

Monkeypox transmission: time to revisit the medical strategy of public health

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ABSTRACT:

Viral disease outbreaks pose an unprecedented challenge to public health, particularly in areas with limited access to healthcare and infection control resources. Monkeypox is a rare viral zoonosis associated with the monkeypox virus. It was first identified in humans in 1970 in the Democratic Republic of Congo, and since then, there have been sporadic outbreaks in central and West African countries. In the initial days, the infected person develops flu-like symptoms, fever, and a persistent rash, which are difficult to discriminate from other viral illnesses such as measles or chickenpox. The virus can be spread through direct contact with bodily fluids, such as blood, saliva, or respiratory secretions, or through contact with contaminated objects and infected individuals, such as looking for or living with someone sick with monkeypox. However, the recent outbreak of this disease has been associated with sexual and homosexual transmission. Currently, there is no approved treatment specifically available to contain the disease. Infected patients may treat with re-purposed antiviral drugs such as Tecovirimat, approved by the Food and Drug Administration (FDA) for smallpox, which is used in the management of the monkeypox virus. While cidofovir, ribavirin, and tiazofurin have proven to be efficacious in animal and *in vitro* trials, no specific medication or vaccine has been developed so far. Hence, new and specific antiviral chemotherapy is required and may be helpful in reducing the transmission and mortality associated with the monkeypox virus. Apart from this, smallpox vaccination is quite effective in preventing the monkeypox virus epidemic.

Keywords: *Infectious disease, Monkeypox, Virus, Re-emerging, Ribavirin, Cidofovir.*

INTRODUCTION

In the 21st century, the emergence of viral infectious diseases seems to be common. The complexity involved in controlling emerging and re-emerging infectious diseases, as well as their current rapid transmission, may be related to globalization. Monkeypox is a re-emerging zoonotic disease caused by a DNA virus that belongs to the orthopoxviral genus of the *Poxviridae* family¹. Monkeypox virus was isolated for the first time from monkeys;

however, squirrels, Gambian pouched rats, and dormice are also natural hosts of this virus². In 1970, monkeypox was first reported in humans in the Democratic Republic of the Congo. Since then, this disease has become endemic in many African countries, including Nigeria, Benin, and Liberia³. The possibility of a global spread of monkeypox has been recently observed in the Western Hemisphere, with the first cases of monkeypox due to the accidental importation of infected animals. Many important concerns about the dynamics of monkeypox



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viral transmission remain unanswered. According to the World Health Organization (WHO)⁴, monkeypox outbreaks have been detected in 70 countries, with over 16,600 confirmed cases of this viral disease. On July 23, 2022, WHO declared monkeypox a global health emergency⁴. It is still a challenge to achieve clinical recognition, diagnosis, and prevention, especially in the resource-poor endemic areas where monkeypox can be found. Due to the close similarity of the clinical features of monkeypox and smallpox, it is difficult to distinguish one infection from another, unless specific targeted tests are done⁵. It is also a matter of concern that, on one side, there is limited availability of smallpox vaccination and, on the other side, outbreak of monkeypox human pathogen. The transmission of the monkeypox virus can occur through direct contact with infectious materials like infectious sores, scabs, or body fluids and shared bedding or clothing⁶. Recently, in several cases⁷, it has also been reported to be sexually transmitted, especially between men or bisexuals. The signs and symptoms of monkeypox infection are like those of smallpox but less severe than smallpox². At present, the case of monkeypox is found to be atypical, starting with rashes in genital areas^{2,7}. Although there is no specific treatment for monkeypox virus infection, some minor cases are being controlled by using vaccines used for smallpox, antiviral, etc. Despite this, there is an urgent need to revisit the medical strategy and develop target-based medical treatment in favor of public health, so that the transmission can be controlled, and the mortality associated with the monkeypox virus reduced. Additionally, there is a need for in-depth knowledge of the biological characteristics of the re-emerging virus, the transmission mode, diagnosis, and preventive measures to contain the rapid outbreak. This article attempts to review current disease research progress and provide up-to-date clues with the salient features for disease prevention and control.

