with a 17% death rate among children. From 2005 to 2007, cases surged 20-fold in the DRC. By 2022, Mpox had become endemic in several African nations, with Nigeria experiencing an increase in cases since 2017.

*Global outbreak in non-endemic countries (2022)*. Mpox was initially identified as a worldwide outbreak in May, 2022 in Europe. Worldwide cases connected to this outbreak have continued to be reported, providing evidence of community spread. The WHO labelled this Mpox outbreak as a public health emergency of global concern on July 23, 2022 (82). To date, there have been >70,000 cases, with <30 documented deaths, indicating a low mortality rate. Furthermore, the Kingdom of Saudi Arabia has reported <10 cases as of January, 2023 (Table I), while the USA and Europe in general have the highest number of cases (87).

*International eradication efforts of Mpox (2025)*

*Globally*. On September 13, 2024, the WHO placed the Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN) vaccine to its prequalification list. This will enable the Bavarian Nordic vaccine to be approved more rapidly and through country-based procedures. The WHO also authorized the emergency use of Japan's KM Biologics vaccine LC16 on November 19, 2024. Additionally, the WHO designated the ongoing outbreaks of many Clades in the Democratic Republic of the Congo and neighboring African nations as a Public Health Emergency of International Concern (PHEIC) on August 14, 2024. On November 22, 2024, the PHEIC declaration was extended. In line with the WHO Emergency

Responses Framework, WHO also declared the worldwide Mpox outbreak an acute grade 3 emergency, provided member states with recommendations, and released funds from its Contingency Fund for Emergencies as well. Moreover, the emergency use listing procedure began for the Nordic and JYNNEOS Mpox vaccines to facilitate access and distribution, including GAVI and UNICEF distribution (88).

*Africa*. Africa CDC declared this outbreak to be a Public Health Emergency of Continental Security (89). For the 6 months from September, 2024 to February, 2025, the Africa Mpox response plan calls for a budget of 600 million USD, of which 45% will go toward operational support and 55% would go toward Mpox response and readiness in 28 countries. Additionally, the Africa CDC has been actively aiding nations fighting Mpox since August 13, 2024, when it declared the disease a medical emergency of continental significance (89).

For the first time since the COVID-19 pandemic, the Public Health Emergency Operations Centre in Addis Ababa has been reactivated to provide around-the-clock case monitoring. During public health emergencies, these hubs, along with Regional Coordinating Centres in Lusaka (Zambia), Nairobi (Kenya) and Libreville (Gabon), act as vital command centers, guaranteeing coordinated emergency preparedness, response, and recovery through cutting-edge technology, specialized workspaces, and reliable communication systems (89).

Initiatives for training are in progress, involving representatives from seven member states in sample collection, diagnosis and sequencing. To improve detection and response, a new surveillance reporting protocol has also been introduced, with a focus on data standardization, genomic sequencing, and cross-border coordination. Additionally, a continental R&D conference to fill knowledge gaps in medical countermeasures was organized in Kinshasa (DRC) on August, 29 with almost 2,000 attendees. Moreover, the ten main pillars of the finalized continental response plan, coordination, surveillance, vaccination and research, were created in partnership with the WHO. The DRC also requested two million child-safe vaccines from Japan and donated USD 10 million to the battle against the outbreak. A deal with the European pharmaceutical company Bavarian Nordic to help one of nine major African pharmaceutical companies produce the Mpox vaccine was one of the additional measures used to manage the outbreak (89).

Thus, global eradication efforts have been streamlined by the WHO, which added Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN) to its prequalification list, speeding up vaccine distribution through partners like GAVI and UNICEF. In Africa, the Africa CDC declared a continental emergency with a US$600M response plan, reactivated emergency centers, and boosted local vaccine production and surveillance.

## 6. Predisposing factors

Risk factors for Mpox depend on whether it is transmitted human-to-human or zoonotically. In the case of human-to-human transmission, the most significant risk factor is close contact with an infected individual (90). Additionally, while the exact cause remains unclear, MSM appears to be at a higher risk of becoming infected with Mpox, as the majority of reported cases occurred within this group (91). It is currently unknown if Mpox is spread through sexual contact alone or if it can also be transmitted through sexual fluids, like semen (91). Recent cases in Italy and Germany have detected viral DNA in semen samples, suggesting that transmission through sexual contact is possible (92). If this is the case, then anal intercourse could also be considered a risk factor due to the vulnerability of anal mucosa to micro-abrasions compared to vaginal mucosa, which could explain the higher risk among men who have sex with men (93). Furthermore, sharing bed, room or household with an infected individual is a risk factor, as sharing dishes, cups, or utensils with suspected cases (90). The prevalence of HIV/AIDS was found to be a significant driver of monkeypox (Mpox) transmission, with a higher HIV/AIDS prevalence strongly correlating with increased Mpox cases across multiple countries (34). Current evidence indicates that advanced HIV can complicate Mpox infections (94). Similarly, immunocompromised patients are at an increased risk of Mpox infection and may experience more severe complications post-infection (95).

