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Review Article

Mpox Outbreak 2024: Epidemiological Shifts, Challenges, and Future Directions

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Abstract:

Mpox was once a zoonotic viral disease confined to a few countries in Central and West Africa. Its primary reservoir animals included rodents and nonhuman primates inhabiting the tropical rainforests of the region. The disease began to flourish in humans primarily after the 1980s, when smallpox vaccination was discontinued. This vaccine provided 85% cross-protection against mpox, limiting its spread in earlier decades. Over time, the mpox virus has undergone mutational evolution, enhancing its adaptability to human hosts and establishing itself as a globally infectious human virus. Following the challenges posed by the COVID-19 pandemic, mpox now looms as a potential new global health threat. It is crucial to raise awareness and implement rigorous precautionary measures to prevent its further spread. This requires a thorough understanding of the virology, evolution, and current disease patterns of mpox.

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Introduction:

Mpox has been classified as a neglected tropical disease since its first human case was detected in the Democratic Republic of Congo (DRC) in 1970.[1,2] Over time, this once-local zoonotic endemic disease has evolved into a global infectious threat due to a lack of adequate attention and prevention strategies. Notable outbreaks include the large 2017 outbreak in Nigeria, marking the virus's re-emergence in the country after 39 years; the 2022 international outbreak; and the 2023 major outbreak in the DRC, which exhibited atypical disease patterns in several aspects.[3,4,5] According to World Health Organization (WHO) data, from January 2022 to June 2024, a total of 99,176 laboratory-confirmed cases and 208 deaths were reported across 116 countries spanning all six WHO regions.

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According to World Health Organization (WHO) data, from January 2022 to June 2024, a total of 99,176 laboratory-confirmed cases and 208 deaths were reported across 116 countries spanning all six WHO regions. The highest number of cases were recorded in the African region, followed by the Americas and Europe.[6]

To date, Bangladesh has not reported any confirmed mpox cases. However, its neighboring country, India, reported 23 confirmed cases, including one death, during the 2022 outbreak, and one confirmed case in the 2023 outbreak. These developments signal a potential risk for Bangladesh.[7,8]

It is imperative to act now, fully acknowledge the emerging challenges, and implement appropriate preventive measures to safeguard the future. Without proactive efforts, we risk facing another catastrophic pandemic while still recovering from the traumatic experiences of COVID-19. A comprehensive understanding of

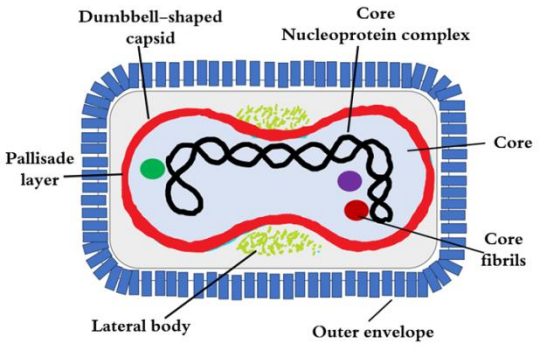
the virology, evolution, and emerging strains of the mpox virus, as well as its changing epidemiological patterns, is essential to formulate effective strategies. This review article will provide an overview of these critical points.

The Mpox virus:

Mpox is caused by the mpox virus, first isolated in Denmark in 1958 from a captive monkey colony infected with a pox-like disease. As a result, it was initially named 'monkeypox'.[2] However, subsequent research has suggested that rodents are likely the virus's primary reservoir. To combat the racist and stigmatizing attitudes that arose during the 2022–2023 outbreak, the World Health Organization (WHO) officially renamed the disease 'mpox' in November 2022.[9]

The mpox virus belongs to the *Orthopoxvirus* genus, part of the *Poxviridae* family and *Chordopoxvirinae* subfamily. Other members of this genus include the variola virus, vaccinia virus, camelpox virus, and cowpox virus. All are human pathogens, but mpox and variola viruses are the most significant due to their high virulence. These two viruses share 96.3% genomic similarity,[4] which is why the vaccinia virus vaccine, originally developed for smallpox (variola virus), provides 85% cross-protection against mpox.[10]

Figure 1: Different parts of the mpox virus *(courtesy: Dr. Tamanna Afroze)*



Among human pathogenic viruses, poxviruses are the largest, enabling them to be observed with a light microscope. Structurally, they are also the most complex. Under an electron microscope, the mpox virus (Figure 1) appears as an enveloped, double-stranded DNA (dsDNA) particle measuring 200–250 nm in diameter. The virus envelope consists of two layers, the outer and the inner. Numerous tubular-shaped proteins are attached to the outer layer, interacting with glycosaminoglycans (GAGs) and other host cell proteins. The nucleocapsid is dumbbell-shaped or resembles a box with concavities on the upper and lower surfaces. Each concavity contains an amorphous protein complex known as the lateral body. While their exact function remains unknown, lateral bodies are believed to play a role in immune modulation. The genome of the mpox virus is a large ds DNA molecule approximately 70 kbp in length, with terminally attached strands. Unlike other DNA viruses, mpox replicates in the cytoplasm of the host cell, showcasing a unique feature of poxviruses.[8,11]

Clades of the virus:

Before 2022, mpox viruses were classified into two distinct clades: the Central African clade, or clade I, typically found in the Congo Basin of Central Africa, and the West African clade, or clade II, primarily found in West Africa. Clade I is more virulent, causing severe clinical symptoms and a mortality rate of up to 10%. In contrast, clade II is less virulent, associated with milder symptoms and a mortality rate of less than 1%.[12,13]

Historically, both clades were primarily transmitted through zoonotic pathways, with limited human-to-human transmission. The maximum sequential human transmission chains were limited to six, with household transmission rates of approximately 10%. Consequently, previous outbreaks were confined to the rainforests of Central and West Africa, where reservoir hosts such as rodents and non-human primates had contact with impoverished local populations. Outbreaks outside Africa were rare, small, and localized, typically linked to travel to endemic areas or the importation of infected animals.[14]

The 2017 outbreak in Nigeria marked a significant shift, leading to the emergence of a mutated subclade of clade II capable of sustained human-to-human transmission. The older strain was then designated as clade IIa and the new one was named clade IIb. The B.1 lineage of the clade IIb was responsible for the

2022 international outbreak. Similarly, during the September 2023 outbreak in the Democratic Republic of Congo (DRC), genomic analysis identified a new subclade of clade I, named clade Ib, which demonstrated higher transmissibility among humans compared to the older mother clade Ia. Despite the enhanced transmissibility of these mutated strains, their virulence was significantly lower than that of their parent clades. As a result, while both the 2022 and 2023 outbreaks affected a large number of people, hospitalization and death rates remained low (Table 1).[15,16]

Table 1: Global outbreaks due to different clades of mpox

	Clade Ia	Clade Ib	Clade IIa	Clade IIb
Origin	Central Africa	2023 DRC outbreak	West Africa	2017 Nigeria outbreak
Distribution	Congo basin of central Africa	Africa specially DRC	West Africa	Global
Mode of transmission	Mainly zoonotic	human to human mainly through sexual contact	Mainly zoonotic	Human to human mainly through sexual contact
Affected population	Children	Adult (middle aged men)	Children	Adult (middle aged men.
Symptoms	Severe than IIa	More severe than Ia	Less severe than Ia	Less severe than IIa
Mortality rate	10%	5%	1%	0.2%

Epidemiological shift:

After the first isolation of virus, from 1958 to 1968, nine outbreaks occurred among non-human primates kept in laboratories and zoos, but no research person or zoo keeper was infected during handling the sick animals. This indicates, at that time the virus was incapable of infecting humans. After the 1st human case detection in the DRC in 1970, mpox has been confined for many years to the tropical rainforest regions of Central and West Africa with endemic and sporadic outbreaks.[14,2] As of 2003, cases have been reported from 11 African countries namely Benin, Cameroon, Central African Republic, Congo, Côte d'Ivoire, DRC, Gabon, Liberia, Nigeria, Sierra Leone and South Sudan.[13] The most affected country is the DRC with less than 500 cases in 2001 but more than 2500 cases in 2018.[17,18] Until 2021, all the outbreaks outside Africa have been linked to contact with infected animals or travel to endemic countries in Africa (Table 2).[19,20,21]