PRIMARY FINDINGS AND SCIENTIFIC FEATURES OF THE MONKEYPOX VIRUS

In 1958, the Monkeypox virus was first identified in monkeys. Its primary hosts are rodents, and it can be transmitted from animals to humans. The incubation period is 6-13 days. Sporadic human-to-human transmission has been reported through proximity, and droplet exposure further sexual transmission is also possible⁸. However, it is unknown whether this spread occurs through sexual transmission pathways (such as semen or vaginal fluids) or direct skin-to-skin contact with lesions during sexual activities⁴. Current evidence supports human-to-human transmission, including nosocomial and domestic transmission⁹. Increased transmission in the home is likely due to a lack of use of personal protective equipment during daily activities and prolonged contact with suspect objects. Prior research¹⁰ indicates a secondary attack rate of approximately 8% (range 0-11%) among household contacts who were unvaccinated against smallpox. Uncertainty exists regarding the therapeutic importance of persistent viraemia

and skin shedding, and knowledge of *in vivo* viral kinetics and infectivity is still inadequate¹¹.

GLOBAL MONKEYPOX VIRUS BURDENS AND MORTALITY

More than 1,300 cases of monkeypox have been confirmed in 40 non-African countries. The current monkeypox outbreak is in the West African region with a fatality rate of less than 4%, compared to another region in Central Africa with a fatality rate of up to 10%. There is no evidence of virus mutation¹². The WHO warning about an increase in monkeypox cases outside of Africa could be a symptom of a larger problem. The re-emergence of monkeypox was first reported in the UK in early May 2022, but to date, it has spread to several countries. It is thought to be the largest ever outbreak outside of Africa (Figure 1)¹³.

ETIOLOGY

Monkeypox belongs to the family *Poxviridae*, the genus *Orthopoxvirus*, and the species monkeypox virus. Pox viruses are round, lipoprotein-enveloped viruses with a linear double-stranded DNA genome¹⁴. The first case of re-emerging monkeypox virus infection was reported through sexual transmission¹⁵. As compared to the past, sexually transmitted diseases may become more widespread. Erazo et al¹⁶, during their study of murine gamma herpes virus as a standard lab model for human herpes viruses, found that male-to-male transmission was the highest. Viral pathogens, like the Zika virus, Human immunodeficiency virus (HIV), and Hepatitis B, were reported *via* male-to-male transmission. Although it is known that monkeypox is a zoonotic disease, its animal reservoir is still unknown. Though, this viral disease is considered self-limiting, it poses serious public health concerns due to its complications and pandemic potential¹⁷. The scientific community is serious and fearful that this virus could establish a long-term foothold in Europe or North America, allowing it to infect several animal hosts. Once the virus circulates among these animals, it can continue jumping back into humans who might encounter infected animals.

EPIDEMIOLOGY

The rapid spread of the monkeypox virus has sparked concerns about the start of a new epidemic. It has been reported⁴ about the 2022 pandemic that some cases had no travel history to endemic areas or contact with anyone from endemic areas of the monkeypox virus, which indicates a possible unknown transmission chain that may help to further spread the monkeypox virus. This report suggests either commuting from an endemic region with consecutive unrecognized local chains of transmission or at least a single moment to a non-endemic region where a substantial transmission event occurred.

