

# Mpox Outbreaks, Challenges of Management, Smallpox to the Rescue: A Review Article

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**Abstract:** Mpox is a viral zoonotic disease caused by the monkeypox virus. Its incidence has risen in recent years due to the decline in immunity from previous smallpox infections and the cessation of smallpox vaccinations following its eradication. This article reviews published studies and webpages from various organizations, focusing on the history and updates of mpox outbreaks and their management. Research articles, book chapters, review articles, and other pertinent literature were gathered from online databases such as PubMed, Google Scholar, ScienceDirect, and PubMed Central. Mpox morbidity can range from mild to severe, with secondary complications that may be fatal. Several outbreaks have occurred in recent decades. The recent global outbreak of mpox, which began in May 2022, primarily affected men who have sex with men. The increase in the global spread of mpox has gained international attention and in 2024, mpox was declared a Public Health Emergency of International Concern (PHEIC) by the Africa Centre for Disease Control and Prevention (Africa CDC) and the World Health Organization (WHO). Smallpox has played a vital role in the management of mpox through research on treatments and vaccines. The eradication of smallpox provides hope for effective control of mpox, as eradicating mpox may be challenging due to the presence of nonhuman hosts. Surveillance and research are crucial in achieving this objective.

**Keywords:** Mpox, monkeypox, history, outbreaks, vaccination, smallpox.

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## I. INTRODUCTION

Previously referred to as monkeypox, mpox is caused by the monkeypox virus, a member of Poxviridae family (Orthopoxvirus). This family also includes the variola virus, cowpox virus, vaccinia virus, camelpox virus, taterapox virus, ectromelia virus, and horsepox virus [1], [2]. These zoonotic pathogens are primarily transmitted from animals to humans, though human-to-human transmission is also possible. The term 'mpox' replaced 'monkeypox' to mitigate racial stigmatization and to reflect the virus' primary reservoir, rodents, rather than monkeys [3]. Concerns over potential discrimination prompted the World Health Organization's (WHO) formal adoption of 'mpox' in November 2022, with both terms used concurrently for a transitional period [4], [5].

## II. MATERIALS AND METHODS

Information on the history, outbreaks, clinical features, management and recent advances in the control of mpox were sourced from various literature. Research articles, book chapters, review papers, and other pertinent references were retrieved from digital repositories, including PubMed, Google Scholar and ScienceDirect.

### III. RESULTS

#### A. History

The monkeypox virus was first identified in laboratory monkeys transported from Singapore to Denmark in 1959. The initial human case was reported in Zaire (now the Democratic Republic of Congo) in 1970 [6]. Subsequent cases emerged in Côte d'Ivoire, Liberia, Nigeria, and Sierra Leone [7], [8]. Following the WHO's 1980 declaration of smallpox eradication, smallpox vaccinations declined, increasing mpox susceptibility [9]. Immunity from smallpox, through previous infection or vaccination, gives long-term protection against pox. However, post-2022 outbreaks have included cases among individuals presumed to have immunity [10].

Although Mpox was historically confined to West Africa, the first documented Western Hemisphere cases emerged in 2003, linked to African animal trade to the United States [11]. Human-to-human transmission accelerated in May 2022 [12], with the United Kingdom reporting the first outbreak outside endemic regions. By July 22, 2022, the UK had confirmed 2,208 cases, with England accounting for 2,115, Scotland 54, Wales 24, and Northern Ireland 15. The outbreak primarily affected men who have sex with men without travel history to endemic regions [13]. Mpox remains endemic in Central and West Africa [14], with studies in the Democratic Republic of Congo (DRC) suggesting heterosexual transmission, particularly among female sex workers (9%), as a contributing factor [15], in contrast to the 2022 European outbreak.

Two primary clades of the monkeypox virus exist. Clade I, subdivided into Ia and Ib, is more virulent, highly transmissible, and has a fatality rate reaching 10%, primarily affecting Congo. Clade Ib has been linked to the 2024 outbreak. Clade II (subclades IIa and IIb) is less transmissible, exhibits lower virulence, and has a survival rate of 99.9%. This clade is predominantly found in West Africa, with Clade IIb responsible for the 2022-2023 global outbreak [16], [17], [18].

Mpox spreads through respiratory droplets during prolonged close contact, direct exposure to infected animals, and ingesting contaminated animal products [19], [20], [21]. The 2022 outbreak was primarily driven by human-to-human transmission through direct contact, including sexual contact [22]. Indirect transmission via fomites and vertical transmission from mother to foetus has also been reported [19], [20], [21].

