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Monkeypox Resurgence: Transmission, Clinical Features, and Advances in Countermeasures and Treatment

Fathimath Ina Shareef[1], Mariyam Luba Abdulla[1], Aminath Efa Ibrahim[1], Kannan Subbaram[1*]

[1] School of Medicine, The Maldives National University, Male', Maldives.

***E-mail** ✉ Kannan.subbaram@mnu.edu.mv

Abstract

The present study aimed to investigate the transmission, clinical features, and advances in countermeasures and treatment of monkeypox. Monkeypox is a DNA virus in the Poxviridae family, specifically classified under the *Orthopoxvirus* genus. Historically confined to central and western Africa, monkeypox made global headlines in 2022 due to widespread outbreaks in regions where it was previously rare, including North America, Europe, Asia, and Australasia. On 23 July 2022, the World Health Organization (WHO) declared the outbreak a public health emergency of international concern (PHEIC), prompting global efforts to curb its spread. Though monkeypox is primarily a zoonotic disease, human-to-human transmission occurs through direct or indirect contact with infected bodily fluids, skin lesions, or respiratory droplets. The 2022 outbreak saw a higher incidence among homosexual men, and in pregnant women, the virus was linked to congenital infection and miscarriage. Clinically, monkeypox progresses through four stages of lesions: macules, papules, vesicles, pustules, and scabs. Complications such as septicemia, pneumonia, eye infections, and neurological problems have also been reported. Available antiviral treatments include tecovirimat (TPOXX), cidofovir, and brincidofovir, while vaccines such as LC16, MVA-BN (JYNNEOS in the U.S.), and ACAM2000 offer preventive measures.

Keywords: Monkeypox, Global outbreak, Transmission modes, Clinical progression, Vaccination, Antiviral treatments

Introduction

Monkeypox (MPX) infections in humans were first detected in the early 1970s, following the global eradication of smallpox in West and Central Africa [1]. Before this, the virus was initially observed in laboratory monkeys in 1958. While there is no definitive primary host for the monkeypox virus, it is commonly found in various rodents, shrews, and other small mammals [2].

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The first recorded human case of monkeypox occurred in Bukenda, the Democratic Republic of Congo, where a 9-month-old infant presented with a vesicular rash. By 1971, additional cases had been reported in neighboring countries such as Ivory Coast, Liberia, Sierra Leone, and Nigeria.

The Democratic Republic of Congo has seen the highest number of monkeypox cases, with over 6,000 reported, followed by Nigeria with around 3,000 cases. Since 2017, Nigeria has experienced a resurgence in monkeypox cases, marking its first outbreak in nearly 40 years [3]. Outside of Africa, the first notable outbreak occurred in 2003 in the United States, specifically in the Midwest, where 72 cases were confirmed in just two months. This outbreak was traced to prairie dogs that had been exposed to African rodents imported from Ghana. Following this, the U.S. government imposed a ban on

the importation and breeding of African rodents, after genomic analysis confirmed similar viral strains in humans, prairie dogs, and rodents [4].

The monkeypox virus is classified within the *Orthopoxvirus* genus of the Poxviridae family, sharing close similarities with variola, the virus responsible for smallpox. Both diseases have similar clinical symptoms, making laboratory differentiation challenging. The structure of MPXV includes a central core, lateral bodies, an outer membrane, and an enveloping lipoprotein membrane that houses various polypeptides, including orthodox hemagglutinin [5].

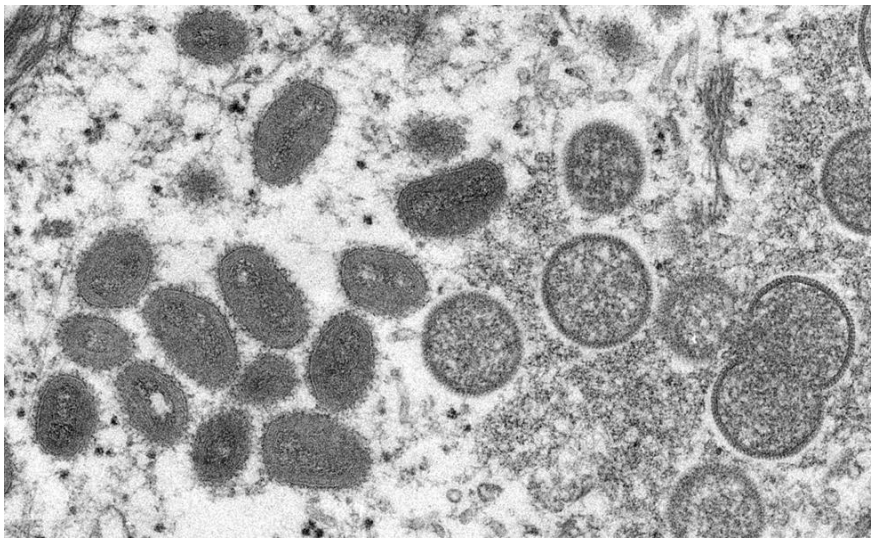

Figure 1. Electron micrograph of monkeypox virus particles–CDC

The present study aimed to investigate the transmission, clinical features, and advances in countermeasures and treatment of monkeypox.

