

# Exploring the Historical Dissemination and Contemporary Resurgence of Monkeypox: A Comprehensive Examination of its Evolution, Global Impact, and Treatment Approaches

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## ABSTRACT

Monkeypox, an Orthopoxvirus genus zoonotic ailment, has resurfaced as a global public health issue, with outbreaks in 2022 and 2024 highlighting alterations in its epidemiology and transmission dynamics. This narrative synthesis amalgamates data from historical outbreaks, recent research, and official health documents to scrutinize the evolving epidemiological trends, clinical presentations, and current treatment and prevention strategies for monkeypox. Analysis indicates a notable demographic shift in the 2024 outbreak, with a rise in cases among children, healthcare professionals, and immunosuppressed individuals. Non-sexual transmission has emerged as a significant mode of infection in specific regions, particularly in areas affected by humanitarian crises. Progress in diagnostics, antiviral medications like tecovirimat, and vaccines such as JYNNEOS has substantially enhanced disease management. The resurgence of monkeypox underscores the imperative for comprehensive surveillance, fair vaccine distribution, and targeted public health measures to combat emerging zoonotic hazards.

**Keywords:** Mpx, Orthopoxvirus, Lymphadenopathy, Tecovirimat.

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## INTRODUCTION

The Orthopoxvirus genus, a member of the Poxviridae family, serves as the source of the resurgent zoonotic infection known as Monkeypox (Mpx) (Otu *et al.*, 2022). Initially discovered in 1958 among monkeys and later in humans in 1970 during a smallpox surveillance program in the Democratic Republic of Congo (DRC), Mpx predominantly affected unvaccinated children in its early cases (Gessain *et al.*, 2022a). Prior to the 2022 outbreak, Mpx was endemic to West and Central Africa. However, following a reported case in the UK, infections surged, leading to an outbreak across multiple nations with unclear connections to endemic regions (Huang *et al.*, 2022). The World Health Organization (WHO) Director-General declared Mpx a Public Health Emergency of International Concern (PHEIC) twice: first in May 2022 and again in August 2024 (Mpx, n.d.). The DNA virus MPXV is categorized into two genetic clades - West Africa (WA) and Congo Basin (CB) - with an average incubation period of 4 to 21 days (Alakunle and Okeke, 2022). Symptoms can vary

from fever to respiratory distress, resembling those of smallpox but with Lymphadenopathy (LAD) as a distinguishing feature. Mpx transmission occurs through various routes, including animal to animal, animal to human, and human to human contact (Karagoz *et al.*, 2023; Sah *et al.*, 2022). This study aims to provide a comprehensive review of Mpx epidemiology and therapeutic strategies, drawing from past outbreaks and current approaches to enhance future public health responses. Understanding the virus's transmission dynamics and treatment options is crucial as the global community grapples with new and emerging threats posed by this previously localized disease.

## Tracing the Origin and Historical Outbreaks of Mpx

The discovery of Mpx dates back to 1958, when it was first identified in monkeys. The inaugural human case was recorded in 1970 during a smallpox eradication campaign in Africa (Zahmatyar *et al.*, 2023). Since then, Mpx has predominantly circulated in Central and West Africa, with primates and rodents serving as key virus carriers (Lu *et al.*, 2023). The most significant outbreak of Mpx was documented in the DRC between 1996 and 1997, with 511 reported cases, primarily affecting children under the age of 16 (*Human Monkeypox -- Kasai Oriental, Democratic Republic of Congo, February 1996-October 1997, 1997*). The first human Mpx epidemic overseas from Africa, occurred in the United States in 2003, associated with Gambian pouched



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rats that were smuggled from Ghana and infected prairie dogs (Ilic et al., 2022; Jezek et al., 1987a). During the 1980s, sporadic cases of Mpox in Central Africa were frequently misdiagnosed as chickenpox due to their similar clinical presentations (Rizk et al., 2022a). In 2017, Nigeria experienced its first substantial Mpox outbreak since 1978, with 146 suspected cases and 42 confirmed cases across 14 states (Yinka-Ogunleye et al., 2018). Subsequently, between 2018 and 2019, sporadic cases of Mpox emerged in non-endemic countries such as the UK, Israel, USA, and Singapore (Monkeypox - United States of America, 2021; Taha et al., 2023; Thakur et al., 2022), as summarized visually in Figure 1.