Table 2: Global epidemiological shift through the century

Year	Affected country	Number of cases	Source
2003	US	47	Imported infected rodents from Ghana.
2018	UK	3	travel to Nigeria
2018	Israel	1	travel to Nigeria
2019	Singapore	1	travel to Nigeria
2021	US	2	travel to Nigeria
2021	UK	3	travel to Nigeria

Here should be noted that Nigeria was facing the biggest mpox outbreak in its history since 2017. Till 2021, 226 laboratory-confirmed cases and eight deaths were reported from here.[22]

In 2022, the first large international outbreak of mpox occurred, marking a significant departure from all previous non-endemic outbreaks. Most cases were reported from non-endemic countries with no direct links to endemic regions or signature cases. The initial case in the UK, reported on May 6, 2022, involved an individual with recent travel history to Nigeria.[23] However, shortly thereafter, thousands of cases were identified across a wide range of non-endemic regions, particularly in Europe and the Americas.[22,24] Less than 1% of cases originated from endemic zones.[15,25]

Genomic analysis later confirmed that the mpox virus had undergone multiple genetic mutations, enabling better adaptation and transmission between human hosts. This led to the emergence of a new genetic variant of the West African clade (clade IIb). The outbreak also exhibited several unprecedented characteristics, including the demographics of affected populations,

modes of transmission, and clinical presentations.[23,26]A study by Ilic et al, analyzing data from 43 locations across 16 countries, revealed that 98% of the affected individuals were male, with a median age of 38 years. Among these, 99% identified as gay or bisexual men.[27]Although mpox virus DNA was detected in semen in some cases, the evidence is insufficient to classify it as a sexually transmitted virus. It is believed that the virus entered the MSM (men who have sex with men) group coincidentally through close physical contact.[24] The clinical features of this outbreak included atypical presentations, such as the absence or mild nature of prodromal symptoms, rashes preceding prodromes, or rashes manifesting as isolated ulcers or lesions, often confined to the anogenital and/or perineal areas. Predominantly, inguinal lymphadenopathy was observed. The severity of the disease was generally mild to moderate, with hospitalization rates ranging between 4–10%.[28]

Due to the rapid rise in cases, unusual transmission patterns, and atypical symptoms in non-endemic regions, the World Health Organization (WHO) declared the outbreak a Public Health Emergency of International Concern (PHEIC) on July 23, 2022.[29]Thanks to efficient surveillance and control measures by local and international health authorities, the number of cases began to decline in January 2023. In May 2023, WHO announced the end of the emergency declaration. As of October 2024, sporadic low-level infections with the new strain continue in various regions. A total of 110,570 confirmed cases and 237 deaths have been reported across 123 countries.[8]

2024 outbreak in DRC:

In September 2023, mpox cases began to rise again in the Democratic Republic of Congo (DRC). Genomic analysis of samples revealed that this outbreak originated from the Central African clade. While clade Ia was already endemic in the DRC, the human-to-human transmissibility of clade Ib in this outbreak was significantly higher than in previous instances.[12] The initial cases were reported from the Kamituga Health Zone in South Kivu Province, located in eastern DRC. This is a densely populated mining region with numerous bars forming part of the local sex industry. Demographic analysis of PCR-confirmed cases from September 2023 to May 2024 showed that over 50% of cases were female, with a median age of 22 years. Approximately 30% of these cases involved individuals engaged in sex work, suggesting transmission primarily through sexual contact or close physical interaction.[30]

Subsequently, adult-to-child and child-to-child transmission became apparent, leading to an increase in cases among children. Pregnant women were also affected, with reports of miscarriages linked to the outbreak. Cases began to emerge from various provinces across the DRC, including regions previously unaffected, as the outbreak expanded.[8,16,17]

According to the African CDC, the number of mpox cases in the DRC increased by 160% in 2024 compared to 2023. Children under the age of 15 accounted for 70% of reported cases and 85% of deaths. The outbreak also spread to neighboring countries, including Burundi, Rwanda, Uganda, and Kenya, marking them as newly affected African nations. Additionally, cases were reported in two new countries outside Africa, Sweden and Thailand.[24] As of August 24 over 21000 cases have been reported from 15 countries and over 96% reported from the DRC. On 14 August 2024, WHO again declared the epidemic as a PHEIC.[13,31]

