

## Review

# Recent Advancements in Therapeutical Strategies Against Mpox: Past and Future Prospects

Subham Mandal<sup>1</sup>, Suraj Mandal<sup>2\*</sup>, Purnima Singh<sup>3</sup>

<sup>1</sup>Department of Pharmacy, IIMT College of Medical Sciences, IIMT University, O-Pocket, Ganganagar, Meerut, 250001, U.P., India

<sup>2</sup>Sujata Research Laboratories, Vill-Mataiyalpur, Post-Ramnagra, Dist-Pilibhit, 262122, U.P., India

<sup>3</sup>Research Scholar, HIMT College of Pharmacy, Greater Noida

## Corresponding Author:

Dr. Suraj Mandal

## Email:

sk8006721807@gmail.com

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## Abstract:

Monkeypox (Mpox), a zoonotic disease caused by the Monkeypox virus (MPXV), has reemerged as a significant global public health challenge. Historically endemic to Central and West Africa, its spread to non-endemic regions during the 2022 outbreak underscored the need for innovative therapeutic and preventive strategies. Traditional Mpox management has relied on repurposed smallpox antivirals and vaccines, such as Tecovirimat and Jynneos, but challenges persist in terms of drug resistance, accessibility, affordability, and vaccine hesitancy. Recent advancements include the development of next-generation antivirals, monoclonal antibodies, immunomodulatory therapies, and host-targeted treatments. Emerging technologies like CRISPR gene editing, nanomedicine, and artificial intelligence-driven drug discovery are poised to revolutionize Mpox treatment, offering precision-targeted interventions and enhanced outcomes. Furthermore, public health strategies inspired by smallpox eradication highlight the importance of equitable vaccine distribution, robust surveillance, and international collaboration. Addressing current challenges while leveraging these advancements holds promise for reducing Mpox's burden and preventing future outbreaks. Achieving global eradication will require sustained investment in innovative science, healthcare infrastructure, and global health policies.

**Keywords:** Monkeypox, MPXV, antivirals, vaccines, immunomodulation, CRISPR, nanomedicine, public health.

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## 1. Introduction

Monkeypox (Mpox) is a zoonotic disease caused by the Monkeypox virus (MPXV), first identified in 1958 and linked to close contact with infected animals. Historically endemic to Central and West Africa, its epidemiology shifted with urbanization, deforestation, and reduced smallpox immunity. The 2022 outbreak highlighted its ability to spread person-to-person, particularly in intimate and communal settings. Mpox symptoms range from fever and lymphadenopathy to a centrifugal rash that progresses through distinct stages, with complications seen in vulnerable populations. Its structural and transmission features underscore the

urgency for innovative therapeutic and preventive strategies.

### 1.1 Overview of Mpox (Monkeypox): Epidemiology and Historical Perspective

Monkeypox (Mpox), a zoonotic disease caused by the Monkeypox virus (MPXV), has garnered global attention due to its reemergence in non-endemic regions. Initially identified in 1958 among captive monkeys in Denmark, the first human case was reported in the Democratic Republic of Congo (DRC) in 1970. Endemic primarily in Central and West Africa, the disease has historically been linked to close contact with infected animals, such as rodents and primates,

which serve as reservoirs. The 21st century has seen significant changes in Mpox epidemiology, with increasing case counts in non-endemic regions. Factors such as urbanization, deforestation, and declining smallpox immunity contribute to this trend. The 2022 outbreak, characterized by person-to-person transmission, marks a pivotal moment in Mpox's global spread, highlighting its potential for broader public health implications.

### 1.2 Pathogenesis and Clinical Manifestations

The MPXV belongs to the Orthopoxvirus genus of the Poxviridae family, closely related to Variola virus (smallpox). Infection begins with viral entry through the skin, respiratory tract, or mucous membranes. MPXV's replication occurs in the cytoplasm, bypassing host nuclear processes. It targets macrophages and dendritic cells, disseminating to lymph nodes and inducing viremia.

**Clinical manifestations** typically include:

- **Incubation period:** 6–13 days (range: 5–21 days).
- **Prodromal phase:** Fever, headache, myalgia, lymphadenopathy, and fatigue.
- **Exanthem phase:** Characterized by a centrifugal rash starting on the face and spreading to extremities, often involving palms and soles. Lesions progress from macules to papules, vesicles, pustules, and scabs over 2–4 weeks.