## 2022 Outbreak

In 2022, the world faced its first widespread Mpox outbreak across multiple countries, with a significant portion of cases lacking clear epidemiological ties to endemic regions (Huang et al., 2022). The sudden emergence of Mpox outbreaks in Europe, USA, and Australia starting on May 7, 2022, caught global authorities off guard, despite previous calls for preventive measures (Zumla et al., 2022). Between January 1, 2022, and December 11, 2022, the WHO reported a total of 82,624 laboratory-confirmed cases of Mpox, resulting in 65 deaths, across 110 countries spanning all six WHO regions. The outbreak predominantly affected young men, with 96.8% of cases being male and a median age of 34 years. A small percentage of cases (1.2%) were individuals aged 0-17, with a concentration in the Americas. Among cases with reported sexual orientation, a significant proportion (85.9%) identified as gay, bisexual, or men who have sex with men, with skin and mucosal contact during sexual activities identified as the primary mode of transmission. Limited data from Africa suggested frequent contact with infected animals as another common transmission route (*Multi-Country Outbreak of Mpox, External Situation Report#12- 14 December 2022, 2024*).

During the 2022 Mpox outbreak, typical symptoms included fever, LAD, and a distinctive vesiculopustular rash. However, many cases exhibited atypical characteristics, such as localized lesions in the vaginal and perianal areas accompanied by proctitis, and some individuals did not experience typical prodromal symptoms like fever. This unusual presentation led to misdiagnoses, with the symptoms resembling conditions such as varicella-zoster, syphilis, and genital herpes (Minhaj et al., 2022). Despite a lower mortality rate compared to other zoonotic diseases, the 2022 Mpox outbreak claimed the lives of 65 individuals. Severe complications, particularly in immunocompromised patients, were the primary cause of death during this unprecedented global health crisis (*Multi-Country Outbreak of Mpox, External Situation Report#12- 14 December 2022, 2024*).

## The Resurgence of Monkeypox in 2024: A Global Overview

In 2024, Mpox reemerged on the world stage, with 14 nations reporting a total of 31,427 suspected and confirmed cases, including 844 suspected and confirmed deaths (*2022-24 Mpox (Monkeypox) Outbreak: Global Trends, 2024*). The August 2024 statistical report, which recorded 2,082 new cases - the highest monthly total since November 2022 - highlighted a concerning upward trend on a global scale. The outbreak of clade Ib MPXV is spreading to new regions, including Sweden, Thailand, and Gabon, while the clade I outbreak persists in endemic countries, particularly in the DRC and Burundi (Minhaj et al., 2022). In July 2024, clade IIB resurfaced in South Africa, contributing to over 300 cases across previously unaffected nations and over 100 confirmed cases in other African countries, with significant morbidity and mortality observed in individuals with advanced HIV. Mobile populations in eastern DRC have facilitated the spread of clade Ib monkeypox to Burundi, Kenya, Rwanda, and Uganda (Kuppalli et al., 2024). Additionally, cases of Mpox have been documented in Asia, Europe, and North America, with clusters linked to travel and close contact transmission ("Asia Sees Rising Mpox Cases; Takes Action with Control and Treatment Measures," 2024; *Mpox: EU Must Prepare for More Cases, Health Agency Warns, 2024*; Ndemi, 2024). Unlike the 2022 outbreak that predominantly affected men who have sex with men (MSM), the 2024 outbreak has impacted a broader demographic, including immunocompromised individuals, children, and healthcare workers. UNICEF reports indicate that non-sexual transmission through close contact and contaminated objects plays a significant role in infections, particularly in countries like Burundi, where children under five years old constitute a majority of cases. Immunosuppressed individuals and healthcare personnel remain at heightened risk due to increased exposure. The substantial number of suspected deaths in the DRC and Burundi, especially among children, has been linked to the region's humanitarian crisis, characterized by factors such as starvation, conflict, and coexisting diseases that have left many individuals immunocompromised (Jezek et al., 1987b; *Mpox Alert: UNICEF Issues \$58.8 Million Appeal to Halt Outbreak in Africa, 2024*; *Multi-Country Outbreak of Mpox, External Situation Report#35- 12 August 2024, 2024*).

## Africa: The Epicenter of the 2024 Monkeypox Outbreak

By mid-September 2024, Africa continued to bear the brunt of the ongoing Mpox outbreak, with a substantial number of reported cases. The epidemiological landscape underscores the continent's significant impact, with outbreaks concentrated in specific regions. The swift transmission and elevated case numbers underscore Africa's susceptibility during this phase of the 2024 outbreak (Figure 2).

