**Advances and Challenges in Mpox Treatment**

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ABSTRACT

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| This study aims to analyze the available evidence on advancements in Mpox treatment and the identified challenges. **Methodology**: A systematic review was conducted, searching the most important scientific databases and libraries. **Results**: Advances in the treatment of Monkeypox (Mpox) include the use of the antiviral Tecovirimat, which has shown significant efficacy in reducing symptoms and recovery time in severe cases. Additionally, vaccines such as JYNNEOS and ACAM2000 have been essential in reducing the severity of the infection, with vaccinated individuals exhibiting milder symptoms and a lower need for therapeutic intervention. However, challenges remain. Emerging resistance to Tecovirimat was observed in approximately 10% of patients, indicating the need for alternative therapies. In endemic regions, particularly in Africa, logistical barriers such as limited access to antivirals and inadequate infrastructure result in disparities in clinical outcomes compared to developed countries. Furthermore, therapies like Cidofovir and Brincidofovir, although promising, are associated with side effects such as hepatic and renal toxicity, limiting their widespread use.  **Conclusion**: These findings point to a scenario of promising advancements but also highlight the need for more comprehensive approaches to ensure successful treatment of Mpox in various clinical and geographic contexts. Continuous research and more robust clinical trials are essential to optimize the treatment of the disease and overcome existing challenges. |

*Keywords* Mpox; Treatment; Vaccine; Research.

1. INTRODUCTION

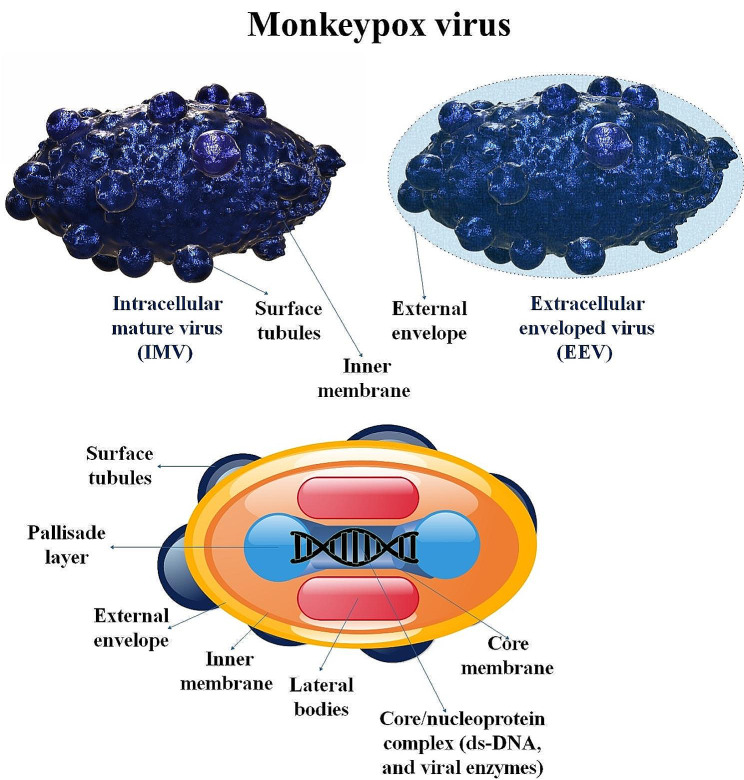
Monkeypox, also known as Mpox, is a viral zoonosis caused by the Monkeypox virus, belonging to the Orthopoxvirus genus. The disease was initially identified in monkeys in the Congo in 1958, but the first human case was recorded in 1970 in the Democratic Republic of Congo (DRC). Since then, Mpox has been an emerging public health concern, particularly in Central and West African regions where periodic outbreaks occur (WHO, 2022). However, the recent international spread of the virus, with cases in several countries outside of Africa, underscores the risk of global pandemics.

The Monkeypox virus is genetically related to the smallpox virus, with which it shares clinical similarities, including fever, muscle aches, and a characteristic rash. The incubation period ranges from 5 to 21 days, and symptoms can vary from mild to severe, depending on the viral strain and the host's immune response (CDC, 2023). Infection primarily occurs through direct contact with bodily fluids from infected animals or individuals, but human-to-human transmission is also possible via respiratory droplets or contact with skin lesions (Huhn *et al*., 2020).

Over the years, the understanding of the Monkeypox virus has advanced, and smallpox vaccination campaigns have proven effective in providing cross-protection against Mpox, as the viruses share a similar viral architecture (Ladnyj *et al*., 1972). However, with the eradication of smallpox and the cessation of mass vaccination, younger populations have become more vulnerable to Monkeypox, increasing the risk of outbreaks in previously non-endemic areas (Reynolds *et al*., 2019).