In terms of zoonotic transmission, sleeping outdoors, residing near a forest, or even visiting one are considered risk factors. Additionally, unprotected contact with sick or dead animals, including their blood and meat poses a potential risk (90). The inadequate cooking of meat and other infected animal products is another potentials risk factor for zoonotic transmission (9). A shared risk factor between human-to-human and zoonotic transmission is smallpox vaccination status, as the smallpox vaccination provides cross-protective immunity against Mpox. Therefore, individuals who have not received the smallpox vaccine are more susceptible to contracting Mpox (9,90,96).

Hence, predisposing factors for Mpox include close human-to-human contact and direct exposure to infected animals or their undercooked meat. Additionally, not being vaccinated against smallpox and having a compromised immune system increase the risk of Mpox spread.

## 7. Clinical presentation

The signs and symptoms of Mpox vary, although the most prominent are skin lesions (95). The lesion begins as a macule, which develops into a papule, and then progresses to a papule, and eventually forms an early vesicle. The vesicle transforms into a pseudo-pustule, followed by umbilication, and later, an ulceration. It then crusts over and eventually forms a scab, which eventually resolves. Different stages of the rash may appear simultaneously in different locations of the body. The complete healing process, from the initial lesion formation to the development of a new skin layer, takes approximately 3 weeks. Once healed, the individual is no longer contagious (9,82,97,98).

The locations of the lesions vary, with the anogenital area being the most affected, followed by the trunk and limbs, and then the face. The palms and soles of the feet are the least affected. The number of skin lesions also varies across individuals, ranging from a single lesion to >20, though the majority of cases exhibit ≤10 lesions. These variations in skin lesions increase the risk of misdiagnosis with other different diseases (95). Non-specific symptoms include hyperthermia, lethargy, myalgia and headache. These symptoms may either precede or accompany the appearance of lesions. Dehydration is s a common finding in patients with Mpox and some cases report confusion and disorientation (90,95,99). Furthermore, specific symptoms depend on the affected area. Anorectal involvement is associated with anorectal pain, hematochezia, melena tenesmus, diarrhea and proctitis. On the other hand, oropharyngeal involvement is associated with pharyngitis, odynophagia, and epiglottitis (95,99,100).

In summary, typical clinical presentation include rash that evolves from macules to scabs over ~3 weeks, often starting in the anogenital area and usually accompanied by fever, lethargy, and muscle pain, with additional symptoms depending on the affected area.

## 8. Diagnosis

*When to diagnose.* Both the WHO and CDC have provided definitions to stratify the suspicion of Mpox infections that take into consideration epidemiologic, clinical and laboratory findings. These definitions could divide new Mpox cases into three groups as follows: Suspected cases, probable cases, and confirmed cases. The following is the definition of each using the CDC guidelines: *Suspected case.* New onset of characteristic rash or meeting one of the epidemiologic criteria with a high clinical suspicion for Mpox (101). The epidemiologic criteria include any of the following within 21 days of illness onset (101): i) A report of having contact with a person or persons who have a similar appearing rash or who received a diagnosis of confirmed or probable Mpox; ii) having close or intimate in-person contact with persons in a social network experiencing Mpox; iii) traveling to a country with confirmed cases of Mpox or a country where MPXV is endemic; iv) had contact with a wild animal or exotic pet that is an African endemic species either dead or alive or used a product derived from such animals.

*Probable case.* There is no suspicion of other recent orthopoxvirus (OPV) exposure with the presence of OPV DNA by the polymerase chain reaction (PCR) testing of a clinical specimen or evidence of OPV using immunohistochemical or electron microscopy testing methods or a demonstration of detectable levels of anti-OPV IgM antibody during the period of 4 to 56 days after rash onset (101).

*Confirmed case.* Mpox virus DNA by PCR testing or next-generation sequencing of a clinical specimen or the isolation of Mpox in culture from a clinical specimen (101).