The data displayed in the Figure 3 graph indicates cumulative reported cases by WHO region from March to August 2024. The African Region consistently records the highest number of cases, highlighting the significant impact of the outbreak on the continent. In contrast, the Eastern Mediterranean Region reports relatively low figures, suggesting a lesser extent of the outbreak in this area. The European Region demonstrates a gradual increase in reported cases over the specified timeframe, indicating a rising trend in infections within this region. On the other hand, the Region of the Americas shows fluctuations in notifications, suggesting varying levels of activity during the period under review.

The Southeast Asia and Western Pacific Regions contribute minimally to the total case count, indicating a lower prevalence of Mpox in these regions compared to others. Overall, the data underscore that the African Region bears the highest burden of the outbreak, with other regions exhibiting differing impacts and levels of involvement in the spread of Mpox during the specified timeframe (Table 1).

### Understanding the Progression of Monkeypox: Exploring the Different Stages of Illness and Clinical Symptoms

Mpox typically progresses through three distinct stages in individuals, affecting both children and young adults: incubation, prodrome, and the eruptive stage characterized by skin lesions (Di Giulio and Eckburg, 2004; Gessain *et al.*, 2022b; Huhn *et al.*, 2005; McCollum and Damon, 2014; Petersen *et al.*, 2019a). The classic form of the illness is primarily transmitted within families and healthcare settings (Antinori *et al.*, 2022). At the same time, the current outbreak appears to be driven by populations, particularly men who have sex with multiple partners (Brown and Leggat, 2016; Perez Duque *et al.*, 2022; Vivancos *et al.*, 2022). Most monkeypox infections are self-limiting and mild, with symptoms typically resolving within two to four weeks. The average incubation period is around 13 days, ranging from 5 to 34 days from exposure to symptom onset (Harapan *et al.*, 2022; Reed *et al.*, 2004). The prodromal phase lasts one to four days and commonly presents with symptoms such as pruritus, fever, LAD, and rash.

A defining feature of Mpox infection is LAD, particularly affecting the neck, groin, axilla, and submandibular glands, helping differentiate it from other poxviruses like chickenpox or smallpox (Antinori *et al.*, 2022; Patel *et al.*, 2022). Additional symptoms may include headache, fatigue, muscle pain, sensitivity to light, joint pain, cough, eye inflammation, nausea, vomiting, and diarrhoea (Benites-Zapata *et al.*, 2022; Breman and Henderson, 2002; *Mpox*, 2024; Patel *et al.*, 2022; Pittman *et al.*, 2022). The eruptive phase is characterized by the development of centrifugally distributed skin lesions, primarily on the face and distal extremities, progressing

through four phases: macules, papules, vesicles, and pustules over a period of 14 to 28 days (Antinori *et al.*, 2022).

### Manifestations of Mpox Infection: Oral Lesions and Clinical Symptoms

In cases of Mpox infection, one of the early signs can be the presence of oral mucosa lesions, with reports indicating that oral and perioral lesions may be observed in varying percentages of patients, ranging from 5% to 70% (Català *et al.*, 2022; Pandey and Reddy, 2024; Tarín-Vicente *et al.*, 2022; Weaver and Isaacs, 2008). Enlarged lymph nodes in the inguinal region, as well as LAD in the submandibular and cervical regions, are commonly observed in most human Mpox infections. Unlike smallpox infections, LAD is considered a hallmark sign of Mpox infection, and odynophagia resulting from ulceration associated with Mpox may also occur (Chittajallu *et al.*, 2023; *How Mpox Spreads*, 2024).

In addition to oral lesions, systemic symptoms such as asthenia, myalgia, proctalgia, headaches, and sore throats may also manifest in individuals with Mpox infection (Kozlov, 2022; Lane and Fauci, 2022; Peiró-Mestres *et al.*, 2022). It is important for healthcare professionals to be familiar with the spectrum of symptoms associated with Mpox to facilitate timely diagnosis and appropriate management (Nyame *et al.*, 2023).