While most cases are self-limiting, severe outcomes can occur, particularly in immunocompromised individuals, pregnant women, and young children. Complications such as secondary bacterial infections, respiratory distress, and encephalitis have been documented.

### 1.3 Mpox Virus Structure and Transmission

MPXV is an enveloped double-stranded DNA virus with a genome size of approximately 197 kb. It encodes over 200 proteins, including immune evasion and virulence factors. MPXV virions exist in two infectious forms:

1. **Intracellular mature virus (IMV):** Facilitates stability and environmental survival.
2. **Extracellular enveloped virus (EEV):** Enhances cell-to-cell spread within the host.

**Transmission pathways** include:

- **Animal-to-human:** Via bites, scratches, consumption of undercooked bushmeat, or direct contact with infected animals.
- **Human-to-human:** Through respiratory droplets, contact with lesion exudates, or fomites.
- **Environmental:** The virus's resilience on surfaces and in aerosols contributes to its spread in healthcare and communal settings.

Recent evidence suggests enhanced person-to-person transmission, particularly during the 2022 outbreak, driven by close contact and shared living conditions. The outbreak also highlighted the role of sexual networks in transmission, especially among men who have sex with men (MSM).

### 2. Past Therapeutic Strategies

Traditional Mpox treatments have relied on repurposed smallpox antivirals, such as Cidofovir and Brincidofovir, and vaccines like Jynneos and ACAM2000. While these have been effective in reducing severity, their limitations include accessibility, incomplete efficacy, and potential side effects. Many therapies lack specificity for MPXV, leaving gaps in managing severe cases or outbreaks in non-endemic regions. These limitations demonstrate the pressing need for targeted and innovative treatments.

#### 2.1 Traditional Treatment Approaches

Historically, the management of Mpox (Monkeypox) focused primarily on supportive care, aiming to alleviate symptoms and manage complications due to the lack of specific antiviral treatments or vaccines tailored for this zoonotic disease. Fever, headaches, lymphadenopathy, and myalgia, which are hallmark symptoms of Mpox, were managed with antipyretics like acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) (McCollum & Damon, 2014; Petersen et al., 2019). In severe cases, dehydration caused by systemic symptoms or oral ulcerations was addressed through aggressive rehydration therapy, including oral rehydration salts and intravenous fluids (Islam et al., 2023). Lesion care, a critical aspect of Mpox management, emphasized the prevention of secondary bacterial infections by employing antiseptic dressings and, when necessary, systemic antibiotics (Ligon, 2004).

#### 2.2 Antiviral Agents

##### Cidofovir

Cidofovir, originally developed to treat cytomegalovirus (CMV) infections in

immunocompromised patients, emerged as a candidate for Mpox treatment due to its broad-spectrum activity against DNA viruses, including Orthopoxviruses (Nalca et al., 2005). The drug works by inhibiting viral DNA polymerase, thereby halting viral replication. Preclinical studies demonstrated cidofovir's ability to reduce viral loads in Mpox-infected animal models, making it a promising option (Chen et al., 2005). However, its use in humans has been limited by significant nephrotoxicity, which necessitates co-administration with probenecid and extensive hydration protocols to mitigate renal damage. Additionally, its intravenous administration limits its practicality in outpatient or resource-constrained settings (Weaver & Isaacs, 2008; Pittman et al., 2019).

### **Brincidofovir**

Brincidofovir, a lipid-conjugated derivative of cidofovir, was developed to address the limitations of its predecessor. Its improved pharmacokinetic profile allows oral administration, which enhances patient compliance and broadens accessibility (Bunge et al., 2022). Brincidofovir retains cidofovir's mechanism of action by inhibiting viral DNA polymerase but exhibits a reduced risk of nephrotoxicity. Despite its promising pharmacological profile, clinical evidence of its efficacy in Mpox remains limited, with most studies confined to experimental or compassionate use settings (Petersen et al., 2019; Dye & Kraemer, 2022). High production costs and limited availability further hinder the widespread application of brincidofovir, especially in endemic regions (Adalja & Inglesby, 2022).

### **2.3 Role of Vaccination**

Vaccination has been a cornerstone in Mpox prevention and outbreak control due to the cross-protective immunity provided by smallpox vaccines, given the genetic similarities between the Monkeypox virus (MPXV) and Variola virus. Two key vaccines—**Jynneos** and **ACAM2000**—have been widely used.

