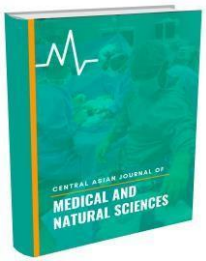

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Article

The Emergence of Monkeypox virus: Review Article

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Abstract: On 14 August 2024, the World Health Organization (WHO) issued a warning about the virus's potential to propagate globally. The WHO labeled monkeypox a world public health emergency, requiring urgent prevention and treatment and more than 22 million international and local visitors flocking to Iraq annually within one of the largest religious gatherings in the world, which coincided with the announcement by the World Health Organization (WHO) of warnings about the spread of the monkeypox virus. This review aims to provide updated information about monkeypox virus for designing better prevention and treatment. An exhaustive systematic review was carried out using the information available in the PubMed, Scopus, Web of Science, Embase, and ScienceDirect databases up to August 19, 2024. This public health emergency of international concern (PHEIC) determination is the second in two years relating to Mpox. Is a zoonotic, caused by an Orthopoxvirus, Human-to-human transmission can happen through skin-to-skin contact, inhaled droplets, or sexual contact. Mpox was first detected in humans in 1970, in the Democratic Republic of the Congo. The disease is considered endemic to countries in central and west Africa. In July 2022, the multi-country outbreak of Mpox, more than 57,995 cases had been reported in 103 locations, especially in Europe and the United States. That PHEIC was declared over in May 2023 after there had been a sustained decline in global cases. Monitoring of MPXV prevalence and transmission is necessary. In this thorough analysis, we covered the fundamental traits and modes of transmission of MPXV, as well as the people who are vulnerable to it. We also emphasized the influence of airline travel on the current MPXV outbreaks. We also go into the clinical consequences, MPXV prevention, and clinical viral detection techniques.

Keywords: Monkeypox Virus (MPXV), Human Monkeypox (HMPX), Epidemiology, Diagnosis, Therapeutics

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1. Introduction

Human monkeypox (HMPX) virus, another deadly Orthopoxvirus (OPXV) that was causing viral sickness in people at the time, monkeypox virus (MPXV) is the etiological agent of a zoonotic disease called monkeypox (Mpox). It is a double-stranded DNA (dsDNA) virus belonging to *Orthopoxvirus* (OPXV) genus within the *Poxviridae* family and *Chordopoxvirinae* as the subfamily, other members of this genus include *Variola virus* (VARV), *Cowpox virus* (CPXV), *Vaccinia virus* (VACV), *Camelpox virus* (CMLV), *Taterapox virus* (TATV) and *Ectromelia virus* (ECTV) [1].

Monkeypox (MPX) is a neglected zoonosis endemic in the tropical rain forests of Central and West Africa [2]. Monkeypox virus (MPXV) was first identified in 1958 in Cynomolgus monkeys in Denmark but nonhuman primates are considered "incidental"

hosts in the same way of human beings with rodents and other small mammals actually considered (although unproven) the natural hosts [3]. The first human case was reported in 1970 in a 9-month child admitted for suspected smallpox to the Basankusu hospital in the Democratic Republic of Congo [4].

World Health Organization (WHO) declared the MPXV outbreak a "Public Health Emergency of International Concern" on 23 July 2022, as of 30 September 2023, a total of 91,123 confirmed MPXV cases and 663 probable cases, including 157 deaths, have been reported to the WHO from 115 countries and territories. Recently, the number of patients suffering from MPXV has increased dramatically, causing great concern. Genomic analysis of the virus has shown two distinct clades-the Congo Basin (CB) clade and the West Africa clade [5], [6].

The former is reported to have better transmission potential between humans and a high case fatality as high as 10% compared to the West African clade, which has a mortality rate lower than 1% [6], [7]. Direct contact with dead infected animals, eating poorly cooked bush meats, and human-to-human transmission have been described as possible routes of infection., climate change, civil conflicts, poverty, and global accessibility are the likely factors driving the current outbreak [8], [9].