### Detecting Mpox: Methods and Procedures for Diagnosis

The best specimen collection for laboratory evaluation of Mpox involves scraping scabs, discharge, or vesicular lesions, which should be kept cold in a sterile setting. For laboratory assessment, viral culture can be carried out utilizing nasopharyngeal or swabs from the oropharynx. To help arrive at a more precise diagnosis, cutaneous vesicular lesions or vesiculopustular rashes can be sampled (Kannan *et al.*, 2022). In certain instances, a number of lab tests may be necessary concurrently to exclude out smallpox (Rizk *et al.*, 2022b). When the Mpox virus's DNA or genetic material is found in skin lesions, active instances of the disease can be identified (Petersen *et al.*, 2019b). Lesion material specimens must be kept in a cold, dark tube in order to detect viral DNA (Rizk *et al.*, 2022b). The primary drawbacks of this diagnostic method are the requirement for skilled professionals and its comparatively high cost (Rizk *et al.*, 2022b). Active cases are also diagnosed by serologic antibody evaluation utilizing the Enzyme-Linked Immunosorbent test (ELISA). Compared to PCR, ELISA can be done more cheaply and with less training. However, because ELISA does not specifically detect the Mpox virus and because orthopoxviruses can cross-react, the results of this test cannot be used to diagnose Mpox infection. Therefore, utilizing serologic evaluation or ELISA for antibody detection to diagnose Mpox is typically not recommended (Grossegeisse *et al.*, 2023).

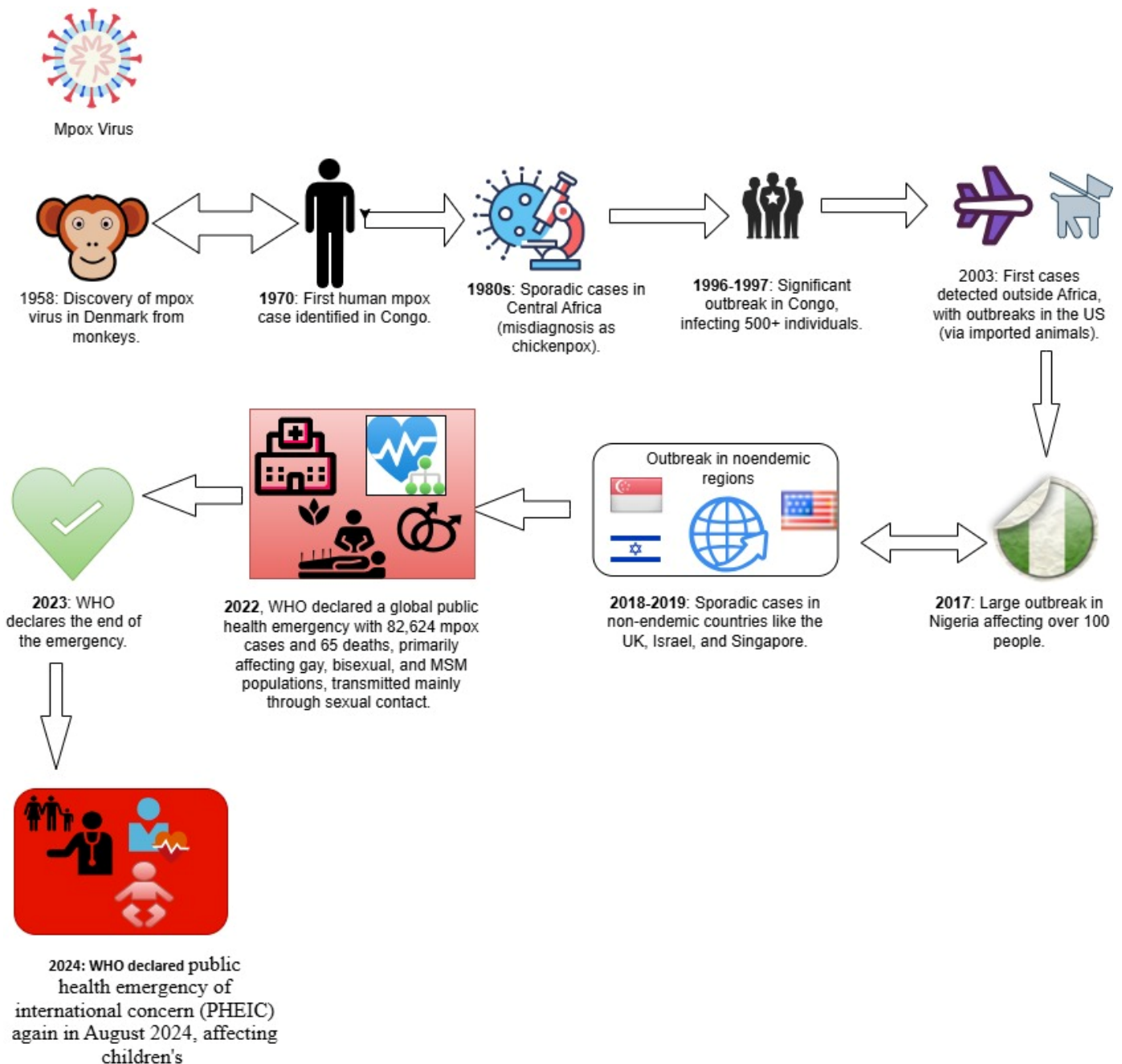
## Comprehensive Care Guidelines for Patients with Monkeypox: Supportive Measures and Therapeutic Interventions

The majority of individuals with Mpox recover without the need for medical intervention; however, approximately half may require pain relief, particularly for oral or anogenital lesions. Supportive care may also involve the use of stool softeners and topical lidocaine for proctitis, antihistamines for itching, and antibiotics for treating secondary bacterial infections. In severe cases, additional interventions such as catheterization, wound care, and intensified pain management may be necessary.

Patients experiencing gastrointestinal symptoms like vomiting or diarrhoea may require oral or intravenous rehydration to prevent dehydration and address fluid loss (Mitjà *et al.*, 2023; Russo *et al.*, 2021).

### Antiviral Treatment

Tecovirimat (TPOXX®; ST-246) was approved by the USFDA in July 2018 for the treatment of symptomatic smallpox. This antiviral medication targets the VP37 protein in orthopoxviruses, which is essential for enveloping mature virus particles with a membrane from the Golgi apparatus. By inhibiting this



**Figure 1:** Chronological Timeline of Monkeypox: A Visual Representation of its Historical Evolution and Global Impact.

envelopment process, TPOXX prevents the virus from maturing and being released, thereby reducing its spread and mitigating the severity of the infection (*Clinical Treatment for Mpox*, n.d.).

TPOXX is recommended as the preferred treatment for Mpox, particularly for patients with severe illness or those at high risk, including immunodeficient individuals, pregnant or lactating women, and children (Russo et al., 2021). The drug was also approved in the EU on January 6, 2022, based on its efficacy in reducing mortality rates in smallpox, Mpox, and cowpox. Animal studies have shown that TPOXX exhibits strong antiviral activity and improves survival rates in animal models even when treatment is initiated after the onset of Mpox symptoms (Calle-Prieto et al., 2023; Russo et al., 2020; *Tecovirimat SIGA*, n.d.). In animal model trials, a human dose of TPOXX (600 mg twice daily) has been found to achieve plasma levels well above the threshold required for maximum efficacy. A typical five-day course of treatment is generally sufficient for a clinical response, while a two-week regimen supports sustained viral clearance and immune development. However, immunosuppressed patients

may necessitate extended treatment beyond the standard 14 days (*Tecovirimat (TPOXX) Prescribing Information*, n.d.). TPOXX is generally well-tolerated and does not typically result in serious drug-related adverse events (Russo et al., 2021). Common reported side effects from oral consumption include headache, nausea, abdominal pain, and vomiting, while injections may lead to localized reactions and headaches (*Brincidofovir*, 2022). Although human randomized controlled studies are limited, TPOXX is currently available under Emergency Use Authorization (EUA), with ongoing clinical trials aimed at evaluating its effectiveness in treating human Mpox infections (Russo et al., 2021).

Brincidofovir (BCV) is an oral antiviral drug effective against smallpox and other DNA viruses. It is approved for treating smallpox virus (variola) infections in humans and has received EUA for treating Mpox (Rana et al., 2023). BCV functions as a prodrug of cidofovir, chemically designed to increase its concentration within cells while reducing levels in the bloodstream. Once inside cells, it is converted into cidofovir diphosphate, which inhibits viral DNA polymerase, ultimately blocking viral replication