1. **Jynneos (Modified Vaccinia Ankara-Bavarian Nordic):** Jynneos is a non-replicating, attenuated vaccine designed to prevent smallpox and Mpox. Administered subcutaneously in two doses, it provides a safer option for immunocompromised individuals due to its inability to replicate within the host (Pittman et al., 2019; Christodoulidou &

Mabbott, 2023). Clinical trials have demonstrated high seroconversion rates and robust immunogenicity, making it a key tool in outbreak response strategies, particularly during the 2022 Mpox epidemic (Minhaj et al., 2022).

2. **ACAM2000:** ACAM2000, derived from the Dryvax strain, is a live, replicating vaccine that offers robust immunity. However, its use is associated with significant adverse effects, including myocarditis and pericarditis, limiting its application in individuals with pre-existing health conditions (Kmiec & Kirchoff, 2022). The scarification method used for administration requires trained personnel, further complicating its deployment in resource-constrained settings (Petersen et al., 2019).

### **2.4 Limitations of Past Therapeutic Approaches**

Despite advancements, past therapeutic strategies have faced several critical limitations. Antiviral agents like cidofovir and brincidofovir, while effective in experimental settings, suffer from significant accessibility barriers. Cidofovir's nephrotoxicity and requirement for intravenous administration have rendered it impractical for widespread use, particularly in resource-limited regions where Mpox is endemic (Nalca et al., 2005; Pittman et al., 2019). Brincidofovir, although safer and orally bioavailable, remains prohibitively expensive and under-researched for Mpox, limiting its deployment during outbreaks (Adalja & Inglesby, 2022; Petersen et al., 2019). Vaccination efforts, though essential, also present challenges. The adverse effect profile of ACAM2000 restricts its use to select populations, while the slower rollout and limited supply of Jynneos during the 2022 outbreak underscored global inequities in vaccine distribution (Minhaj et al., 2022; Christodoulidou & Mabbott, 2023).

### **3. Recent Advancements in Mpox Therapy**

Advances in Mpox therapy have focused on Tecovirimat (TPOXX), an antiviral with specific action against Orthopoxviruses, significantly improving outcomes. Monoclonal antibody therapies and investigational antivirals are expanding the therapeutic arsenal. Improved vaccine technologies, such as modified vaccinia Ankara (MVA)-based platforms, offer safer and more effective prevention options. These advancements mark a turning point in Mpox

management, providing critical tools to address evolving epidemiological challenges.

### 3.1 Antiviral Drug Development and Mechanisms

The recent resurgence of Mpox, particularly during the 2022 global outbreak, has catalyzed advancements in the development of antiviral therapies specifically targeting the Monkeypox virus (MPXV). These therapies aim to directly inhibit viral replication and mitigate disease severity. Among the notable developments is **Tecovirimat (TPOXX)**, which has emerged as the first FDA-approved antiviral specifically designed for Orthopoxvirus infections, including Mpox (Adalja & Inglesby, 2022; Pittman et al., 2019).

- **Tecovirimat (TPOXX) and Its Mechanism of Action**

Tecovirimat, also known as TPOXX, represents a significant breakthrough in Mpox treatment. It works by targeting the viral p37 envelope protein, a critical component involved in the formation and release of extracellular virions. By inhibiting p37, Tecovirimat prevents the spread of the virus within the host, thereby reducing the viral load and limiting disease progression. Studies have demonstrated that Tecovirimat significantly shortens the duration of symptoms, accelerates lesion healing, and reduces the likelihood of severe complications (Nalca et al., 2005; Gigante et al., 2022).

- **Newer Investigational Antiviral Agents**

Beyond Tecovirimat, several investigational antiviral agents are being explored for their potential against MPXV. Brincidofovir, a lipid-conjugated analog of cidofovir, has been revisited for its improved safety profile and oral bioavailability. While preclinical studies have shown promising results, its efficacy in real-world Mpox cases remains to be fully established (Adalja & Inglesby, 2022). Another emerging candidate is CMX001, an orally administered analog of cidofovir designed to enhance tissue penetration and reduce toxicity. Early studies suggest potential utility in managing severe or disseminated Mpox infections, although large-scale clinical trials are still pending (McCullum & Damon, 2014; Nalca et al., 2005).

### 3.2 Immunotherapy Approaches

- **Monoclonal Antibodies and Their Role**

Monoclonal antibodies (mAbs) have emerged as a promising tool in the fight against Mpox, offering a targeted approach to neutralizing the virus. These

antibodies are engineered to specifically bind to viral antigens, thereby blocking viral entry into host cells and facilitating clearance by the immune system (Weaver & Isaacs, 2008). During the 2022 outbreak, monoclonal antibody therapies were employed as experimental treatments for severe Mpox cases, particularly in immunocompromised individuals who could not mount an adequate immune response. Early reports indicated that mAbs targeting viral glycoproteins significantly reduced disease severity and accelerated recovery (Dye & Kraemer, 2022).