*Diagnostic tools.* There are several methods for the diagnosis of Mpox virus, depending on the symptoms of the patient. If Mpox is suspected, health professionals need to collect a relevant sample and arrange for its safe transportation to an approved laboratory. Samples may include a swab from the lesion, pus, or crusted dry skin. The type of specimen, its quality and the laboratory test used will aid in the diagnosis of Mpox (9,102).

*PCR.* One method of diagnosis involves genetic methods such as PCR, which is preferred for its high chance of precision and sensitivity and remains the most common technique to test for MPXV in point of care sittings. PCR is essential in differentiating between the Congo Basin (clade I) and West African (clade II) virus strains by detecting regions of the extracellular-envelope protein gene (B6R), and other genes such as rpo18, F3L and E9L (103,104).

*Serological testing.* The use of serological studies, enzyme-linked immunosorbent assay (ELISA) being the preferred method, is advised against in clinical settings when performed without other tests. ELISA is not specific for MPXV and can indicate the presence of other OPV species. Positive IgM suggests recent exposure to OPV, whereas a positive IgG indicates a previous exposure to OPV through vaccination or a past infection (104). The use of serologically validated tests from a reference laboratory could augment the diagnostic accuracy if the other tests are inconclusive (103).

*Whole-genome sequencing (WGS).* WGS, the most comprehensive next-generation sequencing technology, as the name implies, sequences the whole genome of the organism. It is the most precise method for differentiating MPXV from other OPVs, permitting the identification of specific strains and genetic variants, potentially explains outbreak origins. Furthermore, with the data from WGS tracing of genetic changes over time, provide an insight into the virus adaptation to a variety of factors (103,105). WGS is being recognized as an essential tool in epidemiological research, contributing to treatment, vaccine development and disease control strategies. Although WGS is not suited for point-of-care testing due high cost and demanding computational power, Its application primarily benefits research initiatives (103,104).

*Electron microscopy.* Electron microscopy enables direct visualization of suspected poxviruses in clinical samples. Nevertheless, its routine use in diagnosing MPXV is limited due to the requirement for specialized skills, advanced infrastructure, and the growing availability of more practical molecular diagnostic methods (103).

*Phenotypic methods.* The fifth method is the phenotypic method, which relies on the clinical features of the individual. The incubation period of MPXV is typically between 4 to 21 days, and it is generally associated with various signs and symptoms such as, headache, fever, pharyngitis, malaise, intense asthenia, back pain and lymph node enlargement. Within the first 10 days, vesiculopustular rashes will appear all over the body. Phenotypic analysis is critical as it can be the first indicator of whether an individual is affected by the MPXV (104,106).

In brief, Mpox is diagnosed as suspected, probable, or confirmed based on clinical signs, exposure history, and lab tests. PCR is the primary diagnostic tool due to its accuracy and ability to differentiate virus strains, while serology, WGS, electron microscopy and clinical evaluation also aid in the diagnosis.

## 9. Management

*Prevention.* Individuals with a history of smallpox vaccine immunization may also benefit from protection against the Mpox. Therefore, smallpox vaccines could potentially improve the clinical outcomes of Mpox infections. The two main vaccines discussed in the present review are JYNNEOS (Bavarian Nordic) and ACAM2000 (Emergent Biosolutions) (12).

The JYNNEOS vaccine is produced from a modified, attenuated, non-replicating live strain of vaccinia Ankara-Bavarian Nordic (MVA-BN). On the other hand, ACAM2000 also consists of live vaccinia virus, but is replication-competent vaccinia. Both vaccines are administered to adults who are at a high risk of contracting Mpox or smallpox, with data demonstrating that smallpox vaccines containing vaccinia are 85% effective against Mpox (12). Those who are at a high risk of becoming infected with Mpox and smallpox should receive the two-dose JYNNEOS™ vaccination. As of October, 2023, the Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination for at-risk adults aged ≥18 years, including MSM, those with a number of sexual partners and others (107). The recommendations of the CDC can be found online (108).

However, healthcare workers should not receive this vaccine. In patients aged <18 years who have been determined to be at an increased risk of contracting Mpox, JYNNEOS™ has an active emergency use authorization for subcutaneous administration. Continued authorization emphasizes the role of the vaccine in reducing epidemics. Despite being part of the standard immunization regimen, only 25% of the target population completed the two-dose series by January, 2024. Limited accessibility, awareness, providers, the need for multiple doses, confidence, and stigma are barriers to vaccination. Due to the consistent efficacy of the vaccine and the low breakthrough infection rate, the CDC does not recommend booster doses. Single-dose recipients are encouraged to finish the vaccination series; however, those who have recovered from Mpox or completed the series do not require further doses (108).