Results

2022 Monkeypox Outbreak

In May 2022, along with the regular reports of monkeypox cases from its endemic regions, an unusual pattern emerged with cases being reported from countries outside the usual geographic areas (**Figure 2**) [1]. A significant number of these confirmed cases had a history of travel to Europe and North America. The outbreak primarily affected men who have sex with men, with most cases being detected in healthcare settings during sexual health consultations and other medical services. While monkeypox is not classified as a sexually transmitted infection, the occurrence of rashes in the anogenital area suggests that the virus may be transmitted through close physical contact during sexual activity.

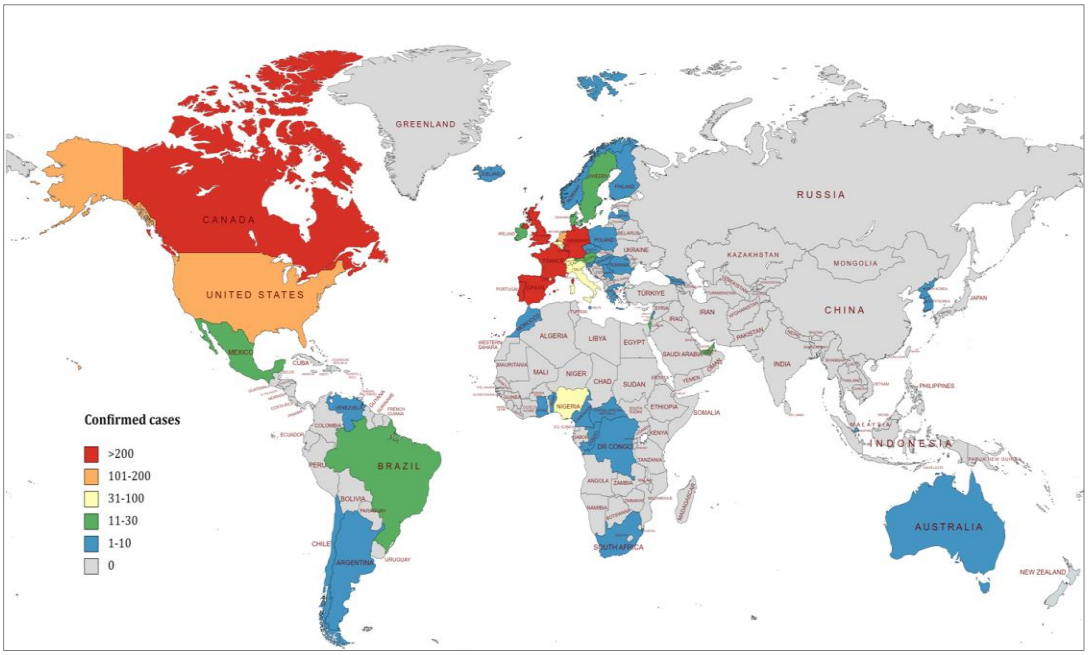

Figure 2. Countries affected by monkeypox virus in the current epidemic-adapted from WHO

2022 Monkeypox Outbreak

In early May 2022, monkeypox cases began to appear outside of its typical endemic regions in Central and West Africa. These cases were notably linked to travel, especially to countries in Europe and North America. The majority of those affected were men who have sex with men, with most cases being detected at sexual health clinics or general healthcare settings. While monkeypox is not classified as a sexually transmitted disease, the presence of lesions in the genital area raises the possibility of transmission through intimate contact.

Global Spread and Contributing Factors

By June 27, 2022, the World Health Organization (WHO) reported 3,413 confirmed cases and one death across 50 nations. The European region experienced the most significant number of cases, representing 86% of the total, followed by the Americas (11%) and Africa (2%). A single death was recorded in Nigeria [6].

The rapid spread to new areas has prompted various theories about its transmission. One hypothesis suggests that the COVID-19 lockdowns may have helped limit the spread of monkeypox. As international travel resumed, the virus spread from endemic regions to new areas. Another contributing factor could be reduced immunity due to a decline in smallpox vaccinations, which could make populations more susceptible to the virus.