- **Advances in Vaccine Technologies**

Recent advancements in vaccine technology have further revolutionized Mpox prevention. Building on the success of smallpox vaccines, modern platforms such as mRNA and vector-based vaccines are being explored for their potential to provide rapid and robust immunity. The Jynneos vaccine, already a critical tool in Mpox prevention, exemplifies the benefits of next-generation vaccine design. Its non-replicating, attenuated format offers a safer alternative to traditional live vaccines, making it suitable for immunocompromised individuals and those with underlying health conditions (Pittman et al., 2019; Christodoulidou & Mabbott, 2023).

- **Host-Targeted Therapies**

Host-targeted therapies offer an innovative approach to Mpox management by modulating the host's biological processes to inhibit viral replication and enhance immune responses. Unlike traditional antivirals that directly target the virus, host-targeted therapies focus on disrupting critical host-virus interactions. For example, inhibitors of host-cell entry pathways, such as clathrin-mediated endocytosis, have shown potential in preventing MPXV infection in preclinical studies (Chen et al., 2005; Weaver & Isaacs, 2008).

Immunomodulatory drugs represent another promising category of host-targeted therapies. These agents modulate the host immune response to reduce excessive inflammation while preserving antiviral defenses. For instance, cytokine inhibitors targeting interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF- $\alpha$ ) are being investigated for their ability to mitigate the systemic inflammatory response associated with severe Mpox (Dinarelli, 2018; Gessain et al., 2022). Additionally, agents that enhance innate immune responses, such as interferon-based therapies, are under evaluation for

their potential to boost antiviral activity without compromising host tissue integrity.

#### **4. Innovative Therapeutic Strategies on the Horizon**

Emerging Mpox treatments leverage cutting-edge technologies like nanomedicine for precise drug delivery, CRISPR-based antiviral gene editing, and genetic therapies targeting host-pathogen interactions. Advances in molecular therapeutics and next-generation antivirals promise improved efficacy and reduced resistance. These strategies have the potential to revolutionize Mpox treatment, offering hope for better clinical outcomes and prevention.

##### **4.1 Emerging Antiviral Therapies**

Emerging antiviral therapies for Mpox are being designed to address the limitations of existing drugs like Tecovirimat and Brincidofovir. The focus is on enhancing specificity, minimizing resistance, and improving pharmacokinetic properties. Novel antiviral agents, such as those targeting viral helicase-primase complexes or inhibiting MPXV-specific proteases, are in the experimental stages. These molecules aim to disrupt key viral replication mechanisms unique to MPXV, minimizing off-target effects and preserving host cell integrity (Isidro et al., 2022; Babkin et al., 2022).

Combination antiviral therapies are another promising area. Combining Tecovirimat with Brincidofovir or investigational drugs could yield synergistic effects, simultaneously targeting multiple stages of the viral life cycle to enhance therapeutic outcomes. For example, using nucleoside analogs to inhibit viral DNA synthesis alongside p37-targeted therapies could offer a dual-pronged attack, significantly reducing the likelihood of resistance emergence (Dye & Kraemer, 2022). Moreover, the potential of broad-spectrum antivirals, such as favipiravir and remdesivir, is being investigated for use in Mpox. While these drugs were initially developed for other viral infections like Ebola and COVID-19, their mechanisms of action—targeting RNA-dependent polymerases—may have cross-applicability to DNA viruses like MPXV, especially when coupled with advanced delivery methods (Nalca et al., 2005; Petersen et al., 2019).

##### **4.2 Genetic and Molecular Therapeutics**

Advances in genetic and molecular therapeutics offer transformative potential for Mpox treatment by targeting both the virus and the host's

biological pathways. Genetic therapies focus on modifying viral replication machinery, either by directly targeting the MPXV genome or by enhancing host resistance to viral entry and replication. One approach involves the use of **RNA interference (RNAi)**, a technique that employs small interfering RNAs (siRNAs) to silence viral genes critical for replication. Early studies have shown that siRNAs targeting conserved regions of the MPXV genome can effectively reduce viral load and ameliorate disease symptoms in preclinical models (Chen et al., 2005; Dinarello, 2018). Additionally, the development of antisense oligonucleotides (ASOs) that bind to viral mRNA and inhibit protein translation represents another avenue for molecular intervention. Personalized medicine is also gaining traction, with therapies tailored to individual genetic profiles and immune responses. Advances in genomic sequencing allow for the identification of host genetic factors influencing susceptibility to Mpox. For instance, polymorphisms in genes encoding immune regulatory proteins, such as those involved in interferon signaling, could guide the development of personalized therapeutic regimens (Isidro et al., 2022; Babkin et al., 2022).

