

# Mpox Virus Variants Clade-I and Clade-II Pathogenesis: Mapping the Genetic Mutations, Impact on Viral Fitness, Efficiency of Human-To-Human Transmission, Epidemiological Surveillance

Yash Srivastav<sup>1\*</sup>, Shivani Singh<sup>1</sup>, Stuti Verma<sup>2</sup>, Vivek Kumar<sup>1</sup>, Kamini Prajapati<sup>1</sup>, Anup Kumar Sirbaiya<sup>3</sup>, Saroj Kumar<sup>1</sup>

<sup>1</sup>D.K.R.R Pharmacy College, Amberpur, Sitapur (Uttar Pradesh), India. 261303

<sup>2</sup>Aryakul College of Pharmacy and Research, Sitapur, Uttar Pradesh, India. 261303

<sup>3</sup>K.P. Singh Memorial Institute of Pharmacy, Sitapur, U.P, India. 261207

\*Corresponding Email: [Yashsrv.108@Gmail.Com](mailto:Yashsrv.108@Gmail.Com)

## Abstract:

The mpox virus (MPXV), which is an emergent orthopoxvirus with zoonotic transmission capability, represents a growing public health threat on a global scale due to the recently reported outbreaks in multiple countries after 2022. In view of the rising prevalence of genetically heterogeneous strains, such as Clade I and Clade II, there has been a growing research focus on the molecular aspects of pathogenesis, evolution, transmission, and epidemiology of MPXV clades. The current review focuses on the genome structure, mutations, viral fitness, immune evasiveness, and human-to-human transmission rate associated with MPXV clades. The comparative pathogenicity between the Clade I and Clade II variants is also discussed, with emphasis on the increased virulence and mortality related to Clade I and increased transmissibility of Clade II variants, including Clade IIb. Recent genomic studies have shown that hypermutations caused by the APOBEC3 enzymes, single-nucleotide polymorphism, and adaptive evolution contribute to viral persistence, immune escape, and epidemic spread. Furthermore, the review explains how epidemiologic surveillance efforts, molecular diagnostic tools, genomics techniques, and public health issues related to mpox epidemic response are managed. This information highlights the crucial role of genomics surveillance, timely diagnostics, vaccines, and the One Health approach in future prevention of mpox outbreaks.

**Keywords:** Mpox virus, Clade I, Clade II, genetic mutations, viral fitness, human-to-human transmission, genomic surveillance, pathogenesis, One Health, epidemiology

Received: March. 13, 2026

Revised: April 28, 2026

Accepted: May. 24, 2026

Published: June 02, 2026

DOI: <https://doi.org/10.64063/3049-1681.vol.3.issue6.5>

<https://aktpublication.com/index.php/jprims/issue/archive>

*This is an Open Access article distributed under the terms of the Creative Commons Attribution (CC BY NC), which permits unrestricted use, distribution, and reproduction in any medium, as long as the original authors and source are cited. No permission is required from the authors or the publishers. (<https://creativecommons.org/licenses/by-nc/4.0/>)*

## 1. INTRODUCTION

The MPXV is one of the most significant viruses re-emerging as an important threat in the twenty-first century because of its rapid geographical spread and dynamic modes of transmission. For many years, it was known as a neglected zoonosis with a limited presence only

in Africa; however, recent global outbreaks have shown that the virus can effectively spread among human populations<sup>1</sup>. With the sharp rise in the number of cases from different countries, it has become evident that MPXV is an important global health issue that calls for continued research by scientists. Recent outbreaks have also indicated genetic diversification among the viral strains, resulting in greater interest in studying the molecular evolution and pathogenesis of the virus<sup>2</sup>.

The application of genomic sequencing methods to studying viruses has led to the identification of mutations, genetic divergences, and adaptation that help improve virus infectivity and persistence. With the appearance of different clades with different levels of virulence and infectivity, there are fears about the future severity of outbreaks, as well as the ability of the virus to adapt to humans. As a result, integration of molecular virology, genomics, epidemiology, and public health approaches to outbreak control has become crucial. Thus, global monitoring, diagnostic testing, and vaccine development are all important tools for controlling MPXV infection.

### **1.1 Background and Context**

The MPXV is a double-stranded DNA virus of the Orthopoxvirus genus, within the family Poxviridae, previously called monkeypox virus. In 1970, mpox was first identified in humans within the Democratic Republic of Congo; until 2022, the disease was considered endemic in Central and West African regions. Since the global outbreaks reported post-2022, mpox has emerged as an alarming public health crisis because of the geographical spread and human-to-human transmission of the virus. Genomic analysis of mpox has resulted in identification of two significant phylogenetic lineages, namely Clade I and Clade II, each differing greatly in terms of their pathogenicity, transmissibility, mutation trends, and epidemiology. While Clade I shows high pathogenicity and higher mortality rates, Clade II is characterized by efficient transmission and wider geographical dispersal<sup>3</sup>. The emerging trend of developing adaptive mutations within the human population has generated various questions about viral adaptation and immunity evasion.

### **1.2 Objectives of The Review**

The major objectives of the present review are:

- To study the molecular pathogenesis of MPXV Clade I & Clade II.
- To study genetic mutations and evolution due to MPXV Variants.
- To study differences in viral fitness and efficiency in human-to-human transmission among the two clades.
- To study the methodology followed for genomic and epidemiological surveillance of mpox outbreaks.