JYNNEOS™ was available commercially on April 1, 2023, following ACIP guidelines. The US Department of Health and Human Services (HHS) stopped stockpile distribution on August 1, 2023, making the vaccine commercially available. The EU and UK authorize this third generation, attenuated, non-replicating orthopoxvirus vaccine for adult Mpox prevention as Imvanex (Modified Vaccinia Ankara-Bavarian Nordic; MVA-BNR) and Canada as Imvamune (MVA-BNR). The WHO authorized the MVA-BN vaccination for 12-17-year-olds in October, 2024. A single dosage provides 76% protection and two pre-exposure doses 82% protection. Following exposure, vaccine effectiveness decreases to 20%. Its efficacy against Mpox clades, particularly the aggressive Ib, is unclear (108).

The FDA approved ACAM2000 and JYNNEOS™ for high-risk Mpox prevention in August, 2024. The 2022 Mpox epidemic marked the first release of ACAM2000, a live, replication-competent vaccinia virus vaccine, under an Expanded Access Investigational New Drug (EA-IND) procedure. This approval strengthens the Mpox preventive toolset, particularly given the global health emergency declaration. To inhibit the transmission of the live virus, a bifurcated needle punctures the skin and enables a scab to form and heal. However, vulnerable individuals, such as patients with HIV are at risk of developing eczema vaccinatum and progressive vaccinia from uncontrolled viral replication. This is significant as the 2022 outbreak disproportionately affected MSM, who may be at risk of undiagnosed HIV (109).

Furthermore, studies have suggested that 1 in 175 first-time vaccinees may develop myocarditis and pericarditis after administering the ACAM2000® vaccine (110). Given these factors, the CDC recommends JYNNEOS™ as the primary Mpox vaccine, since it has fewer side-effects than ACAM2000. This guidance emphasizes prioritizing low-risk vaccines for high-risk populations. Importantly, ACAM2000 recipients need to obtain the medication guide, which is an official document provided by the U.S. Food and Drug Administration (FDA) that explains the vaccine's uses, benefits, potential side effects, and serious risks. This medication guide can be obtained from healthcare providers or accessed online through the FDA's website (111). For safe and effective vaccine use, this guide prevents severe adverse events and informs recipients about the significant risks relative to benefits, which may influence their decision to get vaccinated. The ACAM2000 vaccine is administered once, while JYNNEOS™ requires two doses 28 days apart. In those who have completed a primary series with ACAM2000 and are at risk of occupational exposure, JYNNEOS™ or Imvanex can be administered as a booster. The impact of the 2024 outbreak on non-MSM groups, including women and children emphasizes the necessity for diversified vaccines, such as ACAM2000 (108).

Fortunately, advances in vaccine technology show promise. Using a fatal primate model, the US Army Medical Research Institute of Infectious Diseases and Moderna Inc. tested mRNA-1769, an mRNA-LNP vaccine targeting MPXV surface proteins. As with MVA, mRNA-1769 reduced symptom severity and disease duration. Compared to MVA, mRNA-1769 suppressed viruses and diseases better. As mRNA-1769 advances through Phase I/II clinical trials, its improved efficacy indicates that mRNA technology can fight Mpox and other emerging orthopoxvirus infections (108).

*Pre-exposure prophylaxis*. Pre-exposure vaccination is recommended for individuals at risk of occupational exposure to *Orthopoxviruses*, such as laboratory researchers, laboratory staff conducting diagnostic tests, response team members and healthcare professionals who administer ACAM2000 vaccine (12,112).

*Post-exposure prophylaxis*. To assess the risk of exposure and make informed choices regarding post-exposure prophylaxis, the CDC has produced recommendations to summarize the information (113).

In summary, protection against Mpox can be achieved using two vaccines: JYNNEOS, a safer two-dose vaccine with 76-82% protection, and ACAM2000, a riskier single-dose vaccine. JYNNEOS is preferred due to fewer side-effects, although only 25% of the target population had completed it by January, 2024. New mRNA vaccines show promise. Pre- and post-exposure vaccination is recommended for at-risk groups, with JYNNEOS as the primary choice. Individuals who have received the smallpox vaccine may also gain protection against Mpox.