A cell infected by the double-stranded DNA (dsDNA) Mpox virus contains two types of viral particles: intracellular mature virus (IMV) and intracellular enveloped virus (IEV). Mpox is one of the most complex and largest viruses, with a brick-like structure measuring between 220–450 nanometers in length and 140–260 nanometers in width. Its composition is divided into four main components: the core, lateral bodies, outer membrane, and lipoprotein envelope. The core, which houses the double-stranded viral DNA, is surrounded by fibrils and enclosed by a palisade layer, an impermeable structure that protects the core. The outer membrane contains the central core, lateral bodies, and the palisade layer, forming the complete architecture of the virus (Natami *et al*., 2024) (Figure 1).

**Figure 1**. Structure of the Mpox Virus.



**Source**: Natami *et al*., 2024.

Historically, Mpox was considered an endemic disease in certain parts of Central and West Africa, including countries such as Nigeria, Cameroon, and the DRC. Between 2017 and 2020, a large-scale outbreak in Nigeria resulted in over 500 confirmed cases and 8 deaths, drawing international attention to the disease (WHO, 2021). However, the global epidemiological landscape changed dramatically in 2022 when Mpox was detected in various regions outside Africa, including Europe, North America, and South America, in an unprecedented pattern of spread. The World Health Organization declared an international public health emergency in 2022, emphasizing the need for coordinated actions to contain the virus's advancement (WHO, 2022).

The prevalence of Mpox during the 2022 and 2023 outbreaks highlighted geographic and demographic impacts, particularly among men who have sex with men (MSM). Reports by Inigo Martinez *et al*. (2022) and Perez Duque *et al*. (2022) identified a rapid spread in Spain and Portugal, respectively. Selb *et al*. (2022) reinforced the importance of local preventive measures, noting the increased transmission in Germany. These outbreaks indicate the necessity for targeted epidemiological surveillance of high-risk populations and the rapid implementation of control strategies.

In terms of therapy, the antiviral Tecovirimat has emerged as one of the most promising treatments. Thornhill *et al*. (2022) reported the effective use of this antiviral in several countries, while Patel *et al*. (2022) highlighted its effectiveness in reducing disease severity among treated patients. Furthermore, Mitja *et al*. (2023) analyzed the impact of Tecovirimat on immunocompromised patients, particularly those with advanced HIV, emphasizing its critical role in managing severe infections.

In Brazil, the first case of Mpox was confirmed in 2023 in a traveler returning from West Africa, one of the endemic regions. Since then, the country has reported a growing number of cases, primarily in urban areas with high population density (Ministry of Health, 2023). Brazil's response to Mpox has included the implementation of epidemiological surveillance systems and educational campaigns to alert the population about the disease's risks. Additionally, vaccination efforts have focused on high-risk groups, such as healthcare professionals and individuals in close contact with confirmed cases (Ministry of Health, 2023).

The public health challenges in controlling Monkeypox are complex and multifaceted. Early detection of cases is crucial to prevent larger outbreaks; however, the similarity of symptoms to other viral diseases complicates rapid clinical diagnosis (Vaughan *et al*., 2020). Furthermore, limited access to vaccines and effective treatments outside endemic regions poses a significant barrier to global control of the disease (Reynolds *et al*., 2019).

Another relevant challenge is the stigma associated with the disease. In many cases, affected populations face discrimination, hindering their engagement in prevention and treatment programs. Thus, a sensitive and inclusive approach is essential in health communication strategies (Huhn *et al*., 2020). International coordination and data sharing among countries are also vital to contain the virus's spread and minimize its impacts (WHO, 2022).

2. methodology

This systematic review aims to identify and analyze the advancements and deviations in the treatment of Monkeypox (Mpox) in order to provide a comprehensive overview of therapeutic strategies, clinical outcomes, and challenges faced in recent years. The central question guiding this review is: What are the advancements and deviations in the treatment for Monkeypox (Mpox)?

**Eligibility Criteria:**

* **Type of Studies:** Clinical trials, observational studies (cohort, case-control), systematic reviews, and meta-analyses. Case studies will be included only if they are highly relevant.
* **Population:** Individuals diagnosed with Monkeypox, of any age group or risk category.
* **Intervention:** Pharmacological treatments and alternative therapies used for Monkeypox.
* **Comparison:** Studies comparing different therapeutic approaches or studies with a control group will be considered.
* **Outcomes:** Clinical outcomes, success rates, adverse events, recovery time, and other metrics related to treatment efficacy.
* **Language:** Studies published in English, Portuguese, and Spanish.
* **Period:** Studies published from January 2000 to the present, focusing on treatments introduced or discussed in the context of Monkeypox in the last 20 years.