#### B. Clinical Features and Management

The incubation period ranges from 5 to 21 days, averaging 12 days, but may extend from 1 to 30 days [23], [24], [25]. Prodromal symptoms emerge 1-3 days before rash onset, including fever (38.5 - 40.5°C), chills, sweats, headache, appetite loss, muscle pain, back pain, fatigue, sore throat, respiratory symptoms, and lymphadenopathy [26]. The eruptive phase follows, with a maculopapular rash spreading from mucosal sites to the face and extremities [23], [27]. The rash progresses through macules, papules, vesicles, pustules, and crusts approximately 12 days before resolution [28].

Diagnosis relies on real-time polymerase chain reaction (PCR) tests, with skin lesion samples as the preferred specimen type. Results are typically available within 2-4 days [29]. While mpox is self-limiting, supportive treatment is recommended for symptom relief. Antivirals like tecovirimat, initially developed for smallpox, have been used for treatment. Co-infections, such as HIV, should be managed concurrently [30]. Isolation is essential to prevent transmission, and healthcare providers must adhere to protective measures [31]. Patients remain contagious until all lesions have crusted and a new skin layer has formed [32].

The 2024 outbreak had a case fatality rate exceeding 3.9%, disproportionately affecting children under 15 [33]. Mortality rates are elevated among immunocompromised individuals, including those with HIV [34], [35]. Surveillance, early diagnosis, and continued research are critical in reducing mpox morbidity and mortality.

The case fatality rate (CFR) in the Democratic Republic of the Congo (DRC) due to suspected clade I mpox in 2024 was recorded at 3.04%; however, this figure may be overestimated due to challenges in comprehensive case testing and reporting [36]. A study conducted between 2007 and 2011 on 216 patients with mpox at a DRC hospital reported a CFR of 1.4% among those who received limited supportive care without mpox-specific therapeutics. Another recent study indicated improved survival rates (1.7%) among individuals who received supportive medical care [37]. The diagnosis and management of mpox in Africa face numerous obstacles, including patients withholding their travel history from healthcare providers, avoiding isolation post-diagnosis, shortages of personal protective equipment and PCR testing facilities, vaccine hesitancy or refusal, and inadequate disease notification systems [38].

Vertical transmission of mpox has been documented. Pregnant women are at more significant risk of severe disease due to immunological and hormonal changes that heighten susceptibility to infections during pregnancy. African women seem to have a greater likelihood of mpox infection and adverse pregnancy outcomes [37]. Prior smallpox vaccination results in a milder presentation of mpox [9]. Most mpox lesions do not lead to permanent scarring, although some scarring and discolouration may occur. Similar to chickenpox, many lesions fade over time. However, various types of permanent scars may develop if they are scratched or picked at. To reduce the risk of scarring, irritating topical products should be avoided [39].

### **C. Recent outbreak**

The Africa Centre for Disease Control and Prevention (Africa CDC) and the WHO designated 'mpox' as a Public Health Emergency of International Concern (PHEIC) on the 13th and 14th of August 2024, respectively [11], [31]. A PHEIC is a formal WHO declaration of "an extraordinary event which causes a public health challenge to other nations through international disease spread and may necessitate a coordinated global response" [40]. Since May 2022, a global mpox outbreak has mostly impacted men who indulge in sex with men [12]. In 2024, the DRC reported 19,513 cases before the emergency declaration, with a CFR of 3.1%. This accounted for about 88% of Africa's mpox cases in 2024. The country experienced a weekly average of 591 cases compared to 281 in 2023 [41].

### **D. Smallpox virus stock: to destroy or not to destroy**

Mpox is less severe and less contagious than smallpox. Smallpox, caused by the variola virus, belongs to the Orthopoxvirus genus [42]. The last natural case of smallpox was occurred in Somalia in October 1977, involving a hospital cook who fully recovered [43]. In 1978, a British medical photographer was accidentally exposed to the virus cultivated in a research laboratory below her workplace at the University of Birmingham Medical School, becoming the last recorded person to succumb to smallpox [44]. Following this incident, all known stocks of the virus were either destroyed or transferred to one of two WHO reference laboratories with BSL-4 containment: the CDC in the United States and the State Research Center of Virology and Biotechnology (VECTOR) in Russia [45]. Smallpox was responsible for the death of an estimated 300 million people in the 20th century alone, surpassing fatalities from all other infectious diseases combined [46]. The smallpox eradication was declared by WHO in 1980, making it the only human disease to have been eradicated [47]. Genetically, smallpox and mpox share 85% sequence similarity [48].