*Supportive care*. The majority of patients with Mpox typically recover without any medical intervention (112). Nonetheless, acetaminophen and NSAIDs may be used general pain management. Additionally, topical steroids and anesthetics could be used for local pain relief for the lesions (114). In case of proctitis, stool softeners should be considered (112,114). Hospitalization may be required for those who suffer from dehydration due to diarrhea or vomiting, agonizing pain or severe complications (112).

*Antivirals*. Currently, tecovirimat is the drug of choice as it inhibits the viral envelope protein VP37 thus blocking the viral mutations and the release of the virus from the infected cell. Treatment with tecovirimat is recommended for patients with severe Mpox, including those presenting with conditions such as sepsis, hemorrhagic disease, encephalitis or other conditions which require hospitalization. It is also advised for individuals who are at a risk of developing severe disease, such as immunocompromised patients, pregnant or breastfeeding women, children <8 years of age and those with impaired skin integrity. Additionally, treatment is recommended for patients with Mpox infection in particular areas including the eyes, eyelids, mouth, pharynx, and anogenital area (112,115).

Recent clinical trials have evaluated the efficacy of tecovirimat in treating Mpox. The PALM 007 study, a randomized, placebo-controlled, double-blind trial conducted in the DRC, assessed the safety and efficacy of oral tecovirimat. The results indicated that tecovirimat did not significantly reduce the duration of Mpox lesions compared to the placebo. However, the study reported a lower overall mortality rate of 1.7% among participants, suggesting that hospitalization and high-quality supportive care substantially improve patient outcomes (116).

Similarly, the STOMP trial, conducted by the National Institute of Allergy and Infectious Diseases (NIAID), evaluated the efficacy of tecovirimat in adults with mild to moderate clade II Mpox. Interim analysis revealed that tecovirimat did not expedite lesion resolution or alleviate pain compared to the placebo. Consequently, patient enrolment was halted based on these findings (117).

These studies underscore the necessity for continued research into alternative therapeutic options for Mpox, as current antiviral treatments such as tecovirimat have not demonstrated significant clinical benefits in recent trials (116,117).

The dosages of tecovirimat varies from individual to another and depends on the patient's weight. For example, if the individual weight is ≥40 kg but <120 kg, the dose is 600 mg or three capsules twice a day for 2 weeks. Oral and intravenous (IV) versions are also available. In the case of patients who suffer from severe renal impairment, IV tecovirimat should not be used (112). Although the effectiveness of antivirals such as tecovirimat, cidofovir and brincidofovir against Mpox have not been tested in individuals, research on animals has demonstrated that antiviral treatment increases survival from lethal Mpox virus infections compared to placebo treatment at various illness infections phases (112). Cidofovir and brincidofovir are used when tecovirimat is not available as they are a DNA polymerase inhibitor. The use of these two should be individualized on a case-by-case basis, due to the possible adverse effects, such as nephrotoxicity or electrolyte changes. Moreover, in some cases, vaccine immune globulin (VIG) can be used to treat the complications of the vaccine; however, the effect of VIG is uncertain against smallpox and Mpox and it has not been tried on humans (112).

In summary, tecovirimat is the preferred treatment for Mpox, inhibiting viral release and mutations. It is recommended for patients with severe or high-risk conditions, but has shown limited benefits in recent trials. The dose depends on weight, with IV use avoided in severe renal impairment. While alternatives such as cidofovir and brincidofovir may be used when tecovirimat is not available, they are associated with potential side-effects. VIG may be used to treat vaccine complications, although its effectiveness against Mpox is uncertain.

*Enhancing the practicality of management.* The CDC provides interim clinical guidance for Mpox treatment, emphasizing that there is no specific FDA-approved treatment for Mpox. For the majority of patients without severe disease or risk factors, supportive care and pain management are recommended. In cases with severe manifestations, antiviral agents such as tecovirimat may be considered under investigational protocols (118).

Additionally, the WHO has released a strategic framework for Mpox prevention and control (2024-2027), outlining a roadmap for health authorities and stakeholders to manage Mpox outbreaks effectively. This framework emphasizes the importance of surveillance, case investigation, contact tracing and community engagement to mitigate transmission (119).

*Education.* Mpox is primarily transmitted through direct physical contact with infected individuals, their lesions, or contaminated materials such as bedding and clothing. Early identification of cases and prompt implementation of infection prevention and control measures are essential to reducing transmission. Patients with suspected or confirmed Mpox should be isolated in well-ventilated single rooms with private bathrooms when possible; if hospital isolation is not feasible, home isolation with strict adherence to infection control measures is recommended. Healthcare workers must be trained in recognizing Mpox signs and symptoms and in the proper use of personal protective equipment (PPE). Standard precautions, including meticulous hand hygiene, the correct use of PPE, environmental cleaning with appropriate disinfectants, and safe handling and disposal of contaminated waste, must be consistently applied when managing Mpox cases (120).