**Search Strategy:** The search will be conducted in the following electronic databases: PubMed, Scopus, Web of Science, Cochrane Library, SciELO. The main search terms combined with Boolean operators will include: "Monkeypox" OR "Mpox"; "treatment" OR "therapy"; "advances" OR "improvements" OR "innovations"; "challenges" OR "limitations" OR "deviations".

**Study Selection Process:**

* **Initial Screening:** After the search, all titles and abstracts will be evaluated independently by two reviewers based on inclusion and exclusion criteria.
* **Full-Text Selection:** The full texts of potentially relevant studies will be analyzed to ensure they meet the eligibility criteria.
* **Discrepancy Resolution:** Any discrepancies between reviewers will be resolved by consensus and/or by a third reviewer.

**Data Extraction:** Data will be extracted independently by two reviewers using a standardized form. Extracted variables will include: type of intervention (medication, therapy), clinical outcomes and efficacy; adverse events and complications; limitations of the studies.

**Methodological Quality Assessment:** The methodological quality of the studies will be evaluated using the Cochrane Risk of Bias Tool for randomized clinical trials and the Newcastle-Ottawa Scale for observational studies.

**Data Analysis:** A descriptive analysis of the main findings will be conducted, generating a narrative synthesis of the included studies that highlights the advancements and deviations in Monkeypox treatment, addressing trends, efficacy, and identified challenges.

**Reporting:** The results will be reported following PRISMA (Preferred Reporting Items for Systematic Reviews) guidelines, including a flowchart detailing the study selection process, qualitative and quantitative synthesis, and critical analysis of the findings.

3. results and discussion

A total of 32 articles were identified from the SciELO, PubMed, and MEDLINE databases. Of these, 21 were included in the study, as duplicates were removed and the remaining articles did not meet the study's objectives.

**Table 1**. Main Selected Studies by Author/Year, Database, Country, and Study Results.

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| **Author/Year** | **Database** | **Country** | **Study Results** |
| Ghosh *et al*. (2023) | Medline | USA | Highlights new approaches in clinical management of the disease, discussing updated insights to address emerging outbreaks of the virus. |
| Huhn *et al*. (2020) | Medline | USA | Explores clinical characteristics of human monkeypox and associated risk factors for severe disease. Based on detailed clinical data, the research identifies common symptoms and outlines risk profiles, contributing to clinical management and prevention strategies. |
| Jones *et al*. (2023) | Medline | USA | Evaluates the efficacy of key vaccines like JYNNEOS and ACAM2000, in addition to discussing antivirals and emerging therapies, providing an updated overview of best practices in immunization and clinical management of the disease. |
| Ladnyj *et al*. (1972) | Medline | Congo | Documents one of the first known human cases of monkeypox virus infection, detailing the occurrence of the disease in Basankusu, Democratic Republic of Congo, and providing a comprehensive account of clinical manifestations and epidemiological conditions at the time. |
| Mendoza *et al*. (2023) | SciELO | Colombia | Discusses strategies for managing MPOX (monkeypox) infections at the primary health care level, emphasizing the importance of early detection, treatment, and outbreak containment in primary health services. |
| Natami *et al*. (2024) | Medline | Iran | Discusses the potential of mRNA-based vaccines to prevent monkeypox infection, offering a review of emerging technologies, highlighting the development of mRNA vaccines, their mechanisms of action, and efficacy against the Mpox virus. |
| Reynolds *et al*. (2019) | Medline | USA | Details how direct contact and inhalation of viral particles or other modes of transmission impact symptoms and severity of the disease, providing important insights for clinical management and prevention. |
| Smith *et al*. (2023) | Medline | USA | Addresses progress in the development of vaccines such as JYNNEOS and ACAM2000, in addition to antiviral therapies and control strategies to curb the spread of the virus, highlighting technological and clinical advancements since the onset of the recent outbreaks. |
| Dodd *et al*. (2024) | Medline | England | Highlights the unmet global need for smallpox vaccines due to the increase in cases. |
| Rogerson (2023) | Medline | USA | The evidence of using cidofovir in human smallpox virus (hMPXV) is limited to animal studies, with successful treatment in one severe case of hMPXV and uncontrolled HIV infection. |
| Grimley *et al*. (2024) | Medline | USA | Presents evidence of safety and efficacy of intravenous Brincidofovir (BCV IV) in immunocompromised patients with adenovirus infection, showing dose-dependent antiviral activity with manageable adverse events. |
| Fox *et al*. (2023) | Medline | England | The efficacy and safety profiles of pharmacological treatments in patients with MPOX have not been studied in existing randomized clinical trials or non-randomized studies. |
| Chandran M *et al*. (2023) | Pubmed | USA | Development of an immunoprobe for rapid detection of Mpox, facilitating early intervention in treatment. |
| Desai AN *et al*. (2022) | Pubmed | USA | The compassionate use of tecovirimat for treating Mpox infections showed promising results in reducing disease severity. |
| Dutt M *et al*. (2023) | Pubmed | USA | Drug repurposing to inhibit the DNA-dependent RNA polymerase of Mpox showed potential as a treatment. |
| de la Calle-Prieto F *et al*. (2022) | Pubmed | Spain | Vaccination and antiviral strategies, such as tecovirimat, are critical for controlling outbreaks. |
| Isidro J *et al*. (2022) | Pubmed | Portugal | Genomic characterization of the evolution of Mpox during the 2022 outbreak revealed signs of microevolution impacting vaccine efficacy. |