### **1.3 Importance of The Topic**

The study of the molecular evolution, disease transmission dynamics, and epidemiological traits of the different MPXV lineages is necessary to improve global outbreak preparedness strategies. The rise of genetic diversity of MPXV and increased human adaptation emphasizes the

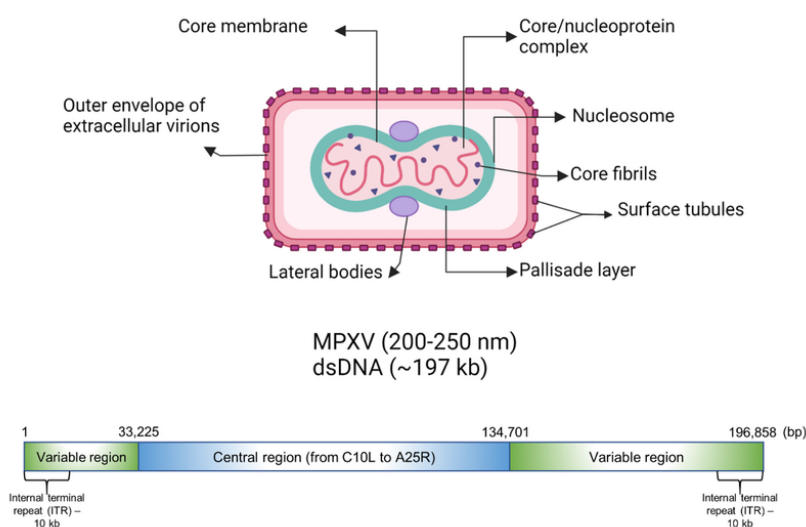
importance of the development of genomic surveillance, fast molecular diagnostics, and treatment options<sup>4</sup>. The comparative analysis between the two lineages Clade I and Clade II offer significant insights about the pathogenesis, immune escape, and transmission efficiency of the virus, and this information is vital for developing efficient vaccines and antiviral drugs. Thus, continuous international collaboration and surveillance approaches must be implemented to reduce the future risk of mpox outbreaks and enhance global health security.

## 2. MOLECULAR PATHOGENESIS AND GENOMIC ORGANIZATION OF MPOX VIRUS

Insight into the molecular pathogenesis and genome structure of the MPXV would play an important role in providing information about the differential virulence, infection efficiency, and epidemiology of the two different clades of the virus, namely Clade I and Clade II. With progress made in the field of genome sequencing and molecular virology, there has been an increased understanding of replication, adaptation, immune evasion, and evolutionary changes due to mutations in MPXV<sup>5</sup>. There are many differences between the two clades, which can be identified through molecular research.

### 2.1 Genomic Structure and Classification of MPXV

MPXV stands for mpox virus and is an enveloped, large double-stranded DNA virus that falls under the genus Orthopoxvirus in the Poxviridae family. MPXV possesses a viral genome of about 197 kilobases which codes for over 190 proteins that are important for its replication, transcription, virion formation, host interaction, and immune system modulation<sup>6</sup>. The internal sections of the genome are conserved, and are mostly responsible for replication processes while the end sections vary greatly, encoding virulence factors and other immune-related genes<sup>7</sup>. MPXV has a unique brick-shaped morphology and a lipoprotein envelope covering its structure.



**Figure 1:** Genomic structure and virion organization of Mpox virus (MPXV)

In the genome structure of MPXV, there are a number of structural and virulence factors that help in promoting the development and progress of disease<sup>8</sup>. Proteins play an important role in the process of membrane fusion, transport in cells, DNA replication, and dispersion in tissues.

Furthermore, MPXV produces various immunomodulators which can suppress the anti-viral response of the host. These proteins can impair cytokine signaling, inflammation, and immune response, thus creating a conducive environment for viruses within the infected individual.

It is evident that there are significant variations in the genome sequence of Clade I strains and Clade II strains in terms of virulence and pathogenicity genes. The former have significantly more powerful virulence factors related to systemic infections and high mortality rates. On the contrary, Clade II strains have more mutations and adaptive evolutionary changes that facilitate increased transmission among humans and spread on an international scale. It has also been found that there are APOBEC3-related mutations in Clade IIb strains<sup>9</sup>.

## 2.2 Molecular Pathogenesis of Clade I and Clade II

MPXV molecular pathogenesis starts with virus attachment to cell receptors, followed by penetration into the host cell through membrane fusion or endocytosis. The main mode of transmission is through direct contact with infectious lesions, droplets, contamination, and broken skin and mucous membranes<sup>10</sup>. After entering the target cell, the virus uncoats and releases its nucleic acid into the cytoplasm where replication takes place without involving the host cell nucleus at all. Early viral gene expression is involved in DNA synthesis and interference with host defense mechanisms.

Infection with MPXV follows several steps in its life cycle, such as transcription at an early stage, replication of DNA, gene expression at an intermediate stage, and finally, the formation of structure proteins at a late stage<sup>11</sup>. The newly made virions get assembled and mature in viral factories in the cytoplasm before being released into neighboring cells. The process of the virus spread happens through lymphogenous and hematogenous routes to affect various organs in the body. Some symptoms include fever, headaches, myalgias, lymphadenitis, and characteristic vesiculopustular.

Pathogenic distinctions occur in regards to the two clades. Clade I is known to be more virulent and causes more disseminated infections, which also come along with higher viral titers and mortality rates<sup>12</sup>. Clade I infections have been shown to be capable of more efficient immune suppression as well as intracellular replication compared to Clade II. However, Clade II is capable of causing much less virulent infections but exhibits greater human-to-human transmissibility efficiency. Recent outbreaks that have resulted in the appearance of Clade IIb lineage show adaptation to humans by the virus<sup>13</sup>.