The capacity to spread quickly and effectively from human to human could facilitate the expansion of the disease's presence in human populations into previously unexplored areas. As a result, active disease surveillance needs to be maintained so that MPXV may be monitored for changes that are compatible with its increased adaptation to humans [10], [11]. Discovering the true geographic spread of this virus requires continued intensive surveillance in the Sankuru District, as well as expansion of that surveillance to all other places where the virus is known to circulate or where it is anticipated to circulate [12]. In light of the apparent rapid evolution of this virus, health authorities in areas that are not yet afflicted by it must be on red alert and actively ready to take immediate action in the event that suspected or confirmed instances of the disease are found in humans [13], [14]. Figure (1). The present review article aims to address the main characteristics of the Monkeypox virus disease, showing aspects of transmissibility, and clinical characteristics, epidemiology, laboratory diagnosis, and treatment measures.

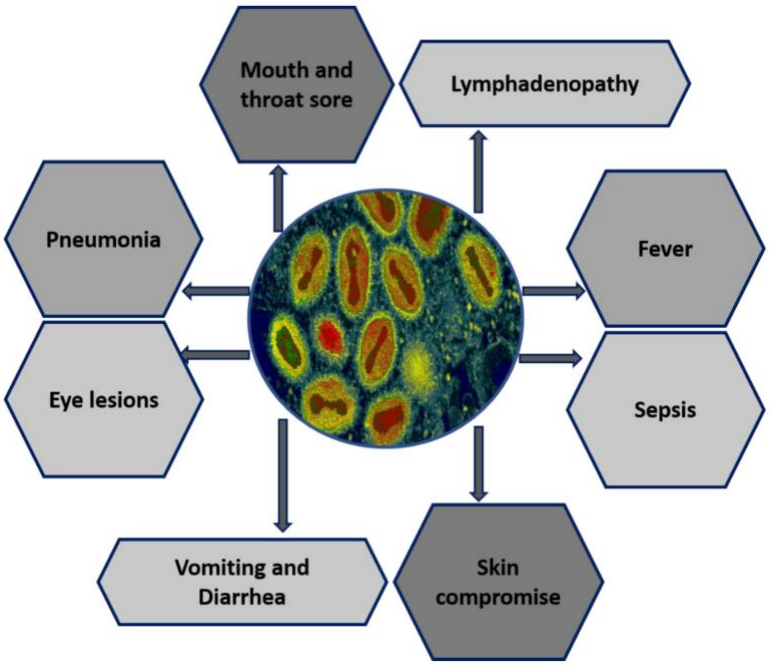

Figure 1. Multiorgan system involvement of MPXV.

Epidemiology of Monkeypox virus

Prior to the 2003 outbreak in the United States, which was the first outside of Africa, human monkeypox received little international notice [15], [16]. A total of 47 cases of confirmed monkeypox (37 patients) and suspected cases (10 patients) were recorded; all cases were caused by contact with prairie dogs (*Cynomys* spp.) kept as pets [17]. The pets became infected through close contact with imported small mammals, including African rodents, tree squirrels (*Heliosciurus* spp.), *brushtail porcupines* (*Atherurus* spp.), dormice (*Graphiurus* spp.), rope squirrels (*Funiscuirus* spp.), and striped mice (Hybomys spp.) from Ghana. The giant rats in Gambian waters were also a source of infection for the pets.

As to the CDC, monkeypox has been discovered in at least three dormice, two rope squirrels, and one giant rat from Guinea. These findings are the result of laboratory studies that involve virus isolation and PCR amplification. The fact that no fatalities or cases of human-to-human transmission were reported68 was explained by the strain's West African origin, according to genomic study [18]. The 2022 monkeypox outbreak affected thousands of people worldwide, following years of rare occurrences outside of Africa [19] Singapore [20] Israel, [21] United States [22].

This global pandemic is one of the worst in history, with wide transmission paths from endemic to non-endemic countries and according to the Centers for Disease Control and Prevention (CDC), there have been 26 cases confirmed in Lebanon, 8 in Saudi Arabia, 3 in Qatar, and 1 in Iran [23]. In 2024, displacement forecast report has reported 16 from 789 cases (14 /151 suspected and 2 /638 confirmed) including 511 deaths (case fatality 3%) from all of the country's provinces, representing the highest number of cases due to clade I in Africa [24].