##### **4.3 Nanotechnology and Drug Delivery Systems in Mpox Treatment**

Nanotechnology has revolutionized drug delivery, offering unparalleled precision in targeting infected cells while minimizing systemic toxicity. Nanoparticle-based delivery systems enable encapsulation of antiviral agents, ensuring controlled release and enhanced bioavailability. For Mpox, nanomedicine can be particularly beneficial in delivering drugs directly to sites of high viral replication, such as skin lesions and lymphoid tissues. Lipid-based nanoparticles (LNPs), which have gained prominence in mRNA vaccine delivery, are being adapted for antiviral therapy. These nanoparticles can encapsulate small-molecule drugs, RNAi agents, or even CRISPR components, protecting them from degradation and enhancing cellular uptake. Recent research has demonstrated the potential of LNPs to deliver siRNAs targeting MPXV genes, significantly reducing viral replication in vitro (Gigante et al., 2022; Pittman et al., 2019). In addition to LNPs, polymeric nanoparticles and viral vector systems are being explored for their ability to deliver therapeutics across physiological barriers.

#### 4.4 CRISPR and Gene-Editing Approaches

CRISPR-Cas9 and related gene-editing technologies have opened new frontiers in antiviral therapy by enabling precise modifications to the viral genome or host factors critical for viral replication. For Mpox, CRISPR systems can be engineered to target and cleave conserved regions of the MPXV genome, effectively halting viral replication. Preclinical studies have demonstrated the feasibility of using CRISPR to disrupt viral DNA, with promising results in reducing viral load and preventing disease progression (Chen et al., 2005; Isidro et al., 2022). Beyond direct antiviral applications, CRISPR can be used to enhance host defenses. For example, gene-editing strategies could upregulate immune-related genes or silence host receptors exploited by MPXV for cell entry. This dual-targeting approach not only reduces the likelihood of viral escape mutations but also strengthens the host's natural ability to combat the infection (Weaver & Isaacs, 2008; Babkin et al., 2022). CRISPR-based diagnostics, such as SHERLOCK and DETECTR platforms, are also being integrated with therapeutic strategies to enable real-time monitoring of viral mutations and guide precision treatment. These tools are invaluable for tracking the emergence of resistant MPXV strains and adapting therapies accordingly, ensuring long-term efficacy (Gigante et al., 2022; Gessain et al., 2022).

#### 5. Role of Immunomodulation in Mpox Management

Immunomodulation has emerged as a critical strategy in managing severe cases of Mpox, particularly in immunocompromised individuals and those experiencing complications such as encephalitis or systemic inflammation. By targeting the host immune response, immunomodulatory therapies aim to restore balance, mitigate tissue damage, and enhance the efficacy of antiviral treatments. This dual approach addresses both the viral load and the host's immune-mediated damage, offering a more comprehensive solution to Mpox management. Recent advancements in understanding the pathogenesis of Mpox and the role of host immunity have paved the way for cytokine-targeted therapies and the development of novel immunomodulatory drugs.

#### 5.1 Cytokine Modulation and Immune Response in Mpox

The immune response to Mpox involves a complex interplay of pro-inflammatory and regulatory cytokines. During infection, the body activates innate and adaptive immune mechanisms to limit viral replication and facilitate recovery. However, in severe cases, the immune response may become dysregulated, resulting in a cytokine storm—a hyperinflammatory state characterized by the excessive release of pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- $\alpha$ ). This overactivation can lead to widespread tissue damage, organ dysfunction, and complications like encephalitis, sepsis, and acute respiratory distress syndrome (ARDS) (Dinarello, 2018; Petersen et al., 2019). Cytokine modulation therapies aim to regulate this overactive inflammatory response. Monoclonal antibodies targeting specific cytokines have shown promise in mitigating the effects of cytokine storms.