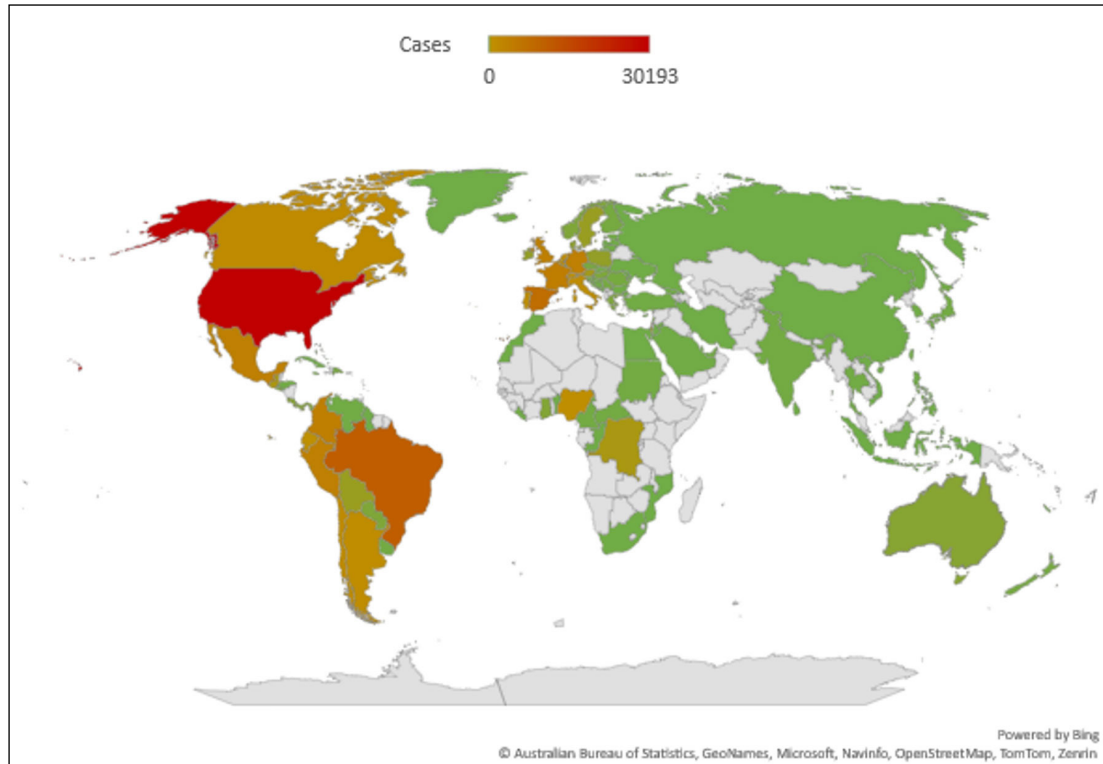


Figure 1. Human Monkeypox outbreak global map: cumulative number of confirmed cases, by countries, as of 15 February 2023.

This might have led to the subsequent reporting of cases in several countries. Mass gatherings have high chances of increasing contact rates among individuals who may be infectious with transmissible pathogens, and high contact rates between people could play a role in spreading viruses, including monkeypox^{18,19}. Nonetheless, the rapid spread of monkeypox virus cases was probably favored by a return to normal social interactions because of the easing of lockdown and travel restrictions after COVID-19 pandemic.

TRANSMISSION

Inter-human transmission of the virus generally occurs through the inhalation of large airborne respiratory droplets of the infectious virus. Transmission usually requires prolonged face-to-face or other close contacts, although airborne transmission over longer distances has also been reported. Person-to-person transmission occurs *via* droplet infection and contact with lesions containing replicating viruses²⁰. The monkeypox virus is classically transmitted through bodily fluids and close skin-to-skin contact from active lesions, and in recent reports²¹, transmission during sexual intercourse has been suggested as a viable route (Figure 2). Girometti et al²² explored 54 people who had the monkeypox virus; more interestingly, all the infected people were men. The majority of the sample consisted of white individuals, half of them were British citizens and one-fourth of the study participants had HIV. Symptomatic representation includes tiredness or lethargy, fever, and