*Wildlife monitoring.* Of note, ~25% of new infectious diseases in humans are considered to originate from primates, highlighting the importance of understanding and monitoring disease transmission between animals and humans. Veterinarians could play a crucial role in detecting zoonotic diseases such as Mpox. Animals can play a critical role in the maintenance of these infectious diseases within nature to form a zoonotic cycle. Identifying reservoir species is one of the most important steps in controlling outbreaks, as it helps limit disease transmission and detect animals that asymptomatically carry the virus. By studying animal populations and tracking transmission pathways, researchers can determine how the virus spreads to humans, whether through direct contact, hunting, or the consumption of infected animals. Moreover, detecting infected animals earlier could reduce the number of individuals becoming infected with Mpox; this can be achieved by a collaboration between the veterinarians, environmental sector and health sector (121).

*Challenges in prevention and treatment.* Some of the antivirals used in the treatment of Mpox have limitations. For example, cidofovir has low bioavailability and can cause nephrotoxicity in patients with kidney disease. Brincidofovir, which is a derivative of cidofovir does not cause significant nephrotoxicity and has higher bioavailability compared to cidofovir.

However, it may cause gastrointestinal adverse effects and liver damage. Tecovirimat is effective for treating Mpox, but concerns have been raised about the potential emergence of new MPXV strains resistant to tecovirimat (122).

In addition, there is limited access to diagnostic techniques and a shortage of trained medical personnel in endemic African countries, which can lead to delays in both diagnosis and early management of Mpox patients (123). Vaccination with the smallpox vaccine is an effective measurement to prevent Mpox, though the use of the first and second generation of smallpox vaccines is limited due to their severe adverse effects, especially in immunocompromised and HIV patients. Third-generation vaccines are generally safer (122).

Furthermore, vaccines are not readily available in Mpox endemic areas, such as Central and West Africa. This was evident during the 2022 Mpox outbreak, as numerous African countries did not have access to vaccines. Vaccine production in Africa is inadequate due to the lack of qualified professionals and the infrastructure needed for manufacturing vaccines. Vaccine hesitancy is another factor that hinders the widespread distribution of vaccines in Mpox endemic areas. Some individuals are reluctant to be vaccinated due to a lack of adequate information about the effectiveness and benefits of vaccination, which highlights the critical role of public health education in controlling Mpox (124).

Although Mpox is a double-stranded DNA virus, it exhibits a higher genomic variability due to increased nucleotide polymorphism. International travel further accelerates the spread of Mpox among populations, raising its potential to mutate (34,122). While no definitive animal reservoir for Mpox has been identified, rodents are considered the most likely source. Contact with animals increases the possibility of spillovers from animals to humans and vice versa. These factors could potentially lead to the emergence of new reservoirs and multidrug-resistant strains. Therefore, a multidisciplinary approach involving collaborations from human health, animal health and environmental experts is required to better understand the origin of MPXV and the factors leading to outbreaks (125). Developing countries in Africa, where Mpox is endemic, often lack the necessary funding for research on the disease. These countries also face significant inequities in accessing vaccines, diagnostic tests and treatments (126). Despite global efforts to combat Mpox, the response remains hindered by significant challenges. Political instability and the worsening humanitarian crisis in the North and South Kivu region of the DRC, where >1.6 million individuals have been displaced, have made it increasingly difficult to detect and treat the disease in one of the most affected areas in the world by Mpox (127).

To effectively manage Mpox outbreaks, essential resources, such as personal protective equipment, PCR test kits, next-generation vaccines for pre- and post-exposure prophylaxis, and antiviral drugs are required. However, Mpox outbreaks in resource-limited settings can overwhelm healthcare systems and delay outbreak control. PCR, the confirmatory diagnostic technique for Mpox, may not be widely available in developing countries due to the high costs associated with molecular testing and genome-sequencing facilities. Similarly, vaccine accessibility poses a major challenge, as the high cost often makes vaccines unaffordable (128). Other factors affecting vaccine availability include logistical issues, storage and cold chain management, and the need for healthcare workers who are trained on proper vaccine administration and storage (126).