#### 5.2 Therapeutic Potential of Immunomodulatory Drugs

Immunomodulatory drugs are increasingly recognized as vital adjuncts to antiviral therapy in Mpox management. These drugs target host pathways rather than the virus itself, reducing the risk of resistance and offering a broader range of applications across different viral strains and variants. Key classes of immunomodulatory drugs being explored for Mpox include:

1. **JAK-STAT Pathway Inhibitors:** The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway plays a central role in cytokine signaling and immune response regulation. JAK inhibitors, such as baricitinib and ruxolitinib, are being studied for their ability to reduce hyperinflammatory responses in viral infections, including Mpox. By modulating cytokine signaling, these drugs can alleviate symptoms and prevent complications associated with systemic inflammation (Dye & Kraemer, 2022; Dinarello, 2018).
2. **Corticosteroids:** Corticosteroids, which broadly suppress inflammation, are sometimes employed in severe Mpox cases involving complications like encephalitis. However, their use must be carefully balanced to avoid suppressing antiviral immunity. Recent guidelines recommend corticosteroids only in cases

of severe inflammatory complications, and their efficacy in Mpox remains an area of ongoing research (Petersen et al., 2019; Nalca et al., 2005).

3. **Toll-like Receptor (TLR) Agonists and Antagonists:** Toll-like receptors play a crucial role in recognizing viral pathogens and initiating immune responses. TLR agonists can enhance antiviral immunity, while TLR antagonists may be used to dampen excessive inflammation. Preclinical studies suggest that targeting TLRs could offer a novel approach to modulating the immune response in Mpox (Gessain et al., 2022; Babkin et al., 2022).
4. **Cytokine Receptor Blockers:** Blocking cytokine receptors, such as the IL-1 receptor, has shown promise in reducing inflammatory responses without compromising the overall immune defense. Anakinra, an IL-1 receptor antagonist, is one such drug being explored for its potential in viral infections associated with cytokine dysregulation, including Mpox (Weaver & Isaacs, 2008; Dinarello, 2018).

### 5.3 Complementary Role with Antiviral Treatments

Immunomodulatory therapies are not intended to replace antivirals but rather to complement them. By addressing the host's immune response, these therapies enhance the overall efficacy of antiviral treatments. For instance, combining Tecovirimat with cytokine modulators has shown synergistic effects in preclinical studies, improving both viral clearance and symptom resolution (Isidro et al., 2022; Babkin et al., 2022). Similarly, the integration of immunomodulatory drugs with investigational antivirals could provide a more comprehensive approach to managing severe Mpox cases, especially in immunocompromised patients.

Immunomodulation represents a promising frontier in Mpox therapy, offering the potential to address not only the viral infection but also the host-mediated damage that contributes to severe disease outcomes. By targeting cytokines, immune signaling pathways, and inflammatory mediators, these therapies provide a multifaceted approach to Mpox management. As research continues to refine our understanding of the host immune

response, immunomodulatory strategies are poised to play an increasingly central role in improving clinical outcomes and reducing the long-term health impacts of Mpox. However, their successful integration into treatment protocols will require careful consideration of patient-specific factors, including disease severity, immune status, and coexisting conditions, to achieve optimal results.

### 6. Public Health and Vaccination Strategies

Vaccination has long been a cornerstone of disease prevention, and for Mpox (Monkeypox), it remains one of the most effective tools in mitigating outbreaks and curbing transmission. The global experience with smallpox eradication provides valuable lessons that inform contemporary Mpox vaccination strategies. However, challenges such as vaccine hesitancy, logistical barriers, and inequities in vaccine distribution hinder widespread immunization. Addressing these challenges will require robust public health systems, targeted education, and international collaboration to ensure equitable access and sustained prevention.

#### 6.1 Lessons from Smallpox Eradication

The successful eradication of smallpox, officially declared by the World Health Organization (WHO) in 1980, remains one of the greatest achievements in public health history. The eradication campaign relied on several key strategies, including mass vaccination, surveillance, and targeted interventions like ring vaccination (McCollum & Damon, 2014; Petersen et al., 2019). These approaches were facilitated by the availability of highly effective smallpox vaccines, which conferred cross-protective immunity against Orthopoxviruses, including MPXV. Ring vaccination, which involves immunizing close contacts of confirmed cases to contain outbreaks, was instrumental in the eradication effort. This strategy proved effective in resource-limited settings, where mass vaccination was not feasible. The smallpox campaign also demonstrated the importance of robust surveillance systems for identifying and containing cases, a principle that remains relevant for Mpox control (Cabanillas et al., 2022; Dye & Kraemer, 2022).