Rapid Risk Assessment Monkeypox virus clade I circulation in Africa: risk for the EU/EEA– 16 August 2024 3 Confirmed Mpox cases have also been reported in five of the eight neighboring countries to DRC in 2024, i.e. Burundi (61 confirmed, 165 suspected), Central African Republic (35 confirmed, 223 suspected), Congo (19 confirmed, 150 suspected), Rwanda (four confirmed), and Uganda (two confirmed) (WHO, 2024). Out of the eight neighboring countries to DRC, only the Central African Republic and Congo reported cases in 2023. Burundi, Uganda and Rwanda reported their first Mpox cases at the end of July 2024 with Burundi reporting the most cases indicating community transmission in the country (WHO, 2024). Besides the neighboring countries to the DRC, Kenya reported its first confirmed Mpox case at the end of July 2024 (The Ministry of Health - Kenya, 2024). MPXV clade Ia has been isolated from cases in Central African Republic and Congo (Africa CDC, 2024). MPVX clade Ib, which was detected first in DRC and reported in April 2024, was also detected in confirmed cases in Burundi, Rwanda, Uganda and Kenya [25].

Biological Features of the Monkeypox Virus

The virus particles are approximately 200–250 nm in size with lengths of 220–450 nm and widths of 140–260 nm and oval shaped [26], so the monkeypox virus is sufficiently large to be distinguished by light microscopy; despite this, electron microscopy requires a higher magnification to analyze ultrastructure [27], see Figure (2).

The exterior lipoprotein membrane is typically present on virions that are released naturally but is absent from virions that are released through cellular disruption [28]. According to a computational study, the *Monkeypox virus* has a big genome with 196,858 base pairs that encode 190 open reading frames with 60 amino acid residues [29], [30].

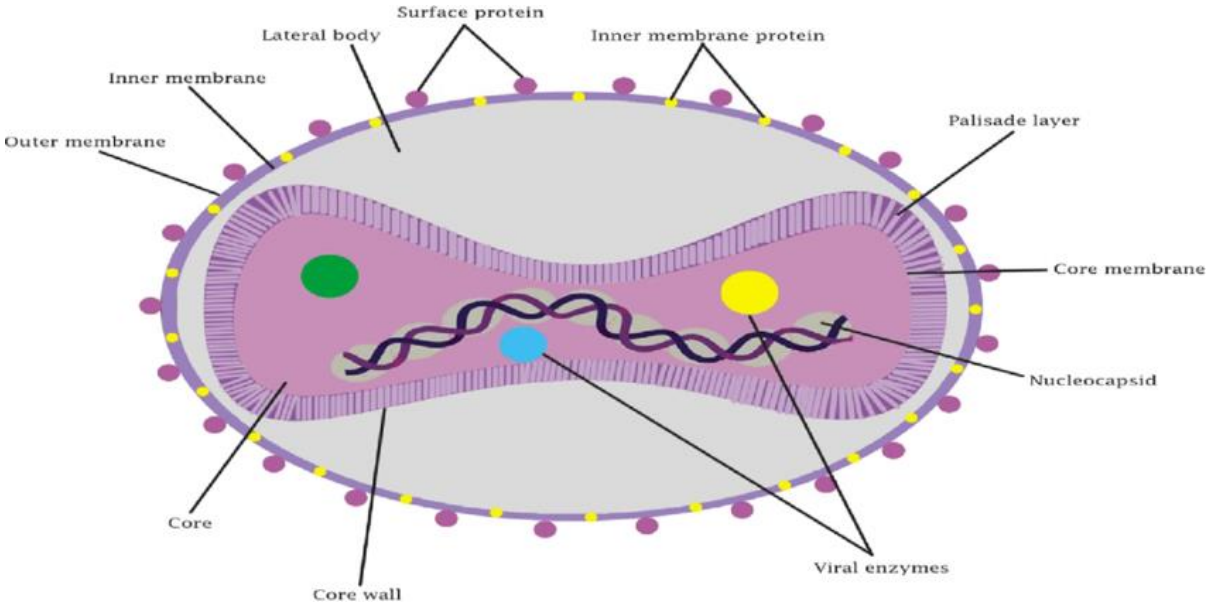

Figure 2. Structure of monkeypox virus

The replication cycle of Poxviruses, Like other viruses, Poxviruses contain proteins that facilitate the virus's attachment to a cell, fusion with the cell's membrane, and entrance into the host cell, the mature virion which has a single membrane, and the extracellular enveloped virion which has a second outer membrane, are broken in the case of the poxvirus [31]. The four viral proteins connected to the mature virion help the virus adhere to a host cell by glycosaminoglycans [32]. Figure (3).Glycosaminoglycans are found on the surface of all mammalian cells and are essential for binding viruses to cell membranes, although not all cellular receptors have been fully characterized [31] Figure (3).