The debate on whether to eliminate the remaining smallpox virus samples continues. Supporters of destruction argue that an accidental release or bioterrorism use could be catastrophic, as half the world's population has never been vaccinated, and smallpox has a fatality rate exceeding 30%. The laboratory in Russia had an explosion in 2019 that injured a worker, but the virus storage facility remained intact and secure. Critics of destruction argue that the samples should be retained for ongoing research and vaccine development to combat potential outbreaks of smallpox and related poxviruses, including mpox [46], [47], [48], [49].

### **E. Vaccines**

All Orthopoxviruses generate cross-reactive immune responses, meaning that antibodies produced during infection with one virus protect others in the genus [50]. This principle underpinned Edward Jenner's cowpox-based smallpox vaccine. Vaccinia virus-based vaccines, which have low virulence, were instrumental in eradicating smallpox and have shown efficacy against mpox in animal studies [51], [52], [53]. Due to the high genetic similarity among Orthopoxviruses, they share many immunological markers. Animal studies in the 1960s first demonstrated that antibodies induced by smallpox vaccination could bind to and neutralize multiple Orthopoxvirus proteins, providing cross-protection against mpox [54].

Several vaccines against mpox have been developed using smallpox virus technology, including MVA-BN, LC16, OrthopoxVac, and ACAM2000 [48]. ACAM2000 has demonstrated strong protection against mpox in animal models; however, concerns remain regarding its safety in humans due to potential cardiac complications and painful skin reactions at the injection site [55]. As a result, the vaccine is no longer licensed in the European Union [56]. Funding remains challenging, with lower-income countries relying on donations from wealthier nations to meet vaccine demands [57], [58]. The vaccine is administered in two doses at least 28 days apart for those unvaccinated against smallpox, becoming effective two weeks after the second dose. As of February 14, 2025, the CDC recommends vaccination for travellers to countries experiencing the Clade I outbreak, including Burundi, the Central African Republic, the DRC, Kenya, the Republic of the Congo, Rwanda, Uganda, and Zambia [59]. A single booster dose is sufficient for those previously

vaccinated against smallpox. Mpox vaccination is advised for high-risk individuals, including healthcare workers, men who have sex with men, those with multiple sexual partners, sex workers, immunocompromised individuals, pregnant or breastfeeding women, and those travelling to outbreak-prone regions. Individuals who have recovered from mpox do not require vaccination [48]. Vaccine hesitancy persists due to multiple factors [60].

#### **IV. CONCLUSION**

Smallpox eradication was achieved with less advanced technology than we have today, suggesting that mpox can be effectively controlled. However, unlike smallpox, which solely infected humans, mpox also affects animals, serving as reservoirs for zoonotic transmission. This complicates eradication efforts. For now, the focus remains on control. Fortunately, mpox is unlikely to cause a pandemic since sustained close contact is necessary for transmission. Healthcare workers should maintain vigilance and a high index of suspicion when identifying cases. Observing patients, non-patients, survivors, relatives, and surrounding environments can provide crucial insights into factors affecting outcomes. Many medical breakthroughs stem from careful observation. Edward Jenner discovered that milkmaids exposed to cowpox were immune to smallpox, which led to vaccine development in 1796. Health workers should also document patient characteristics, including demographics, occupation, and travel history, to facilitate research. Additionally, they must adhere to standard infection control protocols.

#### **Abbreviations**

Africa CDC	Africa Centre for Disease Control and Prevention
CDC	Centre for Disease Control and Prevention
European CDC	European Centre for Disease Control and Prevention
NIAID	National Institute of Allergies and Infectious Diseases
PHEIC	Public Health Emergency of International Concern
WHO	World Health Organization

#### **Declarations**

##### **Ethics approval and consent to participate**

Not applicable.

##### **Consent for publication**

Not applicable.

##### **Availability of data and material**

Not applicable.

##### **Competing interests**

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Chinyerem Cynthia Nwachukwu came up with the idea for the article. Chinyerem Cynthia Nwachukwu, Ifeoma Anne Njelita, Gabriel Ifeanyi Eyisi, Amaechi Chinedu Nwachukwu and Chijioke Amara Ezenyeaku performed the literature search, drafted the manuscript and revised the work.

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