## 2.3 Host Immune Response and Immune Evasion Mechanisms

In terms of host immune defenses against MPXV, there are two kinds of immunological defense systems that work by restricting the replication and spread of the virus due to the involvement of interferons, cytokines, chemokines, and different immune cells such as macrophages, dendritic cells, natural killer cells, and T lymphocytes<sup>14</sup>. Nevertheless, it is essential to note that MPXV has a number of immune evasion mechanisms like interferon signaling inhibition, cytokine expression inhibition, inhibition of apoptosis, and inhibition of complement activation<sup>15</sup>.

Key immune evasion mechanisms utilized by MPXV are:

- Suppresses antiviral response by interferons.

- Regulates pro-inflammatory cytokine response.
- Blocks apoptosis and complement activation.
- Reduces T-cell mediated immune clearance.
- Delayed immune recognition allowing viral transmission.

According to comparative studies, Clade I isolates have enhanced immune suppression abilities as well as greater evasion of the immune system leading to severe clinical symptoms and increased virulence levels. On the other hand, Clade II strains seem to have evolved strategies for long-term transmission and delaying their detection by the immune system rather than evolving high virulence levels<sup>16</sup>. The above differences in interaction with the immune system could be the cause of their greater spread and human transmission.

### **3. GENETIC MUTATIONS, EVOLUTIONARY ADAPTATION AND VIRAL FITNESS**

Genetic mutations and adaptation are crucial factors in establishing the virulence, transmission efficacy, and epidemiological characteristics of the MPXV. Based on the latest genomics research, MPXV has been found to be continually evolving due to genetic mutation, adaptation to hosts, and immune selection<sup>17</sup>. The appearance of new strains, especially in Clade II, has sparked fear that it may lead to increased human-to-human spread, prolonged duration of survival, and increased viral fitness. Thus, knowledge about the mutation profile and evolution of the MPXV virus will help predict future outbreaks and improve surveillance efforts.

#### **3.1 Genetic Mutation Landscape of MPXV**

Genomic studies carried out in the recent past have revealed that MPXV has a mutable genomics landscape whereby mutational changes occur during transmission through humans. Even though MPXV is a double-stranded DNA virus that has more genome stability than RNA viruses, recent cases have exhibited an accelerated rate of mutations<sup>18</sup>. The mutational events identified in circulating strains involve substitution, insertion, deletion, and genomic rearrangement involving genes coding for replication, virulence, interaction with the host, and immune modulation. These mutational events play an important role in virus adaptation and epidemiology.

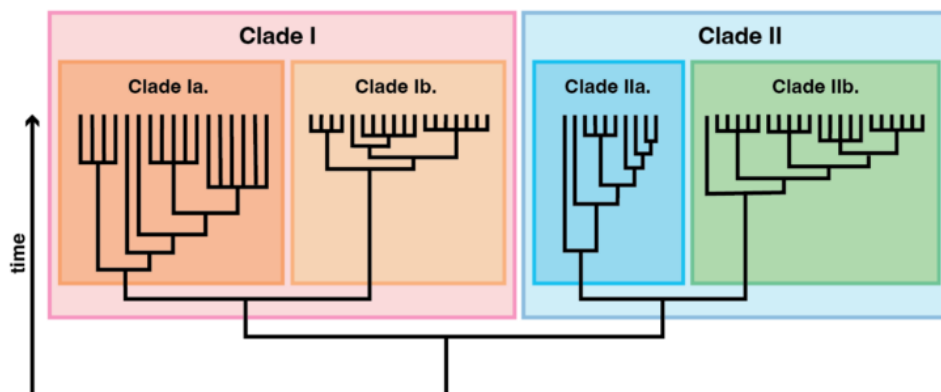
An important discovery concerning recent MPXV evolution is the emergence of APOBEC3-related hypermutations<sup>19</sup>. The term APOBEC3 refers to a group of cytidine deaminases which are capable of causing cytosine-to-thymine mutations in viral genetic material as an innate immunity mechanism. But the long-term interaction of MPXV with these enzymes in the context of repeated human-to-human transmission has led to unique mutation patterns, especially among the strains from Clade IIb that were identified during the 2022 outbreak. These mutations have increased the speed at which virus evolves and may aid transmission between humans<sup>20</sup>.

Apart from APOBEC3-induced mutations, there have been several studies reporting SNP sites and hotspot mutations at various genomic locations of MPXV. Many of the identified mutations appear to occur at locations harboring immune evasion, virulence regulatory, and adaptation genes<sup>21</sup>. Mutation hotspots at genomic sites that code for viral envelope proteins and immunomodulation functions have recently been reported in outbreaks of MPXV strains, implying that

selective pressures might lead to adaptive mutations in these viruses. Accumulated mutations could play a role in pathogenesis, transmission efficiency, and fitness of the virus, hence leading to diversity in MPXV lineages<sup>22</sup>.

### 3.2 Evolutionary Dynamics of Clade I and Clade II

The evolution of the MPXV is shaped by its constant genetic changes, adaptation to hosts, and selective environment. As evidenced by phylogenetic analyses, Clades I and Clade II have taken different evolutionary paths, leading to differences in their virulence, transmissibility, and epidemiology<sup>23</sup>. The emergence of Clade IIb viruses in recent outbreaks indicates further adaptations of MPXV to humans via mutational changes and evolution.