The first stage of infection, they are small DNA-containing structures surrounded by membranes that are generated by the cell's rough endoplasmic reticulum [33]). As DNA synthesis continues, these factories will enlarge and eventually begin to collide and fuse to an irregular shape as cavities filled with viral mRNA and host translation factors develop [34].

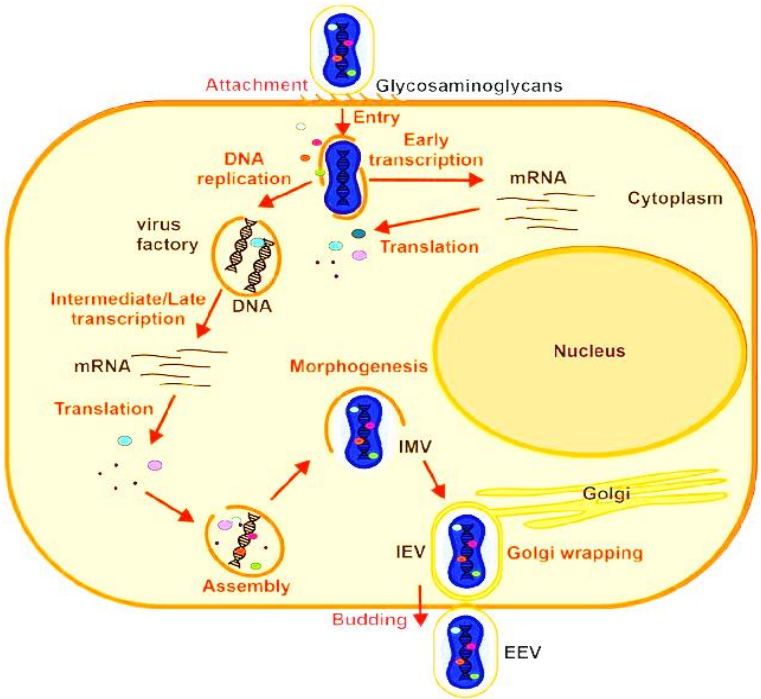

Figure 3. Replication cycle of a poxvirus

In the late stages of the replication cycle, a group of viral membrane building proteins and a group of late gene products work together to disrupt the endoplasmic reticulum membrane in the region and form crescent structures as substrates for assembling immature virions [35].

Monkeypox virus reservoirs

The zoonotic illness monkeypox has an unknown natural reservoir [36], [37] Numerous studies have been carried out to identify the natural hosts or reservoir of the monkeypox virus. [38], [39] have shown that 2 out of the 18 squirrels tested had antibodies to the virus. The infected squirrel, *Funisciurus anerythrus*, was the source of the monkeypox virus, which was isolated for the first time from a wild animal.

Additionally, several studies have hypothesized a connection between squirrels belonging to the genera Funisciurus and Heliosciurus and the DRC's natural monkeypox viral cycle [40], [41].

In March 2012, Radonic et al [42]., isolated the monkeypox virus from a sooty mangabey, a wild monkey. Its full genome sequence revealed that it shared a great deal of resemblance with viruses that cause monkeypox in Western Africa. Numerous studies have demonstrated that a number of animal species, mostly rodents and nonhuman primates, are vulnerable to the virus [43], [44].

Transmission of monkeypox virus

The primary modes of transmission to the human population are through animal-to-human and human-to-human contact [45]. The transmission of a pathogen from animals to humans can take place through various means, including direct contact with an infected or carrier animal, inhalation of aerosols, consumption of infected host animal, and exposure to bodily fluids such as respiratory droplets and blood. In addition, people who come into contact with objects contaminated with the virus, such as bedding or clothing, can also get infected [46].

The virus can survive outside the body for several hours, and therefore, objects contaminated with the virus can remain infectious for some time. Therefore, it is essential to disinfect or discard any objects that come into contact with infected animals or their bodily fluids [47]. Surprisingly, it was observed that congenital transmission through placenta from infected mother to the fetus was documented. This is called ‘congenital monkeypox’ suggesting that monkeypox virus can surpass placental barrier and may result in the developmental anomaly of the fetus [48], see Figure (4).