Variants of Monkeypox

Monkeypox is classified into two primary clades: the Congo Basin (Central African) clade and the West African clade [7, 8]. The Congo Basin variant, which is more virulent, is now known as Clade I. It is associated with more severe cases and higher transmissibility. The West African clade, found in regions between the Equator and the Sahara, is divided into two subclades: Clade IIa and Clade IIb. The ongoing 2022 outbreak is largely attributed to Clade IIb [9].

Transmission Dynamics

While the exact mechanisms of monkeypox transmission are still being studied, it is believed that animal-to-human transmission can occur when humans come into contact with infected animals, such as primates, rodents, and squirrels, either through bites, scratches, or handling of infected meat [10].

Human-to-human transmission is thought to happen through respiratory droplets, which require close contact due to their large size. The virus may also spread via bodily fluids, skin lesions, or contaminated objects. Pregnant women can pass the virus to their unborn child through the placenta, potentially leading to miscarriages. Newborns can also contract the virus during childbirth [11]. An increase in cases among men who have sex with

men suggests that sexual contact is a significant route of transmission.

Clinical Presentation

The incubation period of monkeypox is typically 6 to 13 days. The disease manifests in two stages [12]. In the initial stage, which lasts up to 5 days, individuals experience symptoms such as fever, headaches, back pain, muscle aches, fatigue, and swollen lymph nodes. The second stage, starting 1-3 days after the fever, is marked by the appearance of a characteristic rash and pox-like lesions [13]. These lesions typically start as firm, well-defined, deep-seated bumps and may develop an umbilicated appearance, resembling a dot at the center [14].

The ongoing outbreak has shown unusual patterns, with many lesions concentrated in the anogenital region, while other parts of the body, such as the face and limbs, are less affected. Earlier outbreaks had more widespread lesions, including those on the face, limbs, and oral mucosa. The lesions progress through four stages: macular, papular, vesicular, and pustular, before eventually scabbing over and falling off [15, 16]. Most cases resolve on their own within 4-6 weeks, with only around 2% of cases requiring hospitalization [17].

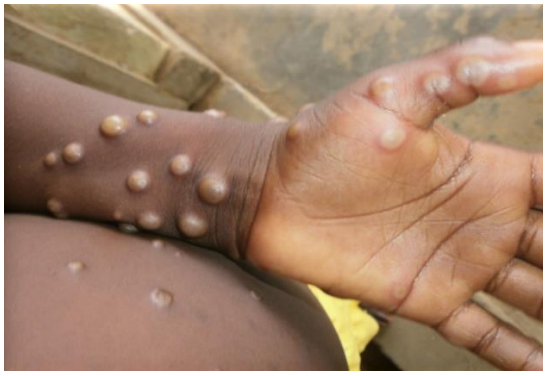

Figure 3. Skin lesions of monkeypox–courtesy of WHO

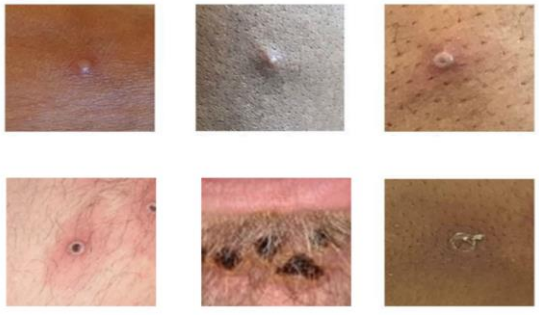

Figure 4. Stages of monkeypox rashes-UK Health Security Agency

Complications of Monkeypox

Monkeypox can lead to several complications, particularly secondary bacterial infections due to the open skin lesions. Septicemia can occur when bacteria spread systemically, and bronchopneumonia is a common concern, given that the virus often enters through the respiratory tract [18]. Conjunctivitis and corneal lesions affect about 20% of patients and, if left untreated, can lead to scarring and blindness [19]. Central nervous system (CNS) involvement may include headaches, fatigue, muscle pain, and nerve pain. Though rare, monkeypox can also cause encephalitis and seizures, with three such cases reported in the ongoing outbreak [20].

Treatment Options for Monkeypox

Currently, no specific antiviral treatment is approved for monkeypox, though drugs developed for smallpox are being used. These include:

Tecovirimat (TPOXX): This antiviral prevents the virus from forming new particles by inhibiting the *Orthopoxvirus* VP37 protein, essential for virion formation. Approved for use in adults and children weighing at least 3 kg, TPOXX is available for treating monkeypox during outbreaks under the investigational new drug (IND) protocol. Side effects include headaches, nausea, abdominal pain, and vomiting, with injection site reactions and headaches reported in some cases [21-25].