**Figure 2:** Phylogenetic classification of Mpxv virus Clade I and Clade II variants

#### 🚩 Clade I

Clade I, which originated in Central Africa, is referred to as being the more virulent strain of MPXV and is marked by increased virulence and increased mortality rates<sup>24</sup>. According to phylogenetic analysis, Clade I shows relative genomic stability, with few adaptations in its DNA in comparison to the recent strains of Clade II. Nevertheless, Clade I does have some virulent characteristics within its genome that promote the development of systemic disease, increased immune suppression, and tissue dissemination.

Evolutionary dynamics of Clade I would be affected by selection pressure from host immune systems as well as environmental interactions in endemic regions. Virulence-related genes would increase viral replication efficiencies and counteract host immune defense mechanisms leading to increased pathogenicity. Although Clade I was associated with lower rates of sustained human-to-human transmission relative to Clade II in history, endemic circulation could facilitate mutation buildup and further adaptation<sup>25</sup>.

#### 🚩 Clade II

Clade II viruses, especially Clade IIb viruses, which led to international outbreaks following 2022, have exhibited a high degree of evolutionary diversity and improved adaptations to the human host. Genetic analysis has revealed considerable mutations among Clade II viruses, suggesting sustained person-to-person transmission and rapid evolution of the virus. The

emergence of Clade IIb viruses was an epidemiologic breakthrough since it involved efficient and sustained human transmission.

There are several ways in which Clade II viruses have evolved to adapt. One is through a mechanism known as the genomic accordion effect where genes temporarily duplicate and then the genome undergoes contraction under the pressure of selection<sup>26</sup>. In addition, hypermutations due to APOBEC3 and selective pressures from the immune system have driven adaptive mutations that have facilitated immune evasion and sustained transmission, thus enhancing their ability to spread globally.

### 3.3 Impact of Genetic Mutations on Viral Fitness

The viral fitness of MPXV is greatly impacted by genetic mutations since these affect the efficacy of replication, adaptation to new environments, resistance to immune mechanisms, dissemination ability, and environmental stability. Fitness of a virus is defined as the ability of the virus to thrive and survive in terms of its replication, dissemination, and sustained transmission in a particular host population. In recent genomic analyses, some adaptive mutations found in circulating strains of MPXV have been associated with the increased ability to sustain themselves under immune and environmental stresses<sup>27</sup>. The increasing number of mutations found in Clade II strains especially worries scientists about MPXV's potential for long-term adaptation to human beings.

- **Replication efficiency:** Mutations in genes involved in the replication of the virus can increase the efficiency of viral DNA synthesis, assembly within the host cell, and production of virions. Increased replication efficiency leads to increased viral loads within the host and increased dissemination from infected individuals to adjacent cells or organs. Some selected mutations present in new Clade II lineages have been thought to lead to prolonged viral shedding and spread in humans.
- **Host adaptation:** Adaptation to the host through mutation will allow MPXV to be more compatible with human cell receptors. Circulating strains could adapt through mutation to be better able to survive in the human host without relying on zoonotic transmission loops. The recent development of MPXV Clade IIb strains that can infect one another easily indicates that the virus is developing the necessary genetics for successful human propagation.
- **Environmental stability:** Genetic mutations may affect the stability of virus particle structure in varying environmental conditions. Environmental stability ensures that the virus retains its ability to infect for a longer period of time when present on contaminated surfaces<sup>28</sup>. Mutations occurring in the structural proteins of the virus or in the virion itself may play an important role in the spread of MPXV.
- **Viral persistence:** Some mutations could help the virus remain persistent in infected people by weakening their immunity and slowing the process of eliminating the infection. The persistence of the virus will help prolong its infectivity and increase chances of transmitting the disease to other people. Additionally, persistence of the infection creates further chances for mutations to occur.

- **Immune adaptation and fitness enhancement:** Mutations that occur within immune-modulating genes can help increase the effectiveness with which MPXV is able to escape from host anti-viral defenses and responses to inflammation. Immune adaptation makes it possible for MPXV to remain effective at replicating itself even when both innate and adaptive immunity are triggered. All of these adaptations together have made it easier for MPXV to spread.

#### 4. HUMAN-TO-HUMAN TRANSMISSION, EPIDEMIOLOGICAL SURVEILLANCE AND PUBLIC HEALTH CHALLENGES OF MPOX VIRUS

The international spread of MPXV that occurred during recent epidemics has brought attention to issues concerning the need for knowledge about transmission dynamics, surveillance systems, diagnostic approaches, and preparedness measures. Recent epidemiology, unlike previous localized outbreaks, has shown continuous human-to-human transmission of MPXV on a global scale, especially those genetically adaptable Clade IIb strains. This situation has caused concern about improved transmission potential, ability to persist, and growth in the size of epidemics in high-density areas. For this reason, effective surveillance systems and public health intervention strategies are crucial<sup>29</sup>.

##### 4.1 Mechanisms of Human-to-Human Transmission

Direct person-to-person transmission of MPXV is mostly via physical touch with infected people, body fluids, respiratory droplets, or any other infected material. Direct contact between two skins is still one of the most effective modes of transmission, especially during close encounters with infected individuals who have infections on their skin or mucosal lining. The virus can enter the body either through broken skin, mucous membranes, or respiratory epithelium after being exposed to an infection. This was observed in recent outbreaks where close encounters raised the chances of transmission.