Environmental factors, such as temperature, humidity, and sunlight exposure, can also affect the survival and transmission of the virus. However, the specific impact of these factors on monkeypox transmission from deceased individuals or animals has not been extensively studied [49].

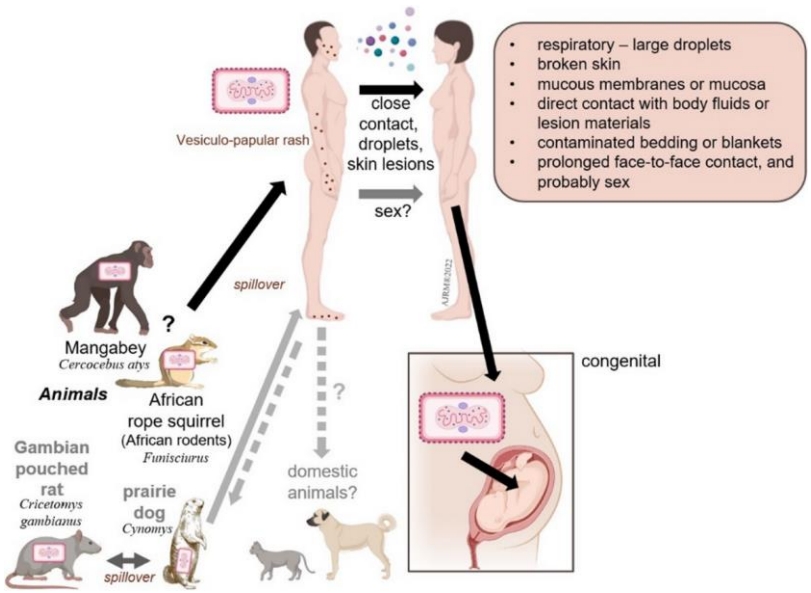

Figure 4. Transmission of human monkeypox virus

Clinical Features

Monkeypox infection is characterized by non-specific symptoms such as general discomfort, chills, fever, muscle pain, back pain, headache, and respiratory symptoms [50]. The progression of infection also includes lymphadenopathy [51] then, a vesiculopustular rash develops lasting for 7–21 days [52]. The rash typically initiates on the face and subsequently spreads to involve the oral mucosa, soles of the feet and palms, conjunctiva, and perigenital, perianal, and perioral mucosa, over the course of 4 weeks. The development of the rash follows a series of stages, beginning with macules (1–2 days), followed by papules (1–2 days), and then vesicles (1–2 days), pustules (5–7 days), and ultimately, scabs (7–14 days) [53]. The mortality rate for Mpox ranges from 1 to 10% [54].

The complications associated with Mpox are numerous and can have serious consequences for the patient. Bacterial superinfections, corneal infections, scarring, bronchopneumonia, septic shock, cellulitis, respiratory distress, and encephalitis have all been reported as potential complications of mpox [55]. In addition, retropharyngeal abscesses [56] and dehydration have also been reported as complications, which is often due to gastrointestinal symptoms, such as vomiting and diarrhea [57], see Figure (5).

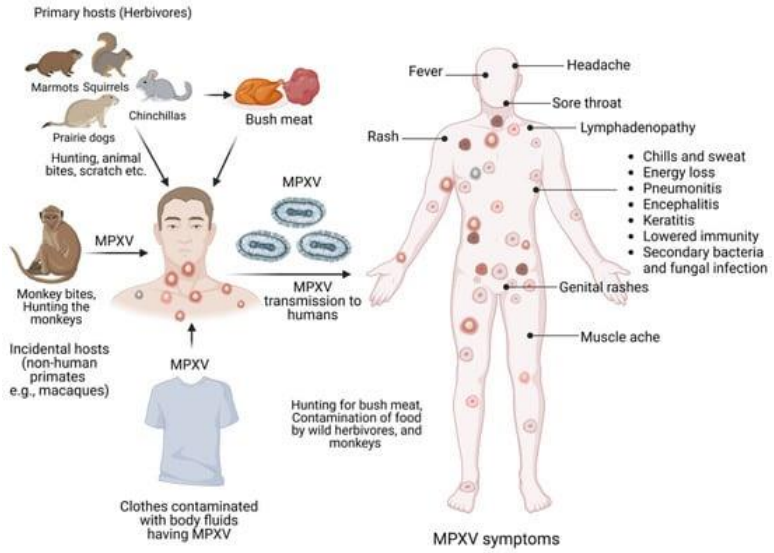

Figure 5. Clinical feature of Monkeypox virus

Diagnosis

Diagnostic tests are essential for verifying the presence of MPV infection, clinical signs, medical history and Laboratory tests all play a role in the diagnosis of MPV infection. The most common symptom that distinguishes monkeypox from illnesses like smallpox and chickenpox, which also have rash signs, is the enlargment of the lymph nodes. Laboratory testing is also necessary to confirm monkeypox [58].