skin lesions found in all patients, twenty percent had no prodromal symptoms. Apart from this, oropharyngeal lesions, skin lesions that affected more than one anatomical region and lymphadenopathies were recorded in some patients. Some patients required hospitalization, which could be due to pain or localized bacterial cellulitis requiring antibiotic intervention or analgesia²². Recently, a study²³ has been conducted in 43 different locations throughout 16 distinct nations, and 528 infections have been recorded. Most of the infected population was gay or bisexual, and nearly forty percent of them had HIV. For more than ninety percent of the infected individuals, sexual activity was thought to be the primary transmission mode. The commonly seen symptoms resembled already known conditions, while some newly evolved symptoms such as rash, skin lesions, anogenital lesions, mucosal lesions, fever, fatigue, myalgia, and lymphadenopathy were also seen before the rash in a few individuals who were tested²³. Among patients with uncontrolled HIV infection who suffer from chronic and persistent monkeypox infection, it is possible that new variants of the disease may surface.

DIAGNOSIS

Because of the disease's rarity of monkeypox, other rash illnesses, such as measles or chickenpox, are initially suspected. However, swollen lymph nodes usually distinguish monkeypox from other poxes. A blood sample may be an option to check for the monkeypox virus or antibodies that the immune system makes in defense of it.

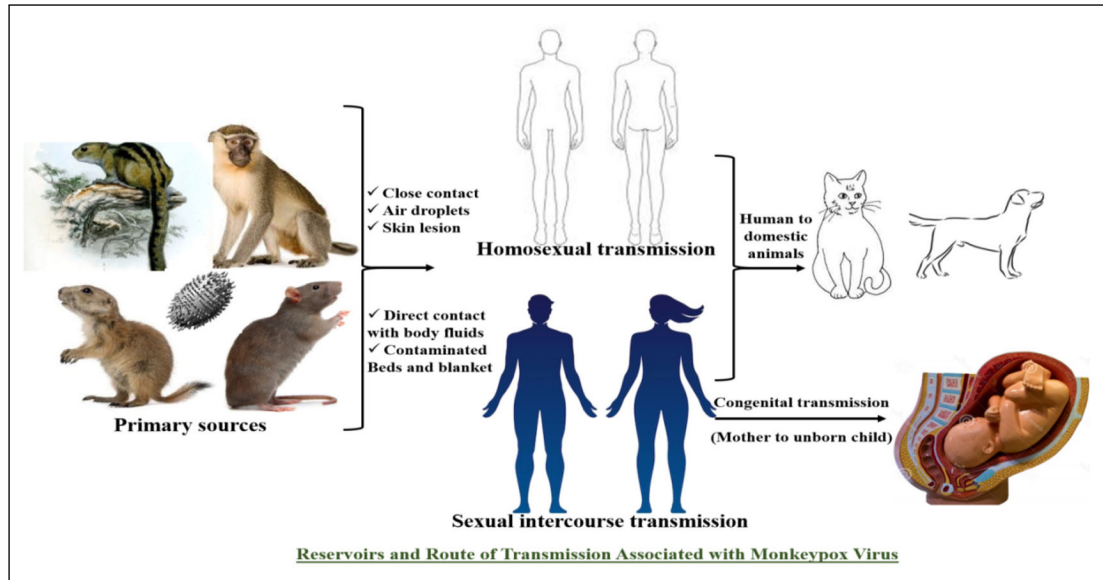


Figure 2. Primary sources and route of transmission associated with Monkeypox virus.

Serologic testing requires paired acute and convalescent sera for monkeypox virus-specific IgM detection within 5 days of presentation or IgG detection after 8 days. In addition to this, to diagnose monkeypox, a tissue sample from an open sore (lesion) is collected for polymerase chain reaction (PCR) testing (genetic fingerprinting)²⁴. Laboratories with all facilities are required to diagnose it, like electron microscopy, culture, molecular analysis, and identification by PCR and sequencing²⁵.

AVAILABLE PREVENTIVE THERAPY

Currently, there are neither any approved medications nor a drug that has been studied in human efficacy trials for treating human monkeypox. However, brincidofovir, Cidofovir, and tecovirimat are three elixirs that have been approved in the USA to treat smallpox in anticipation of a potential bioterrorism incident²⁶. However, there is no comprehensive assessment of the effectiveness of these agents.