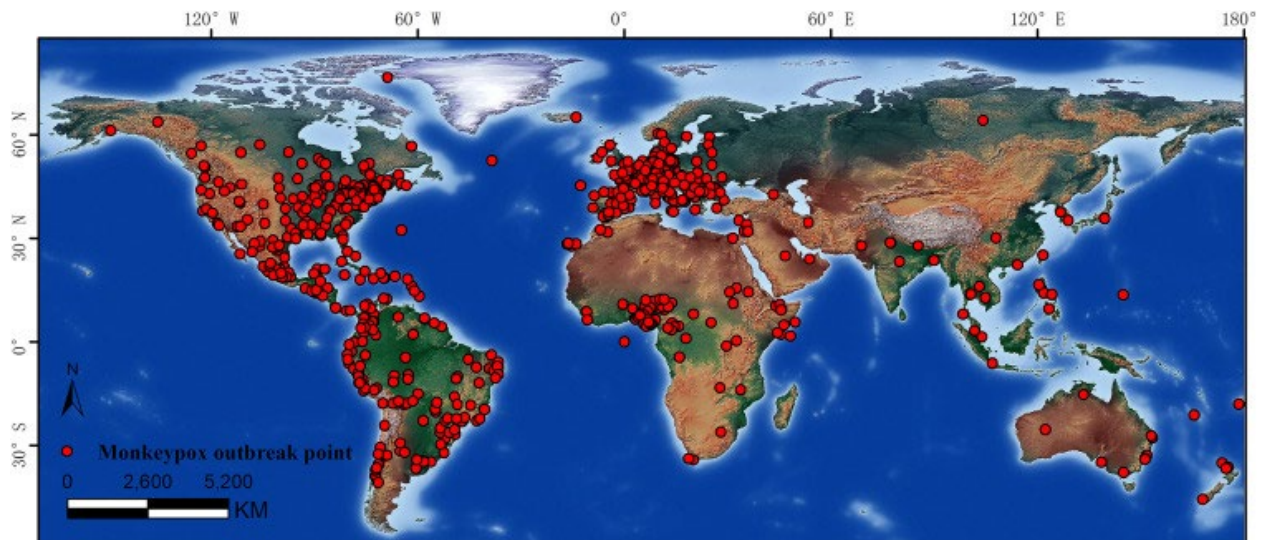
Respiratory transmission has also been identified as an important method of disease transmission for MPXV, especially during face-to-face encounters. Droplets produced during coughing, sneezing, or talking may harbor infectious virions that could infect others. Even though airborne transmission is not as efficient as direct transmission, overcrowded indoor conditions and poor infection control can contribute to the spread of the virus via this route. Furthermore, fomites in the form of clothing, linen, towels, and even medical equipment can also play a role in indirect disease transmission.

The epidemiologic studies conducted recently also pointed out the importance of sexual transmission and mild/asymptomatic infection in maintaining outbreak growth. Most of the reported cases during the multinational outbreaks were part of sexual contact networks, thereby increasing transmission speed through different nations. Moreover, patients who have atypical or mild symptoms may result in silent viral transmission due to late detection and low symptom identification capability for isolation and treatment. All the above modes of transmission account for fast global transmission and human-to-human virus transmission that has been observed in current MPXV epidemics<sup>30</sup>.

#### 4.2 Comparative Transmission Efficiency Between Clades

The transmissibility of the MPXV virus is highly different among Clade I and Clade II, mainly because of differences in terms of pathogenicity, virulence, mutation, and epidemiology. The Clade I viruses that are mainly seen in the central part of Africa are responsible for causing serious diseases. Although more virulent, Clade I variants have had relatively low levels of human-to-human transmission and have generally been restricted to endemic areas only. This is perhaps because the high levels of morbidity caused by such strains mean early detection and quarantine of patients.

However, Clade II strains, especially those belonging to the Clade IIb clade which caused the multinational outbreaks of 2022, showed much more efficient transmission rates and wider international spread. From genetic analysis, it is clear that adaptive changes in Clade II viruses improved their ability for interhuman transmission and allowed them to circulate within the population for extended periods. It is also thought that the relatively mild symptoms of Clade II infection may have aided the spread of the virus<sup>31</sup>.



**Figure 3:** Global distribution of reported Mpox virus outbreaks

A number of epidemiological variables have also served to boost transmission in recent outbreaks. Urban areas, international travel, dense social networks, and global movement provided the right environmental conditions for Clade II to spread quickly. Big cities characterized by a high density of people and inter-human contact facilitated effective transmission routes around the world<sup>32</sup>. Epidemiological comparisons also suggest that whereas Clade I is more pathogenic, Clade II has better epidemiological fitness and hence a greater capacity to create international epidemics.

#### 4.3 Epidemiological Surveillance, Diagnostic Strategies and Public Health Challenges

Surveillance for MPXV, as well as an efficient diagnostic approach, is necessary to detect any newly emerged MPXV variant, track its transmission path, and take appropriate action for controlling the infection outbreak<sup>33</sup>. Real-time and multiplex PCR assays are still vital methods for detecting and discriminating between Clade I and Clade II MPXV variants, while whole genome sequencing and phylogenetic analysis can help in monitoring the mutation rate and

dynamics of the virus. Moreover, genomic surveillance networks, international database systems, and One Health strategies are crucial to enhance disease prediction and zoonotic transmission knowledge.