Challenges with mpox outbreak trends

The mpox virus is undergoing a continuous evolutionary process, resulting in significant changes from its emergence to the present day. This evolution has been explored in various research studies. Deforestation and urbanization have contributed to the decline in reservoir animal populations, disrupting the micro-environments suitable for the virus's development. Consequently, mutations have facilitated increased animal-to-human spillover, adaptation to human hosts, and human-to-human transmission, including through novel routes such as sexual contact.[2,32]

Theoretically, as a DNA virus with the largest and most complex DNA genome among viruses, mpox mutations should occur at a slow rate. However, the 2022 mpox strain (Clade IIb) exhibited an unexpected 6-12-fold higher mutation rate than anticipated, with 46 single

nucleotide polymorphisms (SNPs) identified compared to the NCBI reference sequence NC_063383. This international outbreak was exclusively driven by human-to-human transmission. Similarly, the 2023 Clade Ib strain emerged from mutational variations and is still under genomic analysis. Clade Ib demonstrates higher transmissibility in humans compared to Clade Ia and has expanded into previously unaffected neighboring countries of the DRC, showcasing its pandemic potential.[32,33]

Research has identified the host cell enzyme APOBEC3 as a key factor behind the high mutation rate in both clades, with approximately 20 APOBEC3-driven mutations occurring annually due to human-to-human transmission. Notably, 40% of individuals infected during the 2022 outbreak were HIV-positive, a condition that significantly increases APOBEC3 expression.[16,18,24] This suggests that HIV-positive individuals may play a direct role in mpox mutations. Continued mutation of the virus raises the possibility of the emergence of a novel mpox strain that existing cross-protective vaccines may not counter, necessitating the development of a specific mpox vaccine. Currently, no mpox-specific vaccines or antiviral drugs are available.[4,7,14] Furthermore, if the virus establishes new animal reservoirs in non-endemic areas, it could create new endemic zones, escalating the risk of a future pandemic.[15]

Future directions:

Preventing human-to-human transmission is critical to averting a serious pandemic. Each country must develop a robust strategy through early planning, effective public relations, and multinational cooperation.

Key recommendations include:

1. *Surveillance and Monitoring:* Governments and healthcare authorities should establish strong surveillance systems to prevent mpox from entering through international routes and ensure immediate detection of new cases. This includes training personnel to recognize the early symptoms of mpox.[5,6]
2. *Training on Diagnostics:* Health technicians and relevant personnel should be trained in CDC-recommended guidelines for specimen collection and biosafety for mpox diagnosis. Accurate RT-PCR results, the latest diagnostic method, depend on proper specimen collection, storage, transportation, and testing. Adequate stocks of PCR kits should be maintained for prompt diagnosis.[7,9,26]
3. *Treatment and Management:* Updated treatment and management guidelines should be developed. Sufficient vaccine and antiviral drug supplies should be ensured, prioritizing non-endemic but high-risk countries like Bangladesh, India, Pakistan, and Afghanistan, in addition to endemic regions. Densely populated countries in these regions would face significant challenges in containing outbreaks.[10,24,34]
4. *Vaccine Prioritization and Production:* Countries should create vaccine priority plans to rapidly cover vulnerable populations. Potential countries should consider producing vaccines and drugs domestically. International organizations must accelerate efforts to develop specific mpox vaccines and antiviral drugs.

Collaborative global efforts and proactive measures are essential to mitigate the threat posed by the evolving mpox virus.

Conclusion:

Epidemiological analysis shows a gradual decline in mpox cases. However, in some areas or communities, viral transmission and mutations persist at low, often undetectable levels, increasing the risk of a new strain emerging and potentially triggering another outbreak. While the World Health Organization has already issued public health alerts, heightened vigilance remains essential. Bangladesh must implement meaningful and proactive measures to protect its population and contribute to global health security. Through widespread public awareness, prompt action, and strong national and international collaboration, this emerging global health threat can be effectively managed.

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