Cidofovir: This antiviral, typically used for cytomegalovirus retinitis in HIV patients, is also approved for use during monkeypox outbreaks under the CDC's expanded protocol [26, 27].

Brincidofovir: A lipid-conjugate version of cidofovir, brincidofovir is absorbed by cells and then activated within them to inhibit DNA synthesis in the virus. It is FDA-approved for smallpox but has shown effectiveness against orthopoxviruses in animal studies. Its use for monkeypox is being facilitated by the CDC under an EA-IND protocol [28].

Immunoglobulin Treatment

Two types of vaccinia immunoglobulins (VIGIV) have been approved by the FDA: VIGIV Cangene and VIGIV Dynport. These immunoglobulins are derived from the plasma of vaccinated individuals and are used to treat adverse effects from the smallpox vaccine, such as progressive vaccinia. Though there is limited data on

their effectiveness against smallpox, early studies suggest favorable pharmacokinetics. However, they can cause side effects like anaphylaxis, local stiffness, nausea, and headaches. Vaccinia immunoglobulins are contraindicated for individuals with vaccinia keratitis, previous systemic reactions to immunoglobulins, or IgA hypersensitivity [29, 30].

These treatment options, while helpful, are primarily based on the use of existing medications and are not specifically designed for monkeypox. Research is ongoing to improve therapeutic approaches.

Vaccines for Monkeypox

Vaccination is a crucial strategy in the fight against monkeypox. Currently, three vaccines have received approval for use against the virus: LC16, MVA-BN (JYNNEOS), and ACAM2000. The first two are modern smallpox vaccines designed to be safer and are also believed to protect monkeypox. However, comprehensive data on their effectiveness, especially during the ongoing outbreak, remains limited. Instead of mass vaccination, these vaccines are recommended primarily for individuals at higher risk, based on detailed investigations and contact tracing efforts [31, 32].

At-Risk Groups for Vaccination

Prevention through vaccination is advised for people at higher risk of exposure, such as:

- Men who have sex with men or those with multiple sexual partners.
- Laboratory staff working with infected animals or viral cultures.
- Response teams handling outbreaks [33].

In addition to pre-exposure vaccination, those with confirmed or suspected exposure to monkeypox should receive post-exposure prophylaxis. High-risk exposure includes direct contact with an infected individual's bodily fluids, skin lesions, or respiratory secretions, while medium risk involves proximity to someone symptomatic without wearing protective gear.

Vaccine-JYNNEOS (MVA-BN)

JYNNEOS, also known as MVA-BN, is a non-replicating live vaccine. It contains an attenuated version of the poxvirus, which stimulates the immune system to prepare for future infections without causing disease [34]. This vaccine requires two doses, administered 28 days apart (with the second dose ideally within 35 days). It can be given either subcutaneously or intradermally, with the latter causing fewer side effects but possible irritation such as redness or swelling at the injection site [35].

Although live vaccines are generally contraindicated for immunocompromised individuals, JYNNEOS has been deemed safe for them. However, its use during pregnancy, breastfeeding, and in children has not been fully studied, though it may be used based on clinical discretion. The FDA has approved its use for children over the age of 18 years [36].

Vaccine-ACAM2000

ACAM2000 is a live, replicating vaccine, made from the vaccinia virus, which is in the same family as smallpox. It is administered using a two-pronged needle to prick the skin multiple times, causing a localized infection that heals within weeks. However, this vaccine is associated with more significant side effects compared to JYNNEOS, including swelling, pain at the injection site, fever, headache, and myalgia, as well as potential severe reactions like myocarditis and post-vaccinal encephalitis [37].

This vaccine is contraindicated for individuals with immunosuppression, those who are pregnant or breastfeeding, children under 1 year old, and people with certain heart or skin conditions, including eczema. If someone is unable to avoid close contact with those who have these conditions, they should not receive the vaccine.

While the vaccines available for monkeypox offer hope, their use must be carefully considered based on individual risk factors, with prioritization for those who are at the highest risk of exposure.

Discussion

The dominant strain of Monkeypox currently spreading in the 2022 outbreak is Clade IIb. Although this variant tends to be less severe and has a lower transmission rate compared to others, healthcare professionals must remain vigilant, as it can still cause serious complications like neurological issues, eye infections, and septicemia [16]. One potential strategy to mitigate future outbreaks could be the implementation of stricter travel screening policies, particularly for individuals traveling to and from areas with endemic Monkeypox. The spread of the virus has been partially linked to travelers coming from these

endemic regions, as well as the importation of animals from affected areas [4].

There is significant potential for advancing antiviral treatments to better manage Monkeypox infections, reduce side effects, and increase accessibility. In addition, preventive measures traditionally used against smallpox—spanning primary, secondary, and tertiary prevention—should be accessible to all those at increased risk [38, 39]. However, the use of vaccination as a public health measure remains constrained due to limited data on its effectiveness and safety. Comprehensive international clinical trials are crucial to optimize the use of vaccination during outbreaks [40]. One of the contributing factors to the recent spread may be the reduction in herd immunity against smallpox.

While the search for an effective vaccine solution continues, public education about preventive practices plays a key role in preventing further outbreaks. This may include guidelines on limiting close contact with infected individuals through isolation, proper cooking of meat, and the use of personal protective equipment like masks. Additionally, regularly conducted screening programs targeting high-risk groups could be a valuable tool in reducing future transmission [41]. A diagram outlining the clinical features, complications, treatment options, and preventive measures is shown in **Figure 5**.

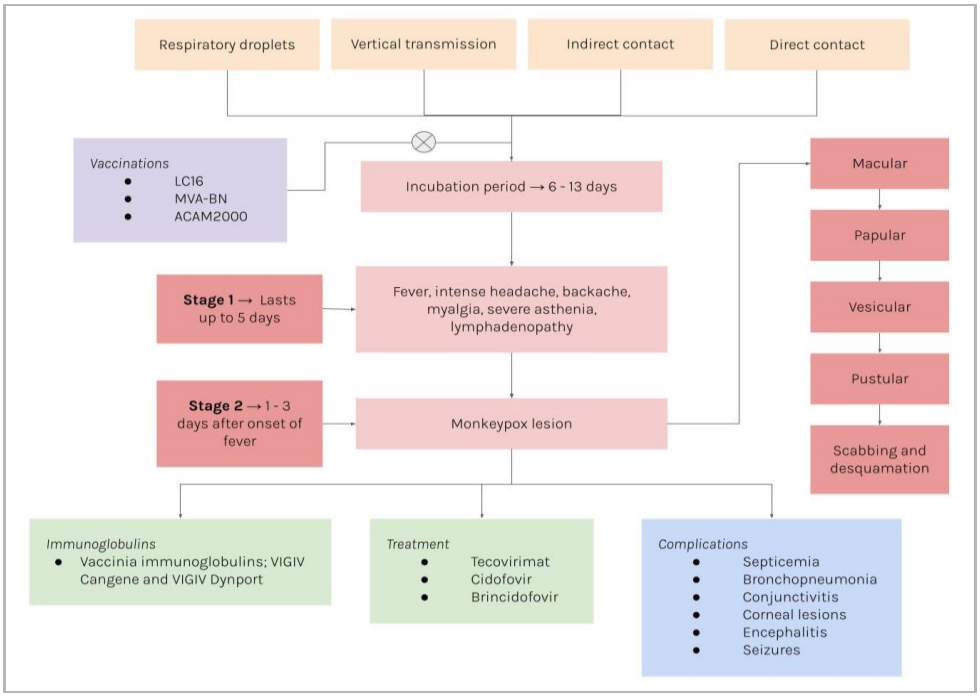

Figure 5. Clinical features, complications, treatment, and prophylaxis

Conclusion

Monkeypox, originally endemic to certain regions in Africa, experienced a significant surge in cases across 50 countries in 2022. The virus, which is believed to spread through both respiratory droplets and direct or indirect contact with bodily fluids, has two primary variants: Clade I and Clade II, with Clade II being further subdivided into Clade IIa and Clade IIb. Infected individuals typically experience a two-stage progression. The first stage involves systemic symptoms such as fever, headaches, and lymph node enlargement, followed by the second stage, where typical skin lesions characteristic of Monkeypox appear.

As the infection progresses, it can lead to serious complications like septicemia, pneumonia, conjunctivitis, corneal scarring, encephalitis, and other central nervous system (CNS) issues. Treatment options include antiviral medications such as Tecovirimat, approved for smallpox, along with cidofovir and brincidofovir. Vaccines, such as LC-16, JYNNEOS, and ACAM2000, have been developed for both pre-exposure and post-exposure prevention. Additionally, passive immunity using vaccinia immunoglobulins is another current treatment option available.

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Conflict of Interest: None

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Ethics Statement: None

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