Brincidofovir is an agent that has antiviral activity against double-stranded DNA viruses. It is a lipid conjugate pro-drug making strides focusing on the cells²⁷. Brincidofovir (oral) is an analog of the intravenous drug cidofovir. It has been seen that brincidofovir has a low renal toxicity risk²⁸.

On the other hand, tecovirimat does not exhibit noteworthy activity against dsDNA. This drug inhibits the maturation of the viral envelope protein VP37, thus inhibiting viral spread from an infected cell. In severe immune-compromised conditions, dual therapy of given drugs can be prescribed²⁹. Reported drugs have also shown efficacy in animal models against other orthopoxviruses, including monkeypox. Reports^{30,31} present compassionate use of tecovirimat for complicated vaccinia^{30,31} and cowpox³² with no adverse signals identified. A news release³³ from 2021 stated that the Central African Republic is currently running an extended access programme

for tecovirimat, where monkeypox outbreaks are frequent. Recent studies³⁴ confirmed that the primary mode of transmission of re-emerging outbreak of monkeypox virus is associated with sexual transmission, which was previously unknown or unexplored. Therefore, the strengthening of antiretroviral treatment programs is urgently needed so that patients with advanced immunosuppression are prioritized for effective antiretroviral treatment and monkeypox vaccination. We believe that the above-cited studies offer special insights into the epidemiology of monkeypox virus household transmission in a mostly unvaccinated community. The high prevalence of symptomatic and asymptomatic infections and the need for frequent testing to detect transient infections highlight the limitations and complexities of current screening and testing protocols. Symptom and temperature screening at entry points (e.g., restaurants, schools, and airports) might be a potential public health infection containment benefit due to rapid globalization. Current public health approaches encourage a combination of vaccination and non-pharmacological measures such as personnel protective gear during the care of patients, sexual activity, self-isolation, and hand sanitation, which can be a potential strategy to prevent monkeypox transmission. Centers for Disease Control and Prevention (CDC) data shows that monkeypox virus transmission is more prevalent in the young male population³⁵. The abovementioned studies also suggest transmissibility through local inoculation during close skin-to-skin or mucosal contact during sexual activity. Additional resources are needed to support sexual health and other specialist services in managing this condition. At present, relying on non-pharmacological interventions as prevention and containment measures is rare, as smallpox vaccines provide some level of protection, and hospitalization is also rare. At this time, vaccination remains the key public health intervention in high-risk populations that can provide immunity and thus mitigate and limit severe infections, complications, and mortality from the monkeypox virus.

CONCLUSIONS

The re-emerging monkeypox virus epidemic imposes a heavy socioeconomic burden on all societies. Hospitalization and specialized treatment are more frequently required in high-risk individuals such as the elderly, immunocompromised patients, and children worldwide. However, the impact of the monkeypox virus cannot be neglected, even in young adults. Monkeypox seems to be infectious by nature, which makes it more fatal and a threat to public health. The spread of the disease requires intense surveillance to prevent further community transmission. Currently, no approved treatment is available. Antiviral drugs for smallpox, such as tecovirimat, approved by the Food and Drug Administration (FDA), are used in the management of the monkeypox virus. While cidofovir, ribavirin, and tiazofurin have proven to be efficacious in animal and *in vitro* trials, no specific medication or vaccine has been developed so far. Hence, new and specific antiviral chemotherapy is required and may be helpful in reducing the transmission and mortality associated with the monkeypox virus. In addition, vaccination against the smallpox virus can help stop the spread of the monkeypox virus.

ETHICS APPROVAL AND INFORMED CONSENT:

Not applicable. This article does not contain any studies with human participants or animals performed by the authors.

CONFLICT OF INTEREST:

The authors declare that they have no competing interests.

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AUTHORS' CONTRIBUTION:

S.P, M.S, A.K, SP contributed to the design the draft of review article, M.S and A.M did literature search, and writing of the manuscript and editing are performed by the S.P, M.S, S.P and A.K.

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