Despite significant developments in molecular diagnosis and genomic surveillance technology, a number of problems exist within the field of public health that prevent efficient prevention of mpox outbreaks. These include issues relating to disease identification, efficiency in reporting, healthcare access, and the ability to implement strategies for outbreak prevention.

- **Limited healthcare infrastructure:** Limited laboratory facilities, scarcity of skilled health practitioners, and limited access to health facilities make it difficult to diagnose and manage mpox cases quickly, especially in endemic areas.
- **Underreporting and surveillance gaps:** Poor quality of reporting mechanisms and lack of diagnostics leads to under-reporting of cases, making it hard to determine disease burden and transmission dynamics.
- **Social stigma and delayed diagnosis:** Fear of being discriminated against and ignorance may prevent infected people from accessing medical help in time, thus making undetected transmission in the community more likely<sup>34</sup>.
- **Challenges in endemic countries:** Insufficient public health funding, lack of genomic sequencing capacity, and inadequate healthcare investment still pose challenges to the effectiveness of surveillance and outbreak response in endemic regions.
- **Global preparedness limitations:** Uneven vaccine distribution, insufficient global collaboration, and lack of antiviral treatments remain a barrier to improved global readiness and response strategies to combat MPXV.

## 5. DISCUSSION

As mentioned in the present review, the significance of MPXV as a zoonotic pathogen with the ability to adapt and spread among humans is rising from a scientific as well as public health perspective. Comparison of Clade I with Clade II shows substantial dissimilarities in relation to pathogenesis, transmission, mutations, and disease pattern. Outbreaks of recent times have highlighted the need for understanding the significance of genome changes, immune evasion techniques, and surveillance systems in relation to outbreaks of MPXV. These observations offer vital information in understanding the emergence of MPXV variants.

**Table 1:** Summary of Selected Literature on Mpox Virus Variants, Genomic Surveillance, and Therapeutic Strategies

Author(s) & Year	Study Focus	Key Findings	Relevance to Present Review
Van Dijck et al. (2024) <sup>35</sup>	Tecovirimat resistance	Reported concerns regarding emerging antiviral resistance in mpox treatment.	Supports discussion on therapeutic limitations and antiviral surveillance.

Wang et al. (2024) <sup>36</sup>	Global MPXV transmission	Highlighted rapid international spread linked with human mobility and transmission networks.	Supports analysis of transmission dynamics and global dissemination of Clade II.
WHO (2025) <sup>37</sup>	Genomic surveillance	Provided guidelines for genomic sequencing and phylogenetic monitoring of MPXV.	Reinforces the importance of genomic surveillance and mutation tracking.
Yadesa Tesema (2025) <sup>38</sup>	Mpox control challenges	Identified healthcare and surveillance limitations in developing countries.	Supports discussion on public health challenges and preparedness gaps.
Yuan et al. (2025) <sup>39</sup>	Nanoparticle vaccine development	Demonstrated protective efficacy of a single-dose nanoparticle vaccine against MPXV.	Supports the review's discussion on vaccine advancement and preventive strategies.

### 5.1 Interpretation and Analysis of Findings

The results obtained from the current review reveal that MPXV has evolved genetically to a great extent with adaptive evolution being noted more in Clade II variants involved in global epidemics post 2022. The pathogens belonging to Clade I have been implicated for high pathogenicity and mortality, while Clade II strains possess better human-to-human transmissibility and geographic spread. The occurrence of hypermutation caused by APOBEC3 enzymes and mutation hotspots indicates continuous viral adaptation and increased epidemiological fitness. Moreover, technological progress in genome sequencing and surveillance technologies has provided new insights into MPXV evolution, epidemiology, and spread.

### 5.2 Implications and Significance

Consequently, the increased adaptation of MPXV to humans is highly significant from the viewpoint of global public health preparedness in anticipation of future outbreaks. Human-to-human infection and continued genetic mutations will lead to further outbreaks with increased chances of spreading geographically. The results highlight the importance of enhanced molecular diagnostic techniques, genomic surveillance, vaccine development, and antiviral research in order to efficiently monitor emerging strains of MPXV<sup>40</sup>. In addition to that, One Health initiatives, international cooperation, swift exchange of genomic information, and even distribution of healthcare resources worldwide are all key elements in this regard.

### 5.3 Research Gaps and Limitations

Although substantial efforts have been made to understand the evolution and epidemiology of MPXV infection, there are still various research questions and deficiencies. Existing research largely relies on genomic and epidemiological data, which restricts insight into how specific

mutations contribute to viral pathogenesis or transmissibility. Lack of surveillance, under-reporting of cases, and poor sequencing facilities in endemic areas remain key impediments to the comprehensive evaluation of MPXV variants. Moreover, inadequate longitudinal and comparative research on Clades I and II indicate the necessity for multidisciplinary research into the subject.

#### 5.4 Future Research Directions

Future research needs to concentrate on identifying and characterizing the functions of adaptive mutations in relation to new MPXV strains to gain insights into how they impact viral replication, immune escape mechanisms, transmission rates, and pathogenicity. Genomic surveillance using bioinformatics and phylogenetic methods can contribute significantly to predicting an outbreak and understanding virus evolution. Additional research is required to test vaccine effectiveness and drug resistance as well as assess immune responses against various MPXV clades. Building genomic sequencing capabilities, global surveillance cooperation, and developing treatment options based on specific clades can greatly benefit future mpox outbreaks.

#### 6. CONCLUSION

This research points out the important differences in genetic, molecular, and epidemiological aspects of MPXV clades I and II, highlighting their unique characteristics related to pathogenicity, efficiency of transmission, and evolutionary patterns. While clade I continues to cause high morbidity and mortality, clade II shows increased human-human transmission and wider global spread because of adaptation and increased fitness of the virus. The article also emphasizes the key role of genomics and mutation surveillance, molecular diagnosis, vaccination programs, and One Health approaches in disease surveillance and control. Enhanced cooperation among countries, increased genome sequencing capabilities, and enhanced readiness in public health institutions will play an important role in preventing future mpox outbreaks and reducing health risks related to novel MPXV strains.

#### REFERENCES

1. Akingbola, A., Abiodun, A., Idahor, C., Peters, F., Ojo, O., Jessica, O. U., ... & Chuku, J. (2025). Genomic evolution and epidemiological impact of ongoing clade Ib MPox disease: a narrative review. *Global Health, Epidemiology and Genomics*, 2025(1), 8845911.
2. Alcamí, A. (2023). Pathogenesis of the circulating mpox virus and its adaptation to humans. *Proceedings of the National Academy of Sciences*, 120(13), e2301662120.
3. Andrei, G., & Snoeck, R. (2023). Differences in pathogenicity among the mpox virus clades: impact on drug discovery and vaccine development. *Trends in Pharmacological Sciences*, 44(10), 719-739.
4. Anjorin, A. A. A., Odetokun, I. A., Ashaka, O. S., Fadipe, T. O., Muhammad, A., Sogbanmu, T. O., ... & Ibrahim, M. A. (2023). Critical appraisal of mpox (monkeypox) in Africa using scoping and systematic reviews: Epidemiology, biochemistry, phylogeny, pathogenesis, clinical features, diagnosis, treatment, biosecurity and one-health.
5. ASSESSMENT, R. R. (2024, August). Risk assessment for the EU/EEA of the mpox epidemic caused by monkeypox virus clade I in affected African countries.

6. Bhojani, M. S., & Bhojani, M. F. (2025). The emerging pandemic threat of H5N1: Evolutionary adaptations for human transmission, zoonotic spillovers and surveillance gaps. *Gene*, 149723.
7. Brooks, J. T., Reynolds, M. G., Torrone, E., McCollum, A., Spicknall, I. H., Gigante, C. M., ... & Hutson, C. L. (2024). How the orthodox features of orthopoxviruses led to an unorthodox mpox outbreak: what we've learned, and what we still need to understand. *The Journal of Infectious Diseases*, 229(Supplement\_2), S121-S131.
8. Brooks, J. T., Reynolds, M. G., Torrone, E., McCollum, A., Spicknall, I. H., Gigante, C. M., ... & Hutson, C. L. (2024). How the orthodox features of orthopoxviruses led to an unorthodox mpox outbreak: what we've learned, and what we still need to understand. *The Journal of Infectious Diseases*, 229(Supplement\_2), S121-S131.
9. Carabelli, A. M., Peacock, T. P., Thorne, L. G., Harvey, W. T., Hughes, J., COVID-19 Genomics UK Consortium de Silva Thushan I. 6, ... & Robertson, D. L. (2023). SARS-CoV-2 variant biology: immune escape, transmission and fitness. *Nature Reviews Microbiology*, 21(3), 162-177.
10. Ezediuno, L. O., Ockiya, M. A., Taofeek, O. O., Senbadejo, T. Y., Elcanah, E. M., & Adeola, S. O. (2025). Genomic Diversity and Regional Epidemiologic Dynamics of mpox Clade II in Nigeria (2017–2024). *Zoonoses*, 5(1), 975.
11. Guterres, A., & Abraham, M. (2025). Importance of emerging lineages of monkeypox virus: an updated narrative. In *The Scientific Basis of Mpox (Monkeypox)* (pp. 59-74). Academic Press.
12. Hill, V., Githinji, G., Vogels, C. B., Bento, A. I., Chaguza, C., Carrington, C. V., & Grubaugh, N. D. (2023). Toward a global virus genomic surveillance network. *Cell Host & Microbe*, 31(6), 861-873.
13. Huang, C. Y., Su, S. B., & Chen, K. T. (2025). A review of epidemiology, diagnosis, and management of Mpox: The role of One Health. *Global health & medicine*, 7(1), 1-12.
14. Irfan Khan, M., Saleh, A. A., Ali, R., Jan, R. U., Gu, J., & Dejun, J. (2025). The evolving mpox threat (2022-2024): clade dynamics, immune evasion, and escalating global health challenges. *Frontiers in Cellular and Infection Microbiology*, 15, 1677762.
15. Kumar, S., Guruparan, D., & Karuppanan, K. (2023). Recent advances in monkeypox (mpox): characterization, diagnosis, and therapeutics-a multidimensional review. *Authorea Preprints*.
16. Kumar, S., Guruparan, D., Karuppanan, K., & Kumar, K. S. (2024). Comprehensive insights into monkeypox (mpox): recent advances in epidemiology, diagnostic approaches and therapeutic strategies. *Pathogens*, 14(1), 1.
17. Lam, T. T. Y., Zhu, H., Guan, Y., & Holmes, E. C. (2016). Genomic analysis of the emergence, evolution, and spread of human respiratory RNA viruses. *Annual review of genomics and human genetics*, 17(1), 193-218.
18. Lessani, M. N., Li, Z., Jing, F., Qiao, S., Zhang, J., Olatosi, B., & Li, X. (2024). Human mobility and the infectious disease transmission: a systematic review. *Geo-Spatial Information Science*, 27(6), 1824-1851.
19. Linh, D. T., & Shabbir, M. N. (2025). Monkeypox in the 21st century: Insights into its pathogenesis and public health implications. *Journal of Virological Methods*, 115223.