Definitive diagnosis can be established using real-time polymerase chain reaction by taking the sample of the suspected skin lesions, preferably using swabs and aspirated lesion fluids; recent rt-PCR can be used to differentiate between the two clades of monkeypox virus (CB and WA) [59]. Testing for orthopoxvirus antibodies and immunohistochemistry have also been employed in the past and are still in use. However, these methods are relatively non-specific and cannot distinguish monkeypox infection from other orthopoxvirus infections due to antigenic cross-reaction [60]. If the mother has MPV, the fetus needs to be checked by ultrasound surveillance to find out if the fetus has MPV by looking for ultrasound abnormalities such as hydrops or fetal hepatomegaly [61].

Prevention and Treatment

There are several ways you can protect yourself and others from Mpox, including [62] Avoiding close, skin-to-skin contact with people who have a rash that looks like Mpox and animals that carry the Mpox virus.Also, learn steps you can take to lower your risk of Mpox during sex or at a social gathering,cleaning and disinfecting surfaces that are frequently touched using personal protective equipment during taking care of people infected with MPV or in areas with high-risk

Currently there is no specific treatment approved specifically for monkeypox virus (MPXV) infections, the main treatment is supportive including relieving pain and pyrexia,maintaining adequate nutrition and hydration,skin care, prevention of secondary bacterial infections and treatment of co-infections such as HIV (WHO in 2024)

some antiviral drugs used for smallpox treatment have been adopted by the FDA, such as brincidofovir and tecovirimat, which were approved in 2018 and 2021, respectively [63]. Brincidofovir (CMX001) and Cidofovir are DNA polymerase inhibitors (broad spectrum against poxviruses) that act by blocking viral synthesis [64].

Tecovirimat is an antiviral drug that targets the F13L gene and VP37 membrane protein to disrupt viral spread [65]. Goyal *et al*. recommended tecovirimat to be administered as the first line of Mpox treatment in pregnant and breastfeeding patients [66]. A tecovirimat analogue (synthesized by the State Research Center of Virology and Biotechnology, Russia) has been highlighted as a promising antivirals against OPXV infections [67]. Other drugs with potential use in monkeypox due to their activity against poxvirus include Ribavirin and Tiazofurin.

Vaccination

Numerous studies have indicated that smallpox immunization is around 85% successful in preventing monkeypox [68]. Due to potential harmful side effects, the first generation smallpox vaccination, Dryvax, is no longer effective [69]. This also applies to the second-generation vaccination, ACAM2000. The Ankara strain of the modified attenuated vaccinia virus is the source of a third-generation vaccine that was recently authorized for use in the prevention of monkeypox. JYNNEOOS is the brand under which the vaccination is sold [70], [71]. Furthermore, fourth-generation vaccine VAC6 is currently undergoing clinical trials [72]. Since the vaccinia virus offers cross-protection to the orthopoxviruses, it is the source of all of these vaccinations. Only those with impaired immune systems or frontline healthcare professionals who are at high risk of exposure are advised to get vaccinated. It is not recommended for healthy individuals to get vaccinated due to the scarcity of vaccinations.

2. Conclusion

Since the disease has spread over the past few years and an outbreak is still ongoing, monkeypox is no longer considered to be "a viral zoonotic disease that occurs mainly in remote portions of Central and West Africa, near tropical rainforests."

Increased monitoring and identification of Mpox cases are critical tools for obtaining a better knowledge of the ever-changing epidemiology of this disease. The outbreak has again highlighted the importance of early diagnostic and preventive methods in effectively tackling the spread of a new and highly transmissible disease, tackling the continual global Mpox outbreak requires early investment in medication development against the disease. Developing efficient anti-Mpox medications at a faster pace will assist prepare for upcoming obstacles and offer more dependable public health protection. In the current age of globalization, no one is safe unless everyone is safe.

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