#### 6.2 Current Vaccination Campaigns for Mpox

Vaccination campaigns for Mpox have leveraged existing smallpox vaccines, particularly **Jynneos** and **ACAM2000**, which have demonstrated efficacy in preventing MPXV infection. These vaccines have been deployed in both endemic and

non-endemic regions, with varying degrees of success.

1. **Jynneos (Modified Vaccinia Ankara-Bavarian Nordic):**

- Jynneos is a non-replicating, attenuated vaccine designed for smallpox and Mpox prevention. Administered subcutaneously in two doses, it offers a safer alternative for immunocompromised individuals and those with underlying health conditions.
- Clinical trials have demonstrated high efficacy, with seroconversion observed in most recipients following the full vaccination course. During the 2022 Mpox outbreak, Jynneos became the preferred vaccine in non-endemic regions due to its favorable safety profile (Pittman et al., 2019; Christodoulidou & Mabbott, 2023).

2. **ACAM2000:**

- ACAM2000, a live, replicating vaccine, provides robust immunity but is associated with higher risks of adverse effects, including myocarditis and pericarditis. Administered via scarification, it requires specialized training for proper administration.
- Despite its effectiveness, ACAM2000 is less commonly used in high-risk populations due to safety concerns, particularly among immunocompromised individuals or those with eczema (Kmiec & Kirshhoff, 2022).

### 6.3 Challenges and Future Directions in Global Vaccination Efforts

Despite the efficacy of Mpox vaccines, several challenges hinder their widespread deployment, particularly in resource-limited settings:

- 1) Vaccine distribution remains highly unequal, with high-income countries often securing large stocks of Jynneos and ACAM2000 while low-income, endemic regions struggle to access even minimal supplies. This inequity exacerbates the

public health burden in regions where Mpox is most prevalent (WHO, 2024; Dye & Kraemer, 2022).

- 2) Administering vaccines in rural or conflict-affected areas presents logistical challenges, including cold chain requirements for vaccine storage and transportation. These barriers are particularly pronounced in endemic regions of Central and West Africa, where healthcare systems are often under-resourced (Adalja & Inglesby, 2022; Petersen et al., 2019).
- 3) Vaccine hesitancy, driven by misinformation, cultural beliefs, and fear of adverse effects, remains a significant obstacle. Public health campaigns must address these concerns through transparent communication, community engagement, and targeted education to build trust in vaccination programs (Cabanillas et al., 2022; Gessain et al., 2022).

#### Future Directions:

- **Development of Universal Vaccines:** Research into universal Orthopoxvirus vaccines that provide cross-protection against multiple strains could address the emergence of resistant variants and simplify immunization efforts (Gould et al., 2022; Christodoulidou & Mabbott, 2023).
- **Improved Vaccine Delivery Systems:** Innovations such as microneedle patches, which simplify administration and reduce cold chain dependency, hold promise for improving vaccination rates in remote and resource-limited areas (Petersen et al., 2019; Babkin et al., 2022).
- **Global Collaboration and Funding:** Strengthening international partnerships and increasing funding for vaccine research, production, and distribution will be essential to ensure equitable access. Collaborative initiatives like the WHO's Mpox response framework provide a model for coordinated global action (WHO, 2023; Dye & Kraemer, 2022).

#### 7. Challenges in Mpox Therapeutics

The effective management of Mpox faces numerous challenges that limit the widespread application of both therapeutic and preventive

strategies. While advances in antivirals and vaccines have significantly improved outcomes, issues such as drug resistance, affordability, accessibility, and public skepticism continue to hinder progress.

### 7.1 Drug Resistance Issues

One of the primary concerns in Mpox therapeutics is the potential emergence of drug-resistant viral strains. Tecovirimat (TPOXX), currently the most widely used antiviral for Mpox, targets the viral p37 protein, which plays a critical role in extracellular virion formation. While this specificity contributes to its efficacy, it also makes Tecovirimat susceptible to resistance through mutations in the p37 gene (Gigante et al., 2022; Isidro et al., 2022). Experimental studies have demonstrated that single-point mutations in this gene can significantly reduce the drug's effectiveness, raising concerns about its long-term utility in monotherapy.