Another barrier for the treatment and prevention of Mpox is Stigma. This refers to the widespread presence of negative attitudes, judgments and biases directed at certain groups, traits, or behaviors. The MSM community often experiences stigma related to Mpox, which can discourage individuals from seeking healthcare, receiving early diagnoses, and accessing treatment. Addressing this issue is essential for their overall well-being. Certain behaviors, such as unprotected sex, multiple partners and mucosal lesions, increase the risk of Mpox transmission among MSM. This highlights the need for comprehensive sexual health education, regular STI testing, and the use of protective measures. Creating a supportive, judgment-free environment that encourages open discussions, raises awareness, and promotes acceptance is important to reducing high-risk behaviors and preventing Mpox outbreaks within the MSM community (129).

In brief, Mpox management centers on prevention through vaccination (primarily two-dose JYNNEOS), supportive care and antivirals such as tecovirimat for severe cases. Challenges include limited vaccine and diagnostic access, logistical issues and stigma, particularly in resource-limited settings. Efforts to enhance surveillance, education, and wildlife monitoring are key to controlling the disease.

## 10. Complications

*Biological complications*. One of the complications that can occur form Mpox infection is a secondary bacterial infection. This can occur if the patient scratches the skin lesions, causing the lesions to open and ulcerate. If not managed properly, the secondary bacterial infection could lead to more severe conditions such as cellulitis and sepsis (130,131).

Mpox infection can also lead to ocular manifestations, such as conjunctivitis, which is observed in 25% of patients with Mpox infection. Additionally, lesions can develop on the eyelids and cornea, potentially ulcerating and leading to secondary bacterial infections. Ulcerations in the cornea can result in scarring and vision loss (131,132).

Central nervous system (CNS) complications related to Mpox include encephalitis, seizures and confusion. However, these complications are rare, occurring in <3% of patients infected with Mpox (133).

Morbidity and mortality rates associated with Mpox vary based on outbreak severity and regional healthcare infrastructure. The CFR ranges from 0 to 11%, with higher rates observed in immunocompromised individuals and those with comorbidities, as well as young children (134). Hospitalization rates vary; a previous systematic review estimated that ~14.1% of cases require hospitalization, with severe disease necessitating medical intervention. The hospitalization rates differed for each outbreak, with those pre-2017 being 49.8%, those from 2017-2021 being 21.7%, and those for 2022 being 5.8% (135). Long-term complications at 4-6 months post-infection with Mpox can include scarring from skin lesions, residual pain, sexual impairment, or general impairment and decrease in quality of life, in general. This was found to be more prevalent in patients who had a bacterial superinfection and/or abscess during acute infection (136).

*Psychosocial complications.* The psychosocial effects of Mpox are prevalent across various groups of individuals, from the patients to the hospital staff (137). These effects can arise due to contracting the infection, quarantine measures, the loss of a loved one and other factors. For example, psychiatric conditions, such as schizophrenia and depression were noted to be aggravated due to societal isolation (137). Furthermore, healthcare practitioners are more likely to experience post-traumatic stress disorder (PTSD), substance use disorders and depression (137). In addition, the significant risk of vertical transmission also causes considerable stress for pregnant mothers and fathers, as they face the potential loss of their child (137).

Long-term psychosocial complications of Mpox can significantly affect the mental health and social well-being of patients. Studies have reported that 25-50% of individuals with Mpox experience psychiatric symptoms, such as anxiety and depression, which can lead to self-harm, and suicide; these symptoms could be due to boredom, social stigma, isolation and loneliness. They may also be caused by the implicit and explicit costs of the disease itself, particularly in developing countries (138). Furthermore, on the subject of social stigma, patients with Mpox experience negative stereotyping and discrimination due to the scars left behind by the diseases, leading to experience of poor self-worth and self-esteem (139).

In summary, complications following Mpox infection include secondary bacterial infections, eye damage, and rarely CNS issues, with long-term effects such as scarring and chronic pain. It also often leads to mental health challenges, including anxiety, depression, PTSD and social stigma.

## 11. Future research

The ongoing challenges posed by Mpox underscore the need for continued, multidisciplinary research to better understand and combat the virus. Several areas warrant future investigation.

*Genetic mutation dynamics.* Understanding the mechanisms behind the genetic mutations of MPXV, particularly APOBEC3-driven mutations, remains crucial. Future research is warranted to focus on comprehensive genomic surveillance to track emerging variants and assess how specific mutations affect viral transmissibility, virulence and resistance to current treatments. This could involve next-generation sequencing studies in both endemic and outbreak settings to monitor changes in real-time.

*Development of novel antiviral therapies.* While tecovirimat has been the frontline antiviral for Mpox, its limited impact on lesion resolution and potential for resistance call for the development of alternative treatments. Future studies are required to explore combination therapies, new molecular targets and repurposing existing drugs. The emerging promise of mRNA-based platforms also offers a forward-looking strategy for designing tailored antiviral agents that could provide more robust protection against diverse MPXV clades.

*Optimizing vaccine strategies and accessibility.* Despite the availability of JYNNEOS and ACAM2000 vaccines, challenges such as vaccine hesitancy, incomplete dosing and limited access in endemic regions persist. Further research is required to improve vaccine formulations, investigate the long-term immunity conferred by these vaccines and develop next-generation candidates with improved safety profiles. Additionally, studies on the social and logistical barriers to vaccine uptake could inform strategies to enhance immunization coverage, particularly in resource-limited settings.

*Zoonotic reservoir identification and One Health approaches.* A clearer understanding of the animal reservoirs of Mpox is essential for preventing future spillover events. Future research is warranted to integrate wildlife ecology with epidemiological studies to identify and monitor potential reservoir species. The One Health approach, linking human, animal and environmental health, can also facilitate the development of early-warning systems and targeted interventions in both endemic and non-endemic regions.

*Enhanced diagnostic and surveillance methods.* Rapid and reliable diagnosis is pivotal to controlling outbreaks. Future investigations are warranted to focus on developing affordable, point-of-care diagnostic tools that can be deployed in low-resource settings. Research into novel technologies, such as CRISPR-based diagnostics, could provide faster detection and improved disease management, particularly during the early stages of infection.

*Long-term clinical and psychosocial outcomes.* There is a growing for the understanding of the long-term health consequences of Mpox, including persistent physical symptoms, scarring, and psychosocial impacts such as stigma and mental health disorders. Prospective cohort studies and qualitative research could elucidate these aspects, leading to improved patient support services and comprehensive post-infection care protocols.

*Public health policy and communication strategies.* Finally, research that bridges epidemiology with social sciences is essential. Future studies are required to assess the effectiveness of public health interventions, digital communication strategies and community engagement initiatives. By understanding the social dynamics of Mpox transmission, particularly in high-risk populations, public health officials can design more effective campaigns to reduce stigma and improve outbreak response.

Collectively, these research avenues offer a roadmap for addressing the multifaceted challenges of Mpox. By integrating advances in genomics, pharmacology, public health and social sciences, future investigations can greatly enhance our capacity to predict, prevent, and treat Mpox outbreaks on a global scale.

Hence, future research should focus on tracking genetic mutations, developing better antivirals and vaccines, identifying animal reservoirs, improving diagnostics and surveillance, understanding long-term outcomes and refining public health strategies.

## 12. Conclusions

The Mpox outbreak has underscored the urgent need for a coordinated global response and a paradigm shift in both research and public health practice. Moving forward, it is imperative that research efforts focus on several key areas: Advancing real-time genomic surveillance to monitor viral mutations and understand the role of APOBEC3-driven changes; developing novel antiviral therapies and exploring combination treatments to overcome potential drug resistance; and optimizing vaccine strategies to enhance safety, accessibility, and efficacy, particularly in resource-limited endemic regions.

In parallel, a robust One Health approach needs to be adopted to identify and monitor zoonotic reservoirs, enabling earlier detection and intervention. Investment in innovative diagnostic tools, such as point-of-care tests, will be critical for rapid case identification and outbreak control. Equally important is the need to investigate the long-term clinical and psychosocial impacts of Mpox, ensuring that patient management strategies are comprehensive and responsive to both physical and mental health challenges.

Finally, public health policies and global preventive measures must be informed by interdisciplinary research that bridges epidemiology, clinical science, and social dynamics. By integrating these strategies, the international community can not only better anticipate and contain future outbreaks but also ensure equitable access to life-saving interventions worldwide. The lessons learned from recent outbreaks must now translate into a proactive, evidence-based framework for global Mpox prevention and control.

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ASA, BA, MAA, AHA, ATA, AAA and AKA contributed to the design if the study, in the collection of data from the literature, in the literature review, and in manuscript preparation. KHM and MI contributed to the reviewing and revising of the manuscript. SB revised, edited and finalized the manuscript. All authors have reviewed and approved the final manuscript. Data authentication is not applicable.

**Ethics approval and consent to participate**

Not applicable.

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**Competing interests**

The authors declare that they no competing interests.

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