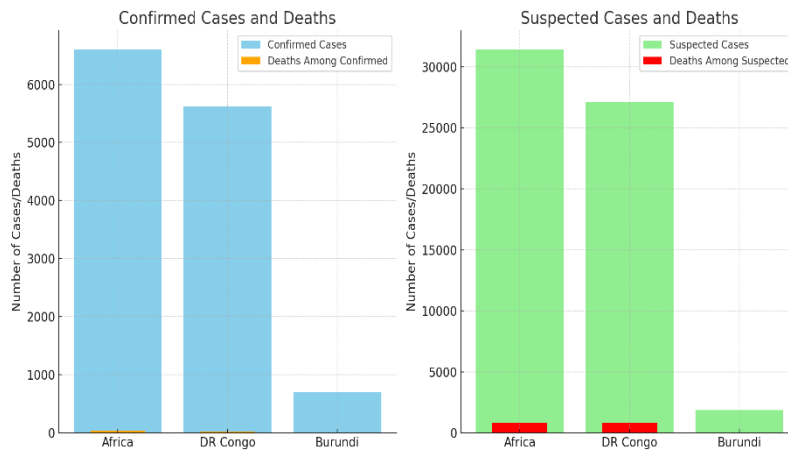


Figure 2: "Epidemiological Status of Africa: The Most Affected Region in the 2024 Outbreak as of Mid-September" (Source: WHO).

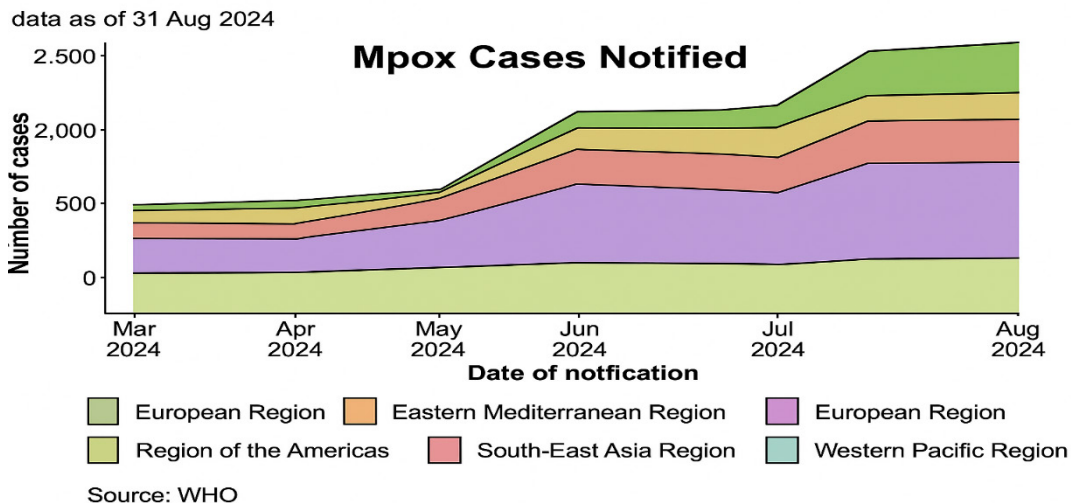


Figure 3: Graph Analysis- Monkeypox Cases by WHO Region (March-August 2024).

**Table 1: "Mpx Case Counts in WHO Regions as of August 2024".**

WHO Region	Total Cases (from Jan 2022)	Total Deaths	Cases in Jul 2024	Cases in Aug 2024	Monthly % Change in Cases
Region of the Americas	64,879	148	447	207	-54.0%
European Region	27,965	9	151	285	89.0%
African Region	7,662	54	1,016	1,298	28.0%
Western Pacific Region	3,979	10	163	274	68.0%
South-East Asia Region	956	11	15	16	6.7%

(Siegrist and Sassine, 2023). When given early in the course of infection, BCV has proven to be quite effective in treating animal models of Mpx, as seen by studies demonstrating increased survival rates in mice, rabbits, and prairie dogs. While common adverse effects include gastrointestinal and hepatocellular toxicity, BCV offers advantages such as lower nephrotoxicity and oral availability compared to cidofovir, making it a promising treatment option for Mpx and other viral infections (Bruno and Buccoliero, 2023).

### Vaccines in Managing Monkeypox: A Crucial Tool in Prevention and Outbreak Response

Three vaccines initially developed for smallpox-ACAM2000, MVABN (Imvamune, JYNNEOS, or Imvanex), and LC16-have been authorized for deployment in Monkeypox outbreaks across different territories. (*Fact Sheet for Healthcare Providers Administering Vaccine: Emergency Use Authorization of JYNNEOS (Smallpox and Monkeypox Vaccine, Live, Non-Replicating) for Prevention of Monkeypox Disease in Individuals Determined to Be at High Risk for Monkeypox Infection.*, 2024; Siegrist and Sassine, 2023).