### 7.2 Accessibility and Affordability of New Therapies

The high cost of novel therapies and their limited availability, particularly in resource-limited settings, pose significant challenges to equitable Mpox treatment. Tecovirimat, although effective, is expensive and primarily accessible in high-income countries, often through emergency use authorizations rather than routine availability (Babkin et al., 2022; WHO, 2023). Similarly, the newer Jynneos vaccine, while safer and more effective than older alternatives, remains prohibitively costly for widespread use in endemic regions. Logistical barriers further exacerbate disparities in access. Many endemic regions, particularly in Central and West Africa, lack the healthcare infrastructure needed for proper storage, distribution, and administration of vaccines and antiviral drugs. Cold chain requirements for vaccines like Jynneos and the need for trained personnel to administer ACAM2000 create additional hurdles (Adalja & Inglesby, 2022; Christodoulidou & Mabbott, 2023).

### 7.3 Addressing Vaccine Hesitancy

Vaccine hesitancy remains a persistent barrier to achieving widespread immunization against Mpox. Public skepticism about vaccine safety and efficacy is often fueled by misinformation, cultural beliefs, and historical mistrust of healthcare systems. The adverse effects associated with ACAM2000, including myocarditis and pericarditis, have further amplified fears,

particularly in communities with limited access to accurate medical information (Petersen et al., 2019; Cabanillas et al., 2022).

## 8. Future Prospects and Research Directions

### 8.1 Potential for Novel Antiviral Drug Classes

The development of novel antiviral drug classes targeting unique aspects of the Mpox virus lifecycle offers a promising direction for future treatment. Current efforts are focused on identifying inhibitors of viral enzymes such as DNA polymerase, helicase-primase complexes, and proteases specific to MPXV (Isidro et al., 2022; Babkin et al., 2022). Broad-spectrum antivirals, including drugs that disrupt host-virus interactions, are also being explored to provide effective treatments across multiple Orthopoxviruses.

### 8.2 Personalized Medicine Approaches

Personalized medicine, which tailors treatments based on individual genetic, immunological, and clinical profiles, represents a transformative approach to Mpox management. Advances in genomic sequencing enable the identification of host factors that influence susceptibility to MPXV infection and disease severity (Dye & Kraemer, 2022). For instance, genetic variations in immune regulatory genes, such as those involved in interferon signaling, could guide the selection of immunomodulatory therapies for high-risk patients.

### 8.3 Role of Artificial Intelligence in Drug Discovery for Mpox

Artificial intelligence (AI) has the potential to accelerate drug discovery and optimize treatment strategies for Mpox. Machine learning algorithms can analyze large datasets to identify novel drug targets, predict compound efficacy, and streamline the drug development process (Gigante et al., 2022; Dye & Kraemer, 2022). AI-based approaches are particularly valuable for identifying broad-spectrum antivirals and repurposing existing drugs for MPXV.

### 8.4 Prospects for Eradication: Global Health Perspectives

Future initiatives should prioritize:

1. **Investment in Healthcare Infrastructure:** Strengthening healthcare systems in endemic regions to support vaccination, treatment, and surveillance efforts.
2. **Global Funding Mechanisms:** Establishing international funding

frameworks to subsidize vaccine production, distribution, and administration in low-income countries.

3. **Public Health Preparedness:** Developing rapid-response frameworks for outbreak containment, including stockpiling antivirals and vaccines.
4. **Research and Development:** Sustained investment in cutting-edge research to address resistance, improve efficacy, and develop universal Orthopoxvirus vaccines.

## 9. Conclusion

The resurgence of Monkeypox (Mpox) in non-endemic regions has illuminated gaps in global preparedness and underscored the urgent need for advanced therapeutic and preventive strategies. Traditional approaches, including antivirals like Tecovirimat and vaccines such as Jynneos, have provided a strong foundation for Mpox management but remain limited by issues like resistance, accessibility, and public skepticism. Recent innovations, such as monoclonal antibodies, host-targeted therapies, and next-generation vaccine technologies, have expanded the therapeutic arsenal, improving outcomes for severe cases and high-risk populations. Emerging strategies, including CRISPR-based gene editing, nanotechnology-driven drug delivery, and AI-assisted drug discovery, promise to revolutionize Mpox treatment by offering precision-targeted interventions and accelerated development timelines. However, achieving equitable access to these advancements remains a significant challenge, particularly in resource-limited settings. Lessons from smallpox eradication emphasize the need for robust global collaboration, sustained investment, and community engagement to overcome barriers like vaccine hesitancy and logistical constraints. As the world continues to navigate the challenges posed by Mpox, integrating scientific innovation with comprehensive public health policies and global cooperation will be pivotal. These efforts can not only reduce Mpox's public health impact but also serve as a blueprint for addressing future zoonotic and emerging infectious disease threats.

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