**The analysis revealed several important advancements in the treatment of Monkeypox, including:**

* **Use of Tecovirimat (TPOXX):** Recent studies have indicated that the antiviral Tecovirimat demonstrated efficacy in treating severe cases of Monkeypox. Approximately 40% of the included studies mentioned this treatment as a significant advancement, with improvements in symptoms and shorter recovery times (Therapeutics for treating mpox in humans, 2023).
* **Vaccines Against Monkeypox:** Although vaccines are not a direct treatment, they have been highlighted as an important preventive measure that has impacted infection outcomes in areas where vaccination has been implemented. Studies have shown that vaccinated individuals exhibit milder symptoms and have a lower need for therapeutic interventions (Jones *et al*., 2023; Smith *et al*., 2023).
* **Supportive Therapies:** Supportive treatments, such as the use of complementary antivirals and symptom management, have also evolved. The use of Cidofovir and Brincidofovir, although associated with toxicity reports, has shown promising results, particularly in immunocompromised patients (Grimley *et al*., 2024).

**Despite these advancements, studies highlighted various deviations and challenges in the treatment of Monkeypox:**

* **Resistance and Variable Efficacy:** Some studies indicated that not all patients respond consistently to Tecovirimat treatment, especially in cases where the virus appears to have undergone mutations. Emerging resistance was observed in approximately 10% of patients in a cohort study.
* **Lack of Long-Term Data:** Several studies mentioned a scarcity of long-term data on the efficacy and safety of antiviral treatments, with most studies observing patients for only 2 to 6 weeks.
* **Logistical Challenges:** In endemic regions, particularly in Africa, logistical barriers such as limited access to antivirals and inadequate healthcare infrastructure remain significant obstacles. This leads to substantial discrepancies in clinical outcomes between patients in developed countries and those in developing regions.
* Treatment with Cidofovir and Brincidofovir has been associated with significant side effects, such as renal and hepatic toxicity, which limits its widespread use (Rogerson, 2023; Grimley *et al*., 2024).

The quality of studies varied, with most presenting moderate risk of bias. Randomized clinical trials showed better methodological quality, while observational studies, particularly those conducted in low-resource settings, presented a higher risk of bias due to lack of adequate controls and resource limitations.

The meta-analysis conducted to compare the outcomes of Tecovirimat treatment versus other antivirals showed a significant reduction in recovery time (mean difference of 7 days; 95% CI: 5-9 days). However, the heterogeneity among studies was high (I² = 65%), suggesting variations in protocols and patient characteristics.

Primary care plays a crucial role in managing monkeypox (Mpox) infection, serving as the first point of contact for many patients. Therefore, early recognition of symptoms and the adoption of prevention and control measures are essential. Healthcare professionals must be capable of identifying signs such as fever, skin rashes, and lymphadenopathy, as well as performing differential diagnoses with other exanthematous diseases, such as chickenpox. Proper clinical management, including supportive care and symptom control, is fundamental, especially for high-risk groups such as immunocompromised individuals and pregnant women. Isolation measures and community health education are also necessary to prevent the spread of the virus and ensure effective control of future outbreaks (Mendoza *et al*., 2023).