20. Mani, S., Ganesan, A., Arunagiri, T., Kumaran, V. R., Kannaiah, K. P., Vellapandian, C., & Chanduluru, H. K. (2024). Epidemiology, virology, and mutation landscape of monkeypox virus from past to present. *Cureus*, 16(8).
21. Monzón, S., Varona, S., Negrodo, A., Vidal-Freire, S., Patiño-Galindo, J. A., Ferressini-Gerpe, N., ... & Palacios, G. (2024). Monkeypox virus genomic accordion strategies. *Nature Communications*, 15(1), 3059.
22. Monzon-Fernandez, S., Varona Fernandez, S., Negrodo, A., Vidal-Freire, S., Patiño-Galindo, J. A., Ferressini-Gerpe, N., ... & Palacios, G. (2024). Monkeypox virus genomic accordion strategies.
23. Moss, B. (2024). Understanding the biology of monkeypox virus to prevent future outbreaks. *Nature microbiology*, 9(6), 1408-1416.
24. Mushebenge, A. G. A., & Mphuthi, D. D. (2025). Emerging Insights into Monkeypox: Clinical Features, Epidemiology, Molecular Insights, and Advancements in Management. *BioMed*, 5(3), 21.
25. Ochieng, M., Kiboi, D., Nasimiyu, C., Osoro, E., Omoga, D. C., & Kuja, J. O. (2025). Phylogenetic Analysis of the Mpox Virus in Sub-Saharan Africa (2022–2024). *Biology*, 14(7), 773.
26. Ogunlaja, A., & Oginni, O. (2022). Molecular epidemiology and phylodynamics of emerging and re-emerging viral infections: Implications for surveillance and control. *Inter J Res Publicat Rev*, 6(2), 2924-41.
27. Probert, W. S., Espinosa, A., & Hacker, J. K. (2025). Clade I or clade II? Targeting essential viral genes to differentiate monkeypox virus clades by multiplex real-time PCR. *Frontiers in Public Health*, 13, 1626030.
28. Scarpa, F., Azzena, I., Ciccozzi, A., Branda, F., Locci, C., Perra, M., ... & Sanna, D. (2024). Update of the genetic variability of monkeypox virus clade iib lineage b. 1. *Microorganisms*, 12(9), 1874.
29. Shi, C., Zheng, X., Lei, L., Xiao, J., Yu, G., Li, Y., ... & Wang, Q. (2025). Phylogenetic and Molecular Evolutionary Insights into Monkeypox Virus Circulation in Shenzhen, China, 2023–2024. *Viruses*, 17(9), 1214.
30. Song, K., Brochu, H. N., Zhang, Q., Williams, J. D., & Iyer, L. K. (2023). An in silico analysis of PCR-based Monkeypox virus detection assays: a case study for ongoing clinical surveillance. *Viruses*, 15(12), 2327.
31. Srivastava, S., Laxmi, Sharma, K., Sridhar, S. B., Talath, S., Shareef, J., ... & Sah, R. (2024). Clade Ib: a new emerging threat in the Mpox outbreak. *Frontiers in pharmacology*, 15, 1504154.
32. Srivastava, S., Sharma, D., Sridhar, S. B., Kumar, S., Rao, G. K., Budha, R. R., ... & Rodriguez-Morales, A. J. (2025). Comparative analysis of Mpox clades: epidemiology, transmission dynamics, and detection strategies. *BMC infectious diseases*, 25(1), 1290.
33. Sukhdeo, S., Mishra, S., & Walmsley, S. (2022). Human monkeypox: a comparison of the characteristics of the new epidemic to the endemic disease. *BMC infectious diseases*, 22(1), 928.
34. Thornhill, J. P., Gandhi, M., & Orkin, C. (2024). Mpox: the reemergence of an old disease and inequities. *Annual Review of Medicine*, 75(1), 159-175.

35. Van Dijk, C., Crozier, I., Vercauteren, K., Brosius, I., Mbala-Kingebeni, P., Dodd, L., ... & Liesenborghs, L. (2024). Beware of drug resistance: let's not lose tecovirimat against mpox. *Clinical Microbiology and Infection*, 30(3), 276-278.
36. Wang, Y., Leng, P., & Zhou, H. (2024). Global transmission of monkeypox virus- a. *COVID and Emerging Infectious Diseases*.
37. World Health Organization. (2025). Analytical considerations for genomic surveillance of mpox virus. World Health Organization.
38. Yadesa Tesema, M. (2025). Mitigation approaches of monkeypox outbreaks in developing countries. *Discover Viruses*, 2(1), 4.
39. Yuan, R. Y., Li, M. J., Lin, X. B., Zhang, X., Yu, F., Zhang, X., ... & Kang, Y. F. (2025). A single-dose nanoparticle vaccine protects against mpox in preclinical models. *Cell Reports*, 44(10).
40. Zahmatyar, M., Fazlollahi, A., Motamedi, A., Zolfi, M., Seyedi, F., Nejadghaderi, S. A., ... & Safiri, S. (2023). Human monkeypox: history, presentations, transmission, epidemiology, diagnosis, treatment, and prevention. *Frontiers in Medicine*, 10, 1157670.