#### JYNNEOS Vaccine

In 2019, the FDA authorized the JYNNEOS vaccine (modified vaccinia Ankara, MVA) for preventing smallpox and Monkeypox, administered in a two-dose series of 0.5 mL doses given four weeks apart (Frey et al., 2015). To enhance vaccine accessibility, EUA was granted on August 9, 2022, allowing intradermal administration of the vaccine in smaller 0.1 mL doses, also given four weeks apart (Deputy et al., 2023; Frey et al., 2015). Vaccination for Monkeypox serves as postexposure prophylaxis for individuals with known or presumed exposure and as pre-exposure prophylaxis for high-risk groups, including men who have sex with men, transgender or nonbinary individuals, and those with HIV or recent STI diagnoses (*ACAM2000 (Smallpox Vaccine) Questions and Answers*, 2024). A case-control study conducted by Nicholas P. Deputy et al., revealed that the JYNNEOS vaccine significantly reduces Monkeypox risk, exhibiting 66% effectiveness for a two-dose series compared to 36% for a single

dose, as indicated by data from a national electronic health record database (*ACAM2000 (Smallpox Vaccine) Questions and Answers*, 2024).

#### ACAM2000

ACAM2000 is a smallpox vaccine made from the vaccinia virus that stimulates an immune response through localized infection via a bifurcated needle. Still, it may cause side effects like myocarditis and pericarditis and is not recommended for individuals with weakened immune systems or certain skin conditions. The effectiveness of the ACAM2000 vaccine in preventing MPXV infection is presently unclear (Morino et al., 2024).

#### LC16 Vaccine

The LC16m8 vaccine, a freeze-dried, cell-cultured live attenuated vaccine derived from the vaccinia virus, has been approved in Japan to prevent smallpox and Mpx. Although LC16m8 effectively protects animals from lethal doses of Mpx and related viruses, data on its use in human Mpx outbreaks are limited. More than 90,000 people, including 50,000 children, have received the vaccine with no significant safety concerns, but it is not recommended for individuals with weakened immune systems, certain skin conditions, or for pregnant women (Grabenstein and Hacker, 2024; Ren et al., 2024).

Both MVA-BN and LC16m8 vaccines protect against lethal orthopoxvirus infections, with MVA-BN showing 76% to 85% disease reduction in real-world MPXV clade IIB outbreaks. In contrast, real-world data for LC16m8 remains limited (Ren et al., 2024).

### Innovative Treatments for Mpx: Advancements in Therapeutic Agents and Interventions

#### *Monoclonal and Bispecific Antibodies*

The global spread of the Monkeypox Virus (MPXV) highlighted the necessity for effective antiviral treatments, resulting in the development of monoclonal Antibodies (mAbs) and Bispecific Antibodies (bsAbs) targeting MPXV proteins M1R and B6R.

In a study led by Zuning Ren *et al.*, two neutralizing mAbs (M1H11 and M3B2) were identified, and it was demonstrated that a combination of these mAbs and the engineered bispecific antibody Bis-M1M3 displayed significant protective effects against MPXV. These antibodies neutralized the virus pre-cell infection and exhibited a prolonged half-life in rhesus macaques (Mohapatra *et al.*, 2022).

## CONCLUSION

The resurgence of Mpox on a global scale, as evidenced by the outbreaks in 2022 and 2024, underscores the urgency for a comprehensive public health intervention to contain its transmission and minimize its repercussions. Improved diagnostic tools, supportive care protocols, antiviral treatments, and efficient vaccination programs play a crucial role in curbing the spread of Mpox. In the face of this evolving challenge, fostering international cooperation, allocating resources effectively, and advancing research on Mpox epidemiology and treatment are essential for addressing ongoing outbreaks and averting potential pandemics.

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None.

## ABBREVIATIONS

**Mpox:** Monkeypox; **DRC:** Democratic Republic of Congo; **PHEIC:** Public Health Emergency of International Concern; **LAD:** Lymphadenopathy; **ELISA:** Enzyme-linked Immunosorbent Test; **TPOXX:** Tecovirimat; **mAbs:** Monoclonal Antibodies; **bsAbs:** Bispecific Antibodies.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHOR CONTRIBUTIONS

M.S., T.V. and A.J. collected the references and drafted the manuscript. M.S. and T.V. drew the figures and tables. M.S. and S.R. reviewed the article. A.J. and S.S. revised the paper and provided professional guidance. All authors critically read the manuscript and agreed to the published version.

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