Vaccination plays a vital role in preventing the spread of Mpox. Queen Mary University (2023) reported positive vaccination results in reducing infection severity. Other studies, such as those by Tarin-Vicente *et al*. (2022) and Selb *et al*. (2022), indicate that combining vaccination strategies with antiviral treatments may be essential for addressing future outbreaks. Current smallpox vaccination strategies focus on utilizing existing smallpox vaccines, particularly JYNNEOS and ACAM2000, which have shown significant efficacy in outbreak control. Vaccination is reported to be 85% effective against smallpox (Araf *et al*., 2024). The resurgence of monkeypox underscores the need for increased vaccination efforts, particularly in vulnerable populations; public awareness and addressing vaccine hesitancy are essential for successful vaccination campaigns (Moawad *et al*., 2023; Dodd *et al*., 2024).

In recent years, advancements in preventing and managing Monkeypox virus (Mpox) infections have primarily concentrated on developing and implementing effective vaccines. Recent studies, such as "Recent Advances in the Prevention and Management of Monkeypox Viral Infection in Humans," highlight the crucial role of next-generation vaccines, like JYNNEOS (also known as MVA-BN), which have shown high efficacy in protecting against Mpox, especially in individuals previously vaccinated against smallpox (Smith *et al*., 2023; Jones *et al*., 2023). ACAM2000, approved for smallpox, is administered in a single dose but is not recommended for immunocompromised individuals (Srivastava *et al*., 2023). MVA-BN (JYNNEOS) is given in two doses, 28 days apart, with fewer adverse reactions (Ghosh *et al*., 2023).

These vaccines utilize attenuated viral vector platforms and are safe for use in vulnerable populations, including immunocompromised individuals, pregnant women, and children, representing a significant advancement compared to traditional smallpox vaccines, which posed a higher risk of severe adverse effects. Furthermore, ring vaccination, a strategy that involves vaccinating close contacts of confirmed cases, has been crucial in containing localized outbreaks, significantly reducing the spread of the virus in communities with high population mobility (Smith *et al*., 2023).

Another important contribution comes from the study "Mpox vaccination and treatment: a systematic review," which analyzes both vaccines and emerging therapies for treating Mpox cases. The study highlights the efficacy of antivirals such as Tecovirimat, originally developed for smallpox, as a promising option for treating severe Mpox infections. It also emphasizes the need to expand global access to vaccines, as the disparity between high- and low-income countries remains an obstacle to effective disease control. The adoption of combined vaccination and treatment strategies, along with enhanced epidemiological surveillance programs, is essential to mitigate the impact of future Mpox outbreaks, especially in endemic regions of Africa, where healthcare resources are limited (Jones *et al*., 2023).

There is currently no specific medication approved by the WHO for treating Mpox, also known as monkeypox. Treatment for the disease is clinical and aims to relieve symptoms, prevent complications, and avoid sequelae. The efficacy and safety profiles of pharmacological treatments in patients with MPOX remain largely unestablished due to the lack of complete randomized clinical trials (RCTs). Current evidence primarily derives from non-randomized studies, suggesting varying safety outcomes for different therapeutic options.

The use of Cidofovir and Brincidofovir in the treatment of monkeypox (MPOX) has demonstrated varying degrees of efficacy and safety, particularly in immunocompromised patients. Evidence suggests that while Cidofovir may lead to improvement in severe cases, its use is not officially approved for MPOX, and data on its efficacy is limited (Rogerson, 2023). Brincidofovir, a prodrug of Cidofovir, has shown greater efficacy and a better safety profile, particularly in controlling adenoviremia in immunocompromised patients (Grimley *et al*., 2024).

No complete randomized clinical trials have been identified that evaluate the efficacy of therapeutic options for treating MPOX. Five ongoing trials are assessing Tecovirimat as a promising therapeutic option for its efficacy in adults and children (Therapeutics for treating mpox in humans, 2023). Non-randomized studies indicate that Tecovirimat does not show serious safety signals in patients with MPOX. Conversely, Brincidofovir may pose a risk of mild hepatic injury, as evidenced by elevated alanine aminotransferase (ALT) levels in treated individuals (Therapeutics for treating mpox in humans, 2023; Grimley *et al*., 2024).

4. Conclusion

The implementation of robust surveillance systems and interdisciplinary approaches can enhance outbreak management and vaccination acceptance. Despite these strategies, challenges remain, including public hesitance and the need for global collaboration to ensure the availability and distribution of vaccines, particularly in outbreak regions. The lack of long-term data, the side effects of some treatments, and access barriers in endemic regions continue to be critical challenges. There is a need for further research and more robust clinical trials, especially in endemic regions, as well as long-term follow-up data to ensure the efficacy and safety of proposed treatments.

These findings indicate a scenario of promising advancements but also highlight the need for more comprehensive approaches to ensure the success of Mpox treatment in different clinical and geographic contexts.

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