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Review

Emerging Insights into Monkeypox: Clinical Features, Epidemiology, Molecular Insights, and Advancements in Management

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Abstract

Monkeypox (Mpox), a re-emerging zoonotic disease, has garnered global attention due to its evolving epidemiology, diverse clinical manifestations, and significant public health impact. The rapid international spread of the Mpox prompted the World Health Organization to designate the outbreak as a Public Health Emergency of International Concern. Accurate and timely diagnosis is hindered by its critical resemblance to other *orthopoxviruses* and viral exanthems, underscoring the need for improved diagnostic tools. Point-of-care diagnostic innovations, including CRISPR-based and smartphone-integrated technologies, have revolutionized outbreak management, offering rapid and accurate detection critical for containment and treatment. The effective control of Mpox outbreak underscores the necessity of strengthened global surveillance, equitable healthcare access, rapid diagnostics, the prompt isolation of infected individuals, and the implantation of ring vaccination strategies. The integration of a "One Health" framework that links human, animal, and environmental health is vital for sustained preparedness. Advances in vaccine development, including novel bionic self-adjuvating vaccines and platforms utilizing DNA, mRNA, and viral vectors, highlight promising prevention efforts. However, issues such as vaccine hesitancy, limited immunization coverage and accessibility in resource-constrained regions remain significant barriers. Therapeutic interventions like tecovirimat and the JYNNEOS vaccine demonstrate efficacy but face challenges in scalability and deployment. To address these multifaceted challenges, this review delves into the molecular insights, clinical features, epidemiological trends, and diagnostic challenges posed by Mpox. This review further highlights the critical need for robust scientific evidence and sustained research to inform effective, evidence-based responses, and long-term management strategies for Mpox outbreaks.

Keywords: monkeypox; pathogenesis; diagnostic innovations; vaccine development; drug repurposing; public health interventions

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1. Introduction

Recently, the attention directed at the disturbing global resurgence of monkeypox (Mpox) has been growing significantly. Mpox is a zoonotic disease caused by the Mpox virus (MPXV). It re-emerged in August 2022 and is found in Central and Western Africa [1,2]. The first incidence of MPXV was in 1970 in the Democratic Republic of Congo (DRC). This outburst was classified under the outbreak category and since then has been known to

target individuals against the backdrop of forest environments, where the human pollutants frequently interact with infectious animal reservoirs [3] (https://www.ecdc.europa.eu/en/all-topics-z/monkeypox/factsheet-health-professionals, accessed on 14 August 2025). The period succeeding the first outbreak saw Mpox become a serious concern, with its sporadic outbreaks; however, the major spike over the past few years has aggravated the situation [4,5]. Mpox resurgence raises increased concern for global health, which calls for attention in molecular, clinical, and epidemiological domains [6].

Following the end of smallpox epidemics in 1980 and the subsequent cessation of vaccination against it, lifestyle gaps in protection from *orthopoxviruses* undoubtedly contributed to the enhanced resurgence of Mpox [7,8]. The affected region is the DRC, a country with dispersed rural societies, generally having contact with infected wildlife reservoirs, in this case rodents and non-human primates [9,10]. Previously, Mpox was a mainly zoonotic disease, with humans only being able to transmit the disease among family members [11]. Conversely, the recent emergence and re-emergence of Mpox cases suggests a worrying development in that there appears to be an increasing trend towards efficient human-to-human transmission directly through body fluid, lesions, and contaminated materials [12]. Furthermore, zoonotic spillover events have been made easier by ecological changes like deforestation as well as the rapid movement towards urbanization and globalization, alongside mass gathering events that have made it especially easier for the disease to spread across borders. This recent development has raised some important concerns about factors involved in the spread of the disease and sufficient control measures [13].

Developments in genomic technologies have resulted in an enhanced understanding of MPXV, its evolutionary history, and its genetic and antigenic properties [14,15]. Genomic studies show that MPXV consists of two subtypes: Clade I and Clade II. Clade I is mostly restricted to central Africa, while Clade II is predominant found in West Africa [15]. Clade I, however, has been documented to have a greater mortality and virulence than Clade II [15,16]. On the other hand, genomic data from recent outbreaks which occurred outside of Africa showed potential mutations that could increase the virus's adaptive capabilities as well as diminish the host's immune response [15]. The 2022 outbreak in the US and other Western countries, to the disease is not endemic, evidenced the viruses plastically and displayed their genomic surveillance weaknesses [15]. Targeting genetic logic is critical in the formulation of relevant therapeutics and vaccines.

Global health systems are faced with the task of diagnosing, containing, and eradicating Mpox while addressing its emergence as a zoonotic disease [17,18]. In the DRC, Mpox control and preventive measures have formed part of extensive research aimed at understanding the dynamics of endemic diseases [15,19]. Vaccines and other public actions, like contact tracing and constructive behavior, have played a significant role in reducing transmission in local settings [20]. However, increasing reports of urban Mpox outbreaks in endemic and non-endemic locations have shown the weaknesses of existing containment strategies and approaches [15]. The economic costs of the outbreaks, together with the mental health effects on the affected population, call for a proper and holistic response [21].

This review sheds light on the preventive measures that could aid Mpox treatment as well as the other contributing factors causing Mpox's increased re-emergence. A comprehensive literature search was conducted across major databases (Google Scholar, Scopus, PubMed, Web of Science, and preprints, among others) and publisher archives up to July 2025, targeting English-language full-text articles on human Mpox research. Keyword searches combined "monkeypox" or "mpox" with epidemiology, clinical features, molecular insights, treatment, and public health. Non-human studies, cases reports, commentaries, and methodological papers were omitted. The final selection focused on cutting-edge research, directly addressing advancements in Mpox. The review underscores the need for

an integrated global response for Mpox by considering its clinical presentations, epidemiological trends, molecular features, and new developments in its management. Additionally, authors present a more holistic approach to understanding and controlling this re-emerging zoonosis. Lessons learned from the DRC and other endemic areas emphasize collaboration and evidence-based interventions. The world can only reduce the burden of Mpox through interdisciplinary research and international collaboration and prepare for future zoonotic threats.

2. Clinical Description of Mpox

Mpox could clinically be described under three subtypes such as typical symptoms and stages of disease progression, comparison with other *orthopoxviruses* infections, and emerging atypical clinical manifestations in recent outbreaks. Mpox disease typically is marked by defining clinical features and the presence of definable stages [22]. The median incubation period of 7 to 10 days is usually followed by prodromal symptoms. The percentage occurrences of these symptoms are 23% to 57% (malaise), 25% to 55% (headache), 31% to 55% (myalgias), 56% to 86% (lymphadenopathy), and 62% to 72% (fever), respectively [23,24]. These systemic symptoms are often followed by the appearance of characteristic mucocutaneous rashes that progress through four stages: macules, papules, vesicles, and pseudo-pustules [23,24]. The pseudo-pustules crusted over in 2 to 4 weeks and healed, leaving residual scarring. The distribution of lesions is variable but includes the face, palms, soles, and mucous membranes [25,26]. The rash is usually a pathognomonic sign that clinically helps in the differential diagnosis of Mpox from some other vesiculopustular diseases, like chickenpox or smallpox. In immunocompromised people, especially those with more advanced HIV infections, the condition can be heavier, with wide areas of lesions, and higher risks of complications [27]. Predominant clinical manifestations identified in recent outbreaks, such as pronounced lymph node swelling among others (see Table 1 below), help in differentiating Mpox from similar conditions like varicella, measles, and herpes simplex. Including key differential diagnoses supports accurate clinical assessment and timely isolation to prevent further transmission.

Table 1. Clinical features of Mpox with their frequency in recent outbreaks and key differential diagnoses.

Clinical Feature/Sign	Estimated Frequency in Mpox Cases (%)	Key Differential Diagnoses	Refs
Skin lesions (papules → vesicles → pseudo-pustules): Lesion count, non-endemic: 1–20 lesions- Endemic: >10 lesions (often >100): Lesions at different stages often present simultaneously	95%	Chickenpox, smallpox, herpes zoster, molluscum contagiosum, HSV-1/2, Varicella-zoster, eczema vaccinatum, syphilis, scabies	[28,29]
Anogenital lesions (clustered, painful, localized vesicles, often in genital areas)	36–73%	HSV, syphilis (chancre, *condyloma lata*), LGV, chancroid	[23,30]
Perioral/oral lesions (clustered, painful, localized vesicles, often in oral areas)	14–25%	Herpes simplex, aphthous ulcers	[31]
Fever	~58% (Common but less frequent than in endemic cases)	Influenza, measles, mononucleosis, Varicella-zoster, measles, bacterial lymphadenitis, EBV, CMV, HIV, bacterial infections, Influenza	[23]

Table 1. *Cont.*

Clinical Feature/Sign	Estimated Frequency in Mpox Cases (%)	Key Differential Diagnoses	Refs
Lymphadenopathy (inguinal/submandibular)	~53% inguinal (Common but less frequent than in endemic cases)	HIV acute, *streptococcal pharyngitis*, bacterial infections, Varicella-zoster, measles, bacterial lymphadenitis, EBV, CMV, HIV, bacterial infections, Influenza	[23,32]
Proctitis/rectal pain (anal pain/inflammation)	15–30% in MSM	STI-related proctitis (LGV, gonorrhea, chlamydia, HSV)	[33,34]
Headache, myalgia, fatigue	Common but unquantified	Influenza, COVID-19, EBV	[23]
Polymorphic lesion stages (uneven)	Common	Unlike synchronous vaccination reactions	[23,35]
Cough	~26–38%	Influenza, adenovirus, pertussis	[23,36]
Ocular symptoms (conjunctivitis, etc.)	5–16%	Conjunctivitis, herpes simplex ocular infection	[23]

3. Pathogenesis and Transmission of Mpox and Related *Orthopoxviruses*

Mpox pathogenesis involves the virus' transmission from likely sources, primarily infected animals, to humans via close contact or the handling of those animals. MPXV relies on the cytoplasm of host cells instead of the nucleus [37]. Numerous viral processes, such as gene expression, replication and proliferation, and virion maturation, occur in the host cytoplasm. The processed virus particles move to the endoplasmic reticulum to be enveloped with bilayer lipid membranes in order to be fully equipped for the transmission and dissemination of infections, as illustrated in Figure 1 [37].

Although Mpox generally is a self-limiting illness in most individuals, with case fatality rates of less than 0.2% in the U.S., it poses substantive risks to severely immunocompromised individuals and those with comorbid conditions, in whom systemic symptoms may be more pronounced, and lesions may coalesce into ulcers [23,38,39]. The management of Mpox is largely supportive, including analgesics for symptom relief and skin care to prevent secondary infections [23]. The polymerase chain reaction testing of lesions remains the diagnostic gold standard, facilitating the early identification and containment of outbreaks [40]. Preventive measures include vaccination with two-dose Modified Vaccinia Ankara-Bavarian Nordic vaccine, which shows an efficacy ranging from 66% to 86%, particularly among the high-risk population [41,42]. While no FDA-approved antivirals specifically target Mpox, agents such as tecovirimat, brincidofovir, and vaccinia immune globulin intravenous are accessible through expanded access programs for use in serious cases or vulnerable populations [43,44].

Furthermore, the *Orthopoxvirus* genus of the *Poxviridae* family includes several human pathogens, such as Variola virus (VARV), MPXV, Cowpox virus (CPXV), Camelpox virus (CMLV), and Vaccinia virus (VACV) [45,46]. These zoonotic viruses are often isolated from animals in close proximity to humans, such as, cows, buffaloes, camels, and monkeys, though their natural reservoirs are typically wild animals [46]. Despite their names, these viruses are not always best represented by their species designation [47]. Smallpox, caused by VARV, was historically one of the most devastating infectious diseases but has been eradicated after global vaccination [48]. In contrast, MPXV is now considered the most consequential orthopoxvirus infection in the post-smallpox era [49,50]. While its clinical presentation mirrors smallpox in some aspects, it is distinguished by lymphadenopathy, lower

mortality rates of 1–10%, and its zoonotic origins, mainly African rodents [51]. The 2022 outbreak revealed an increased capacity for human-to-human transmission in non-endemic regions, like smallpox secondary attack rate, which exceeded 58%. However, MPXV continues to demonstrate a more sporadic and geographically restricted pattern [52–54].

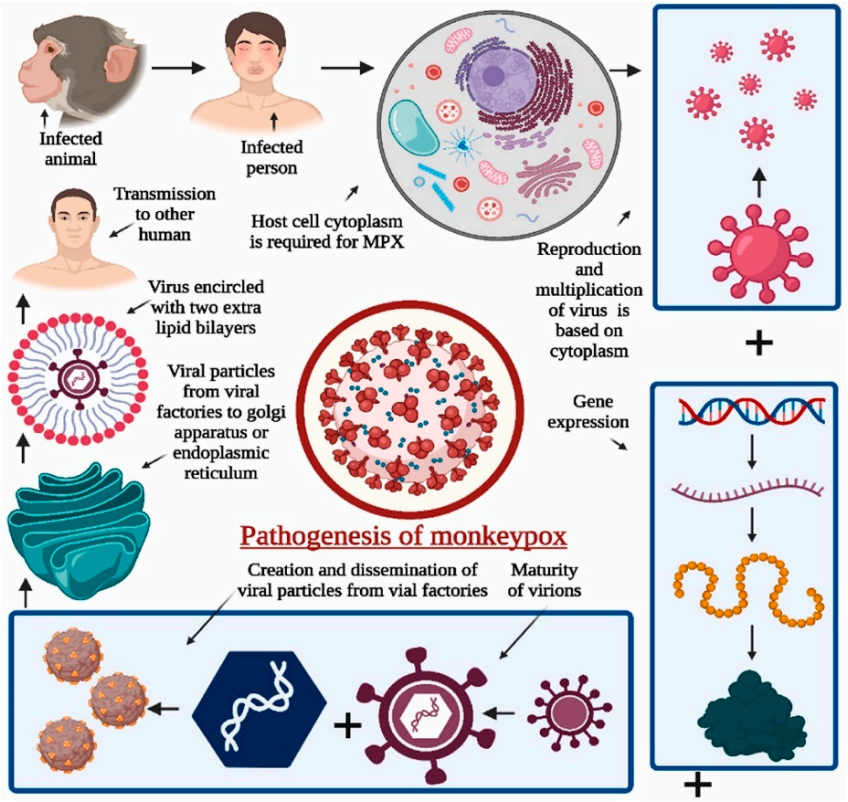


Figure 1. A schematic representation of Mpox pathogenesis and modes of transmission as adapted from the cited source: zoonotic transmission—in which the virus spreads from infected animal reservoirs, usually rodents or non-human primates, to people by direct contact, handling, or exposure to contaminated items, the main mechanism behind the pathogenesis of Mpox. Avoiding the nuclear machinery needed by many other DNA viruses, the MPXV, a member of the Orthopoxvirus genus, replicates exclusively in the cytoplasm of host cells once it has entered the human host. Important viral functions such as virion assembly, transcription, translation, and DNA replication take place in specialized cytoplasmic compartments known as "viral factories." These structures act as regional centers for the expression of viral genes and the development of their morphology. Lipid bilayers from the endoplasmic reticulum and other intracellular membranes encapsulate developing virions during maturation, promoting the formation of contagious viral particles with the ability to spread. The effective intracellular spread and immunological evasion of MPXV are based on this cytoplasmic replication technique. Since respiratory droplets and close contact are thought to be the main ways that MPXV infections propagate among humans, it is critical to comprehend their distinct replicating biology, allowing us to develop efficient treatment and containment measures [37].

Other *orthopoxviruses*, including CPXV, VACV, and CMLV, show diverse pathogenicity and host range [55]. CPXV and VACV are zoonotic, while CMLV, though rare, is phylogenetically closest to VARV [55,56]. These differences highlight Mpox's unique pathogenicity, modes of transmission, and clinical profile, as well as its role as a modern public health challenge demanding vigilant surveillance and targeted research [56]. The recent outbreaks have exposed atypical clinical features, diverting from the classified prodrome of fever, headache, myalgia, fatigue and rash that progresses from macules to crusts and typically involves the face, palms, and soles [57–59]. In addition, genital lesions appeared as initial symptoms in some 2022–2023 cases, especially

in immunocompromised individuals, men who have sex with men (MSM), and people with HIV, resulting in severe systemic symptoms with increased mortality (https://www.cdc.gov/Mpox/hcp/clinical-care/immunocompromised-people.html, accessed on 10 August 2025). Further complications include proctitis, abdominal pain, and severe systemic illnesses such as pneumonia and encephalitis, often without a typical rash presentation [50,60]. These atypical manifestations complicate diagnosis and delay timely appropriate management. Hence, healthcare systems must adopt more flexible diagnostic and therapeutic frameworks. The absence of prodromal fever or the deviation from typical rash progression necessitates a high index of clinical suspicion [61]. These insights inform diagnostic vigilance, public health interventions, and the development of robust surveillance system capable of responding to this evolving viral threat.

4. Epidemiology and Pathology of Mpox

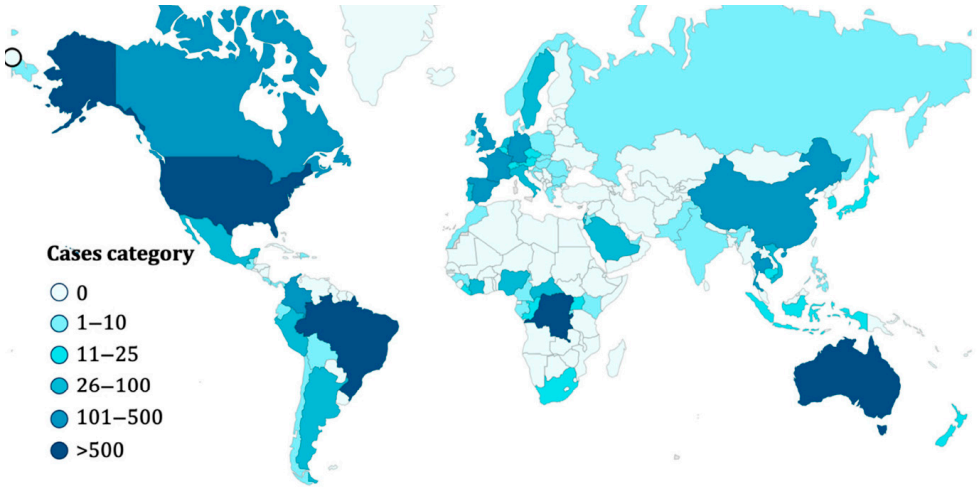
Mpox was first isolated from monkeys in Denmark in the 1950s, and the first human case was reported in 1970 in the DRC [62]. The early outbreaks were confined to Central and West Africa, with notable reservoirs in rodents and primates [63]. The virus has, however, increasingly shown the potential for worldwide spread, including the 2003 United States of America (USA) outbreak. The USA case was suspected to have emanated from imported African rodents and resulted in an unprecedented internationally widespread outbreak in 2022–2024 [25]. In addition, the recent outbreaks have highlighted by new dynamics such as sexual contact, especially among MSM, together with the more traditional modes of zoonotic and close-contact transmission [64]. The 2022–2024 epidemic has reported over 100,000 confirmed cases worldwide, with the U.S. and Brazil contributing the highest numbers [65]. In Africa, the DRC remains the epicenter (see Figure 2), reporting high mortality rates, particularly among children and pregnant women, underscoring the severe pathology of Mpox [6,66]. Public health challenges include stigma, social inequalities, and the emergence of new viral lineages, necessitating robust surveillance and advanced diagnostic tools [67]. Meanwhile, other promising avenues like wastewater monitoring and AI-driven diagnostic models are opening for better control and management of outbreaks [68].

4.1. Mpox Transmission Dynamics and Reservoirs

Recent resurgence of Mpox and its transmission dynamics has put great emphasis on its cryptic animal reservoirs, which are still unidentified, though research in this field is ongoing. Mathematical models involving stochastic Susceptible–Exposed–Infectious–Recovered models have been useful in the realization of how these reservoirs interact with human populations via direct and indirect routes of transmission [69,70]. The confirmation of its zoonotic etiology and the pinpointing of animal reservoirs is one of the major challenges to Mpox epidemiology [71]. Indeed, the fact that strains from Clades I and II of Mpox do not reliably represent animal–human interfaces, even from endemic countries, results in isolated instances of infection within wild animals [56,67]. The squirrel (*Funisciurus anerythrus*) in the DRC and sooty mangabey (*Cercocebus atys*) in Ivory Coast are critical suspected sources of Mpox re-emergence in these countries [72]. Recent studies identified *Funisciurus anerythrus* as the most likely reservoir, but this is a dynamic that is likely to shift with influences from environmental factors like deforestation, climate change, and growing human population [73,74].

Furthermore, Mpox surveillance and outbreak investigations demonstrate significant shortcomings. Even though one Mpox case defines an outbreak, extensive investigations into large outbreaks fail to notice minor frequent outbreaks that happen within the communities where herd immunity is high [75,76]. Such communities might experience no

noticeable occurrence of Mpox, meaning they can be in contact with the undiscovered Mpox reservoir, further complicating its identification [75]. It will, therefore, be important to integrate a One Health approach into the effective prevention and control of Mpox outbreaks, considering interactions between humans, animals, and the environment.



Clade I: Burundi, Central African Republic, Congo, Democratic Republic of the Congo, Kenya, Rwanda and Uganda.
Clade II: Argentina, Australia, Austria, Belgium, Bolivia, Brazil, Bulgaria, Cambodia, Canada, Chile, China, Colombia, Costa Rica, Croatia, Czechia, Côte d'Ivoire, Denmark, Dominican Republic, Ecuador, France, Germany, Greece, Guatemala, Hungary, Indonesia, Ireland, Israel, Italy, Japan, Jordan, Luxembourg, Macao, Malta, Mexico, Morocco, Netherlands, New Zealand, Nigeria, Norway, Pakistan, Panama, Peru, Philippines, Poland, Portugal, Romania, Russia, Saudi Arabia, Singapore, Slovakia, South Africa, South Korea, Spain, Switzerland, Taiwan, United Arab Emirates, United Kingdom, United States of America, and Vietnam.
Clade I & II: Cameroon, India, Sweden, and Thailand.

Figure 2. Global map of geographic distribution of confirmed MPXV infection cases reported during 2024 Mpox outbreak, based on data from CDC (1 January 2024) as adapted from cited source (https://www.cdc.gov/mpox/situation-summary/index.html, accessed on 14 August 2025) [6].

4.2. Risk Factors for Severe Outcomes and Case Fatality Rates

The MPXV infection continues to cause important public health challenges, notably because of its serious outcomes and case fatality rates. These are risks of severe outcomes among older groups, people experiencing immunosuppression, and certain sexual orientations [64]. A very high fatality rate case of 10.6% among children and adults in endemic regions, such as the DRC, is reported due to Clade I MPXV infection, leaving pregnant women particularly vulnerable [77]. Studies in Sankuru Province recorded a 75% rate of miscarriage or stillbirth among infected pregnant women [76,78,79]. In the recent outbreak affecting South Kivu Province, a fetal mortality rate of 50% was observed among pregnant women infected with Clade I MPXV, again underlining the serious consequences for maternal and fetal health [77]. Of note, people living with HIV with low CD4 counts or unsuppressed viral loads are at increased risks for severe outcomes, including hospitalization and mortality, demonstrating how Mpox disproportionately affects people with weakened immune systems [80].

The 2022–2023 Mpox outbreak around the world highlighted various epidemiological features, which included increased person-to-person transmission and changes in transmission patterns [81]. While the case fatality rate for Clade II infections was significantly lower (~0.2%), Clade I infections still have the potential to be of great concern, especially in endemic regions [26,82]. Pediatric populations are still being disproportionately affected, with higher case fatality rates among children from endemic countries compared to non-

endemic areas [60]. The outbreak has so far mainly affected MSM, who show specific clinical features and a high complication rate [83].

4.3. Recent Outbreaks and Global Prevalence

Mpox infections have resurged as a public health concern with increasing incidence in both endemic and non-endemic areas. The global outbreak of Clade II Mpox in 2022 and the continued rise in Clade I Mpox bring attention to the capacity for widespread transmission. This is further complicated by waning immunity from the cessation of smallpox vaccination, which has allowed continued human-to-human transmission and genetic mutations that complicate diagnostics and may alter virulence [75]. These developments indicate the urgent need for improved diagnostics, increased vaccine availability for outbreak response and routine use, and the development of medical countermeasures for the effective management and control of Mpox [84]. Moreover, the additional load Mpox creates for the most vulnerable populations, such as children, pregnant women, and immunocompromised individuals, requires prevention, diagnosis, and treatment-targeted strategies unique to these particular populations [12].

The recent Mpox outbreaks are being characterized by new clade identifications and the expansion of geographical boundaries, a combination that makes all these elements no less than great challenges to the protection of world health security [66]. For the second time, in 2024 Mpox was declared as Public Health Emergency of International Concern (PHEIC) by the World Health Organization (WHO), an identification that led to a global coordinated response for containment [26]. This was further complicated by the dynamics of disease emergence, with a new clade mainly transmitted through sexual networks, adding to the sustained transmission in countries such as the DRC (https://www.who.int/news/item/28-11-2024-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-upsurge-of-Mpox-2024, accessed on 10 August 2025). As a result, targeted interventions based on genomic surveillance are critical to the active management of outbreaks with at least 2863 reported cases and 517 fatalities across 13 African countries [85]. The evolving epidemiology and varied pathological manifestations of Mpox are profoundly influenced by its molecular and genomic traits, with recent findings on viral mutations and lineage diversification providing essential explanations for alterations in transmission dynamics, virulence, and clinical results.

5. Molecular/Genomic Insights into Mpox

5.1. Key Genomic Characteristics of Mpox Virus

MPXV belongs to the *Poxviridae* family, *Chordopoxvirinae* subfamily, and *Orthopoxvirus* genus. MPXV is a sizable, brick-like virus featuring a linear, double-stranded DNA genome that is roughly 197 kb long, which encodes 223 open reading frames (ORFs) [86]. MPXV's double-stranded DNA genome encodes 181 proteins. The linear genome features covalently closed hairpin ends (lacking free 3′ or 5′ ends). The 10 kb inverted terminal repeats (ITR) are positioned at each end of the genome. The typical size of the MPXV varies from 200 to 250 nm. The MPXV multiplies in the cytoplasm of the infected host cell and features a core region containing lateral bodies, double-stranded deoxyribonucleic acid (dsDNA), and a lipoprotein envelope (See Figure 3) [86,87]. It shares genetic and antigenic similarities with other *Orthopoxviruses*, such as VARV (smallpox), CPXV, and VACV, while exhibiting distinct differences in host range and pathogenicity [15]. The MPXV genome consists of three main regions: a highly conserved central region for transcription, replication, and virion assembly, and variable terminal regions with inverted terminal repeats [88]. The genes involved in immunomodulation and host range determination reside in the terminal regions, enabling MPXV to manipulate and evade the host immune response [89]. The

loss or fragmentation of genes such as COP-C10L, an IL-1β-binding protein, and COP-E3L, an IFN-resistant protein, significantly contribute to shaping the virus virulence and adaptability [90,91]. In addition, the genetic polymorphisms and genomic instability drive MPXV evolution, thus enabling it to adapt to novel ecological niches, including human hosts [92].

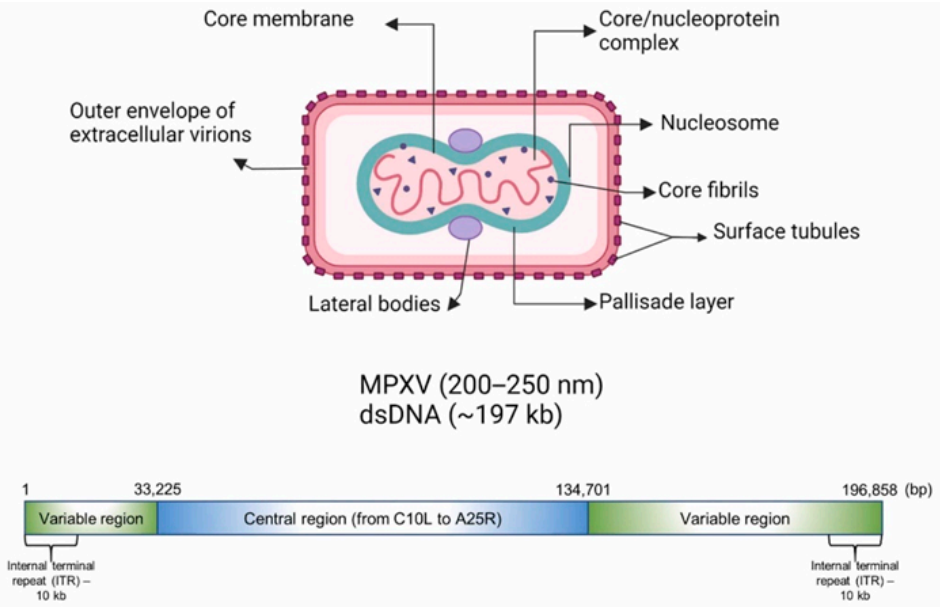


Figure 3. A schematic representation of the structure of the MPXV and its genome as adapted from the cited source: the linear double-stranded DNA (dsDNA) genome of the MPXV is around 197.2 kilobases (kb) long and encodes about 181 proteins. The genome is notable for having ~10 kb inverted terminal repeats (ITRs) at both extremities, covalently bound hairpin structures at the end, and no open 3′ or 5′ ends. Brick-shaped particles with a diameter of 200–250 nanometers are known as MPXV virions. They are structurally composed of a central core that houses the dsDNA genome and related proteins, lateral bodies on each side, and a complex lipoprotein envelope around them. Unlike other DNA viruses, MPXV employs transcription and replication machinery encoded by the virus to reproduce fully inside the cytoplasm of infected host cells. The formation of viral factories, which are specialized subcellular regions dedicated to genome replication, gene expression, and virion assembly, facilitates this cytoplasmic replication strategy [86].

The two genetic clades of MPXV, Clade I (Congo Basin) and Clade II (West African), present more than 99% genomic identity each but differ in their transmissibility and pathogenicity [93,94]. Clade II, responsible for the 2023 epidemic, showed increased human-to-human transmission that may be associated with genomic changes in low-complexity regions (LCRs) and the "genomic accordion" evolution strategy typical of *orthopoxviruses* [87]. These LCRs, previously not considered, have shown remarkable variation in tandem repeats that influence viral protein expression, stability, and function.

In particular, the microsatellite studies have identified molecular markers and hotspots of conserved variations underlying important biological functions, such as in the synthesis of surface protein encoded by the gene OPG153 and interaction with host cells [95]. Different genomic studies described the linear adaptive evolution of MPXV based on mutations involved in ORFs like OPG191, determining the increased transmission of MPXV and adaptation to human hosts [96]. Indeed, comprehensive multi-omics analyses of MPXV infection revealed disturbed immune-related pathways and the phosphorylation of viral proteins, such as the H5 protein, impinging on its DNA binding and replication capabilities [97]. The present data support a better understanding of not only MPXV pathogenesis but also the identification of new potential drug targets represented by inhibitors

of the MTOR and MAPK pathways [97,98]. The genomic complexity of MPXV, with its conserved core, variable terminal regions, and dynamic LCRs, underlines its evolutionary adaptability and pathogenic potential [87]. Ongoing genomic surveillance and multi-omics approaches are critical in addressing emerging MPXV outbreaks and the development of targeted therapeutics.

5.2. Evolutionary Trends and Implications for Virulence

MPXV underwent significant evolutionary changes in recent decades, which led to increased human-to-human transmission, zoonotic spillovers, and international health concern [99,100]. More than 97,745 laboratory-confirmed Mpox cases with 203 deaths were recorded from January 2022 to May 2024 across 116 countries [101]. Key evolutionary mechanisms underlying genetic adaptability of MPXV are recombination and positive selection, allowing the virus to circumvent immune responses and increase its virulence [102]. Indeed, 73.3% of recombination events occur within variable genomic regions, with 25 genes under positive selection mapping to immune response and viral regulation [102]. Clade-specific mutations have included a ~1141 bp deletion within CCP genes and changes to the B22R receptor-binding protein, which further emphasize the potential of this virus for rapid adaptation [103]. The emergence of new modes of transmission, including sexual contact, and possible new animal reservoirs through spillback further underscores MPXV's changing epidemiology and ecology [67].

These are indeed evolutionary trends with great implications for public health, requiring a multidimensional response. In May 2024, while the burden was the highest in Africa, there was a slight reduction in new cases, falling by 2.3% compared to April 2024 [104]. Research on host–pathogen interaction should be directed at the elucidation of next-generation therapeutics, virulence, and immune evasion genetic determinants. A One Health approach, integrating human, animal, and environmental health, is essential to mitigate cross-species transmission and prevent future outbreaks [105,106]. In a study, the Bayesian Skyline Plot depicted a viral population size that was rather constant, but active genomic surveillance was still of paramount importance for the detection of changes in either the virus's behavior or its dynamics of transmission [101,107]. Understanding MPXV evolutionary dynamics informs researchers and policymakers on how to prepare for and respond to the continuing and evolving threat of Mpox.

5.3. Potential Mutations and Their Clinical Significance

The recent advances in genomic studies on MPXV have outlined important mutations and their clinical presentations. MPXV contains more than 50 single-nucleotide polymorphs (SNPs), and its DNA polymerases are known to possess a proof-reading capability; this confers upon them a mutation rate of 10^{-5} to 10^{-6} per site of replication. Notable among them are mutations relating to the cytidine deaminase apolipoprotein B messenger RNA editing enzyme, catalytic subunit B (APOBEC3) protein, representing a family of proteins integral to the vertebrate immune system [37,86]. The MPXV 2022 outbreak exhibited two major evolutionary characteristics: the divergence of the B.1 lineage and the diversification of Clades I and II. First recorded in 2018–2019, B.1 experienced swift microevolution, developing clusters (B.1.1–B.1.8) and gathering 46 mutations, which comprised intergenic, synonymous, and nonsynonymous modifications [108]. These mutations, especially in antigenic proteins such as B21R and H3L-like, improved host detection. The enzymatic action of APOBEC3 resulted in amino acid changes in ten genes, affecting processes like immune modulation and the activity of membrane proteins [109]. The elevated mutation rate in hMPXV1 genomes sets the global MPXV pandemic apart from Clade IIb variants found in Nigeria [110,111]. Previous studies identified a recurring mutational bias, dominated by

5′ GA-to-AA transitions in recent MPXV evolution, while Clade IIb enhanced APOBEC3-related mutations [110,112]. Interestingly, in one remarkable instance in 2024, an epidemic in Kamituga, DRC, introduced a genetically distinct Clade I subgroup, subgroup VI, attesting to the rapid adaptation potential of the virus [113]. These included clinically significant mutations, such as those that confer resistance to drugs, in proteins like F13L, associated with resistance to tecovirimat [114]. Altogether, genomic sequencing identified 13 new and 11 known mutations associated with resistance to tecovirimat, along with changes in VACV proteins A314 and A684 that may provide a mechanism for resistance to both brincidofovir and cidofovir [115–117].

The MPXV mutational landscape is evolving, with comprehensive analyses mapping mutations across 171 viral proteins [117,118]. Among these, membrane-associated proteins have been pinpointed as prime targets for vaccine and drug development because of their sensitivity to mutations and their role in host interactions [119,120]. A novel metric, Average Gene Mutation Sensitivity, highlighted key proteins for therapeutic focus [121]. Further, since the divergence of lineage B.1 from A.1 during the 2018–2019 outbreak, Clade IIb has micro-evolved to give rise to several clusters with 46 B.1-specific SNPs, of which 24 are nonsynonymous [37,122]. Until April 2023, a total of 1428 genomes belonging to Clade IIb had been reported from 32 countries, and newer lineages emerged in the USA, namely, B.1.20 and B.1.22, along with B.1.6 in Australia [123]. The finding shows the increasing adaptability, transmissibility, and immune evasion capabilities of MPXV.

This represents a genetic evolution that challenges therapeutic and preventive strategies. While the case fatality rate of Clade I remained above 10%, that of Clade IIa and IIb subclasses remained below 1% [117,124]. In these genetic changes, implications for viral fitness, virulence, and resistance to antivirals were pointed out [124]. Further, new lineages require continuous surveillance and genomic characterization, especially in endemic areas and those prone to outbreaks [85,125]. Advanced computational approaches integrating mutational effect predictors and structural modeling are needed to understand MPXV evolution. They represent the basis on which next-generation vaccines will be developed, improving therapeutic efficacy and reducing the global health burden of Mpox.

5.4. Genomic Markers as Targets for Diagnostics and Therapies

The global genomic surveillance for MPXV, initiated in 2022, described viral evolution, spatiotemporal spread, and associated genomic markers of the virus [125]. Of note, MPXV Clade IIb showed a significantly increased substitution rate compared with the other *Orthopoxviruses*, driven by APOBEC-3-induced mutations supporting human-to-human transmission [126]. These genomic changes, including cytosine deamination, were also implicated in the structural rearrangements of gene duplication or deletion in the viral genome, contributing to host adaptation and hence the evolution of poxvirus [125]. These observations highlight the importance of genomic markers for improved diagnostics, enhanced therapeutic approaches, and countermeasures, including vaccines and treatments adapted from smallpox interventions. Furthermore, the internationally shared genomic sequence data reveals important information regarding the genetic diversity of the virus, its epidemiology, and its phenotypic manifestations. It is paramount that enhanced molecular diagnostic tools are developed for the early, accurate detection of MPXV.

Techniques such as qPCR, PCR, and PCR-ELISA are helpful; nucleic acid amplification tests represent the gold standard for the confirmation of MPXV infection [127]. Genetic sequencing, through next-generation sequencing, among other methods, further complements these approaches by giving detailed insight into the evolutionary trajectory of the virus and outbreak dynamics [67,128]. Furthermore, the identification of miRNAs, differentially expressed during MPXV, infection represents a promising avenue for noninvasive

diagnostics and therapeutic interventions [129,130]. Validated through highly advanced bioinformatics and molecular biology tools, these miRNAs might control virulent pathways, thereby presenting antiviral potential [130]. The options for the treatment of Mpox are limited; therefore, new antivirals against both viral and host markers are desperately awaited. Computational studies indicate that natural compounds, such as curcumin, can inhibit some of the key proteins of MPXV, like DNA polymerase holoenzyme, VP39, and E8, and modulate host inflammatory pathways like TNF and NF-κB signaling [131].

Moreover, genomic phylogenetic analyses of over 10,670 MPXV sequences have illuminated clade-specific dynamics, including the continued human-to-human transmission of Clade IIb lineage A and the spatially limited circulation of Clade I in Central and Eastern Africa [125]. Such findings stress the use of genomic markers, not only in the development of better diagnostics but also in novel therapeutic development and precision-based public health responses that will continue to expand our capabilities in addressing this emerging global threat.

6. Therapeutic and Preventive Strategies

6.1. Antiviral Therapies and Ongoing Clinical Trials

Recent developments within Mpox management and, to this effect, newer generations of antiviral therapies, being in clinical trials, show great promise in combating the threat to public health. Tecovirimat has emerged as a star among a couple of antiviral agents by providing superior efficacy through a decrease in viral load, thus alleviating the clinical symptoms [132,133]. Other experimental therapies being explored include brincidofovir, lipid-based formulations, and combination therapies that incorporate antivirals with immune-modulating agents [43]. In addition to these pharmacological developments, supportive care is important, with the administration of analgesics and antibiotics to treat secondary infections [134]. Despite such progress, considerable challenges remain, not least the possibility of resistance to antivirals, along with unequal access to effective treatments [15]. These findings bring into focus the dire need for international collaboration and innovation in treatment modalities, with emerging nanomedicine and herbal drug candidates as the way forward in the future. Significant advancements have been made in developing and repurposing antiviral therapies for Mpox, but challenges such as affordability, accessibility, and potential resistance remain (See Table 2).

Running parallel to the therapeutic developments, preventive measures, above all vaccines, have been similarly impressive. In addition, apart from the MVA-BN vaccine adapted from smallpox interventions, mRNA vaccines show higher efficacy in comparative studies and thus offer new hope for preventing Mpox outbreaks [135,136]. The development of polyvalent vaccines and innovations with immunostimulatory sequences, together with improvements in delivery systems, further underlines the potential for protection against a wider array of orthopoxvirus strains [135]. However, crucial areas of limitations exist, including but not limited to the inability to conduct thorough human clinical trials, limited epidemiological infrastructure, and a lack of veterinary vaccines, essential for addressing zoonotic transmission [137]. Diagnostic innovations such the Streamlined CRISPR On Pod Evaluation (SCOPE) and graphene quantum rods offer a diagnosis with more specificity [138]. Above all, the fresh declaration of Mpox as a global health emergency by the WHO highlights the need to optimize current solutions and devise newer approaches. Closing these gaps will be critical for preparedness against Mpox and related *orthopoxviruses*, enabling efficient reductions in future public health threats.

Table 2. Summary of current and potential Mpox antiviral therapies and ongoing clinical trials.

Antiviral Therapy	Mechanism of Action	Current Status	Clinical Trial Details	Key Findings/Challenges	Administration Route	Geographic Scope of Trials	Refs
Tecovirimat (TPOXX/ST-246)	Inhibits the VP37 protein, blocking viral egress	FDA-approved for smallpox; Phase II/III trials for Mpox	Evaluating efficacy and safety in immunocompromised patients; NCT05550006	Demonstrates reduced mortality in severe cases; challenges include drug resistance and limited global accessibility.	Oral, intravenous	United States, Europe	[139,140]
Cidofovir	Inhibits viral DNA polymerase	Off-label use; ongoing trials	Exploring efficacy in severe Mpox cases; NCT04911880	Effective in vitro against *orthopoxviruses*; associated with nephrotoxicity and limited use in resource-constrained settings.	Intravenous	North America, Africa	[43,141]
Brincidofovir	Lipid conjugate of cidofovir with lower toxicity	FDA-approved for smallpox; Phase II trials for Mpox	Assessing dosing regimens and safety profiles; NCT05717313	Improved safety profile over cidofovir; logistical barriers and high cost remain significant obstacles.	Oral	United States, Europe	[141]
Vaccinia Immune Globulin Intravenous (VIGIV)	Neutralizes orthopoxvirus through passive immunity	Emergency use authorization	Combined with antiviral therapy in severe or refractory Mpox cases; observational studies ongoing	Limited evidence on Mpox-specific efficacy; primarily used in conjunction with other antivirals for severe immune compromise.	Intravenous	United States, Global availability	[142,143]
Monoclonal Antibodies (Investigational)	Target viral proteins to prevent replication	Preclinical and early-phase trials	Investigating multi-epitope targeting strategies for enhanced efficacy	Promising early results in animal models; challenges include scalability and high production costs for widespread use.	Intravenous, subcutaneous	Global	[120]

Table 2. *Cont.*

Antiviral Therapy	Mechanism of Action	Current Status	Clinical Trial Details	Key Findings/Challenges	Administration Route	Geographic Scope of Trials	Refs
CRISPR-Based Antiviral Therapy	Gene-editing technology to target and deactivate viral DNA	Preclinical research phase	Innovative studies exploring genome-targeting strategies for MPXV; not yet in clinical trials	High specificity and potential for future personalized treatments; barriers include early-stage development and ethical concerns.	TBD (in development)	Global	[37,141]
Broad-Spectrum Antivirals (e.g., Tilorone, Valacyclovir, Ribavirin, Favipiravir, and Baloxavir marboxil)	Inhibits viral RNA polymerase	Repurposed for Mpox; exploratory trials	Evaluating efficacy in resource-constrained settings with limited access to specific antivirals	Moderate efficacy in reducing symptoms; inexpensive alternative but limited specific activity against MPXV.	Oral	Asia, Africa	[144]

6.2. Vaccine Development and Immunization Strategies

There has been great progress in Mpox vaccine development, utilizing various platforms, including viral vector-based, protein subunit vaccines, DNA, and mRNA technologies. Despite these advancements, challenges persist in ensuring the safety and efficacy of vaccines, as well as access to them [135]. Early strategies involved repurposing smallpox vaccines for Mpox prevention, with the recent development of bionic self-adjuvating nanovaccines. These showed a fourfold increase in antigen-presenting cell activation, hence provoking robust immune responses during preclinical trials [145].

Adaptive immunity to MPXV primarily involves $CD4^+$ and $CD8^+$ T cells. In non-human primate models, strong MPXV-specific $CD4^+$ T follicular helper cell responses have been linked with sustained B cell activation and long-term antibody production after vaccination [146,147]. Both vaccinated and convalescent individuals have shown effective $CD8^+$ T cell responses, particularly when targeting conserved epitopes shared by MPXV and VACV, which are linked to long-term immune memory and milder disease manifestations [148]. Notably, infection induces the persistence of terminally differentiated effector-memory-like $CD8^+$ T cells (T_EMRA) with potent cytotoxic and skin-homing properties, playing a crucial role in viral control [149]. Nevertheless, MPXV uses immune evasion mechanisms that prevent optimal T cell activation, highlighting the need for vaccine that elicit strong cellular immunity [150].

Among available vaccines, JYNNEOS (MVA-BN) and LC16m8, two third-generation smallpox vaccines, offer improved safety profiles and effective cross-protection against Mpox [151]. In contrast, the second-generation vaccination ACAM2000 is less favored because of its increased rate of side effects (See Table 3) [152]. Despite vaccine availability, hesitancy remains a significant barrier, especially in Africa, where hesitancy rates are as high as 32.7% in adults and 38.9% in children [21]. Studies reveal that low vaccination readiness and a lack of prior immunization notably increased vaccine hesitancy, with pooled odds ratios of 7.83 for adults and 12.55 for children [21].

Table 3. Development of vaccines and immunization strategies against Mpox.

Vaccine	Type	Approval Status	Target Population	Administration Strategy	Refs
JYNNEOS (Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN) (Imvamune® or Imvanex®))	Live, non-replicating vaccine	Approved in the U.S., Europe and Canada for smallpox; authorized for Mpox during outbreaks WHO prequalified in September 2024	Adults, including those with HIV; under investigation for pediatric use General population; focus on outbreak control in endemic regions	Two-dose series, subcutaneous injection; studies ongoing for single-dose efficacy	[17,153,154]
ACAM2000	Live, replicating vaccine	Approved in the U.S. for smallpox; available for Mpox under Expanded Access IND	Adults at high risk for Mpox exposure; not recommended for immunocompromised individuals	Single-dose, percutaneous administration using a bifurcated needle	[17,155]
KM Biologics Vaccine (LC16m8)	Inactivated vaccine	WHO Emergency Use Listing granted in November 2024	Children over 1 year old and adults; particularly in outbreak regions like Congo	Single-dose, intramuscular injection; Japan donating 3 million doses to Congo	[153,156]
Tonix Pharmaceuticals TNX-801	Live, attenuated vaccine	Experimental; preclinical development	Intended for broader population; aims for single-dose immunity	Single-dose, intradermal injection; designed for enhanced stability and ease of distribution	[62,157]

Addressing these challenges calls for targeted education campaigns, better vaccination preparedness, and new strategies such as polyvalent vaccines and novel delivery systems. Current immunization strategies include pre-exposure vaccination for high-risk groups and post-exposure prophylaxis to mitigate outbreak severity. Ongoing research aims to optimize dosage schedules, increase vaccination accessibility, and evaluate effectiveness in diverse populations, including children and immunocompromised individuals, thereby strengthening global preparedness against the evolving threat of Mpox.

6.3. Challenges in Therapeutic and Prophylactic Interventions

Challenges to therapeutic and prophylactic interventions against Mpox are a multivariate landscape of diagnostic, therapeutic, and preventive challenges. The preventive practices of 60.6% of the cohort were found to be associated with moderate fear and concern among nursing students, 56.2% of whom were rarely worried, being influenced by variables such as media coverage and family income [18]. The complexities for diagnosis include similarities between Mpox and other *orthopoxviruses*, atypical presentations in the face of climate change and global travel that make clinical differentiation difficult, especially in resource-poor settings [57]. Molecular diagnostics, point-of-care tools, and CRISPR-based technologies have been advancing toward timely and accurate detection, but these are still constrained by sensitivity and access limitations. On the therapeutic front, interventions such as tecovirimat and the JYNNEOS vaccine have promise but also face challenges in efficacy and outbreak management [17,66]. Moreover, breakthrough infections indicate follow-up care and personalized therapies. Novel research investigations, global monitoring, and superior diagnostic capabilities are now called for to reduce the burden of Mpox on public health and adjust its clinical and epidemiological profile. These are significantly enhanced when integrated with robust public health interventions, forming a comprehensive approach to outbreak control and mitigation.

7. Public Health Interventions

7.1. Isolation and Quarantine Measures

Isolation and quarantine are central to the mitigation of Mpox, according to mathematical modeling and analyses in public health [158]. A One Health framework approach indicated that the ongoing transmission of MPX involves animal reservoirs, particularly rodents, within high-risk groups like MSM and bisexual men [159]. The model shows that a reduction in the risk of outbreaks is achieved when at least 65% of symptomatic cases are well isolated, and when there is comprehensive contact tracing [74]. At the same time, neglect of infections in animal reservoirs may result in increased transmission among humans [72,134]. Indeed, quarantine and post-exposure vaccination have been shown to improve containment; these findings are supported numerically: simulations with quarantine yield a lower basic reproduction number compared to simulations without quarantine [160]. Furthermore, learning from experience around COVID-19, non-pharmacological measures in support of vaccination—such as mask use, hand hygiene, and social distancing—could play a significant role in the response to Mpox. Beyond infection control, the psychological impacts of quarantine, including heightened risks of depression, PTSD, and substance use disorders, predict the continuing need for training and psychological support among health professionals [161]. Furthermore, the implementation of multidisciplinary and holistic approaches can help identify and manage atypical signs and symptoms, among which one finds severe pain; improve patient outcomes; and avert chronic conditions. They thereby underscore the need for integrated public health responses in the fight against Mpox [23].

7.2. Public Health Campaigns and Behavioral Strategies

The Mpox outbreak in 2022, therefore, increased the need for innovative non-pharmacological interventions and public health strategies to limit the spread of this infectious disease and its social stigma. To address the complex challenges of Mpox and its impact on public health, it is important to look at effective public health approaches, placing a strong emphasis on awareness campaigns, training for healthcare professionals, and targeted communication. Furthermore, there is an urgent need for improved global surveillance, equitable access to healthcare, and ongoing research into personalized and adaptive management strategies [162]. These strategies should contribute to combating the subtle determinants of social stigmatization, especially among MSM and other vulnerable populations [163,164]. A study emphasized that interventions were important along three axes: raising awareness and training among healthcare professionals, 71% of the studies; sensitive and targeted communication, 57%; and medical care with anonymity and respect for patients, 57% [162]. These are very important in creating an enabling environment for patients, especially because of the psychological effects of the disease and stigmatization. The attention to mental health support was also very important and came out in 63% of the studies as one of the key components of integration in managing Mpox-related stigmatization [165].

In addition, behavioral strategies will be important in the fight against the spread of Mpox, especially in settings that have different levels of access to health and awareness among the public. Studies from Nigeria and other regions have shown the need to understand socio-demographic factors influencing vaccine hesitancy and acceptance [166]. A study in Benue State, Nigeria, surveyed 377 respondents and yielded findings indicating that 83% of the health workers had high vaccination intention and could, therefore, be a source of trusted information within the community. The level of vaccine trust was associated with a higher education level ($p = 0.003$), whereas lower levels of education were associated with less awareness and more stigma [166]. Targeted approaches, like social behavioral change communication, focus on educating and empowering communities for the adoption of safer behaviors [167]. Adaptive surveillance coupled with proactive public health interventions with a dash of international collaboration has proved crucial in containing outbreaks and reducing the geographic spread of disease in the case of India [168]. These efforts highlight the necessity of coordinated multifaceted strategies that combine public health education, behavioral insights, and technological advancements to address the complexities of infectious disease outbreaks effectively.

7.3. The Role of Community Engagement in Controlling Outbreaks

Community engagement plays a pivotal role in controlling outbreaks, as evidenced by studies in regions like Southwest and Littoral Cameroon, where a comprehensive understanding of social determinants significantly influences Mpox acquisition and severity [169]. A descriptive cross-sectional study involving 394 participants highlighted multiple knowledge gaps regarding Mpox, with 69.8% acknowledging the virus' role, while 87.4% identified bushmeat consumption and traditional treatments as key socio-behavioral determinants increasing risk [169]. Additionally, 46.7% of participants reported close contact with confirmed or probable cases, demonstrating the critical need for community-driven approaches to mitigate transmission [169]. These findings underscore the importance of integrating community engagement into public health strategies to address cultural practices and enhance awareness, ensuring the effective prevention and control of infectious diseases.

The reclassification of Mpox as a PHEIC underscores the global need for inclusive community participation in health responses [170]. This approach is essential to over-

come disparities in health resource access, particularly within low- and middle-income countries. Studies reveal that community health nurses face systemic barriers such as delayed resource allocation and inconsistent communication, which hinder effective response efforts [171,172]. Addressing these challenges through targeted training, resource distribution, and streamlined communication is crucial for empowering communities and ensuring that health policies are culturally appropriate and effective. By fostering collaboration between local communities and healthcare systems, the global health response can become more resilient and inclusive, becoming capable of managing future outbreaks effectively.

8. Discussion and Postulated Hypotheses on Mpox Evolution

8.1. Factors Driving Re-Emergence and Epidemiological Shifts

Understanding the recent worldwide spread of Mpox requires knowledge of its historical background. The re-emergence of MPXV has been a critical concern in global health driven by various factors, which include the decline in immunity post-smallpox vaccination and rapid changes in human behavior and epidemiological surveillance [6]. In fact, since the cessation of widespread smallpox vaccination following its eradication in 1980, populations have grown increasingly vulnerable to *orthopoxviruses* [173]. Several studies showed that waning immunity from previous smallpox vaccinations contributed substantially to the increased cases of MPXV infection [136]. In areas where the number of MPXV cases is increasing, recent research indicates that booster shots might be required to improve population immunity against the MPXV. Following the report of a non-travel-associated cluster of Mpox cases by the United Kingdom in May 2022, 41 countries across the WHO European Region reported 21,098 cases and 2 deaths by 23 August 2022 [174]. Nonsynonymous mutations in the MPXV genome, particularly in regions associated with host recognition, have also been implicated in the enhanced adaptability and transmissibility of the virus [94]. These mutations confer a benefit in immune evasion and increased transmissibility of the virus, underscoring the dynamic nature of Mpox evolution [117]. Understanding these driving factors is important for the development of targeted interventions and enhanced surveillance to control the spread of Mpox worldwide.

The interaction of waning immunity and rapid viral evolution has increased concerns over the outbreaks of Mpox. In 2022, countries such as Portugal, Spain, and Canada registered their first cases, which then spread very fast across Europe and beyond [37]. The detection of the B.1 MPXV lineage marked a turn of events, with some studies suggesting that it evolved quickly in Europe to play a major role in the global spread of Mpox [124]. This lineage carries various mutations associated with increased transmissibility and immune evasion, raising concerns about its adapting potential [94,124]. In addition, the rise in more international travels and contacts between African endemic areas and other continents favored the spread of Mpox as an important issue challenging the public health authorities [66]. These findings underscore the need for continued surveillance, studies on viral evolution, and a coordinated global response to mitigate the impact of Mpox outbreaks.

8.2. Potential Links with Changing Ecological and Human Behavior

This was an epidemiological shift as groups, such as young adults and a large number sex workers, who were for the first time the major groups of persons affected by the new infectious disease, the Clade I Mpox lineage, in comparison with previous major infections, affecting children below age 15 in South Kivu [175]. Such change would have much relevance with increase in human mobility and behaviors from more than 80% of affected population [25,176]. Alarming, too, was the fetal loss of more than half of the Mpox-infected pregnant women, while cross-border transmission already introduced Clade Ib into North

Kivu and into neighboring countries such as Burundi, Uganda, Rwanda, and Kenya [77]. Such dynamics illustrate how changes in ecological factors, human behavior, and social interactions, as well as the possible establishment of enzootic reservoirs, may complicate disease control and point to the importance targeted interventions at the human–animal interface, especially in urban areas. Evolutionary and behavioral studies provide critical insights into Mpox's transmission dynamics and control measures.

The genomic analyses pointed out an intense recombination process within Mpox, with 73.3% found in variable regions, and revealed 25 genes under positive selection related to immune response and viral regulation [102]. Such findings shed light on the adaptability of this virus and point to the need for proactive monitoring of zoonotic spillover and evolutionary changes [102]. This is further driven by the positively selected genes that influence immunity, the regulation of apoptosis, and viral virulence, hence suggesting phenotypic heterogeneity among viruses within Clade I [94]. Coupled with delayed epidemic peaks for suboptimal quarantine and low protection measures, these findings emphasize the urgent need for improved behavioral interventions, vaccination, and environmental decontamination [120]. Mathematical modeling further stresses the cost-effectiveness of such strategies as vaccination and infected animal removal, projecting the avoidance of several thousand human and animal infections [177]. These findings underscore the need for integrated public health approaches that address ecological changes and human behaviors driving Mpox outbreaks.

8.3. Predicting Future Trends Based on Zoonotic and Environmental Factors

The unprecedented global spread of Mpox, with over 20,000 cases reported in Africa alone in 2024, highlights the need for predictive models that integrate zoonotic and environmental factors (https://www.ecdc.europa.eu/en/news-events/Mpox-epidemiological-update-week-36-2024-clade-i, accessed on 10 August 2025). The resurgence of the Clade Ib variant, identified across Africa and as far away as Sweden and Thailand, underlines enhanced transmissibility and the potential for international proliferation [124]. Advanced simulation models, adapted from COVID-19 frameworks, reach very high prediction accuracy, assuming only a 15% difference between estimated and reported cases [178]. Model estimates predict that the vaccine may reduce infection rates by just about 29%, assuming only 30% of the population receives a 78%-efficient vaccine, a useful insight into one potential proactive measure [179]. These models have emphasized the role of targeted interventions, particularly in high-risk regions, and the role of waning immunity, travel, and intimate contact in accelerating transmission. Advanced statistical methods, including ARIMA modeling, Random Forest machine learning, and ensemble forecasting, have continued to improve predictions of Mpox trends in a variety of geographic and epidemiological contexts [180].

Random Forest models outperform ARIMA in six of the ten most affected countries, while ensemble models efficiently forecast cumulative cases, offering four-week projections critical for planning containment efforts [181]. These predictive tools provide actionable insights into disease dynamics and can inform policymaking in the attempt to mitigate outbreaks. Furthermore, they deal with broader implications for zoonotic spillovers, viral mutations enhancing transmissibility, and the environmental persistence of the virus [182]. This will be an important integrated approach in forming adaptive public health responses to ensure readiness against the ongoing Mpox crisis and any future emerging diseases.

9. Conclusions and Future Perspectives for Mpox Research

The re-emergence of Mpox has underlined critical lacunae in the knowledge base of its epidemiology, transmission dynamics, and clinical management as a public health threat.

Since the eradication of smallpox in 1970, Mpox has continued its spread from rural Africa to several continents, including a declared outbreak across the world in 2022. As of October 2023 over 91,000 confirmed cases have been reported across 115 countries [183]. This review has highlighted some of the most crucial steps, including the efficacy of tecovirimat in clinical trials, the potential of mRNA-based vaccines to provide enhanced protection against Mpox infection compared to classical smallpox vaccines, and the development of novel diagnostic tools like the SCOPE platform and graphene quantum rods. These developments have enhanced detection sensitivity and accuracy.

Despite these milestones, the outbreak has exposed several challenges, most notably, the limited preparedness and diagnostic confidence of healthcare providers in non-endemic countries. These shortcomings call for culturally responsive education initiatives, expanded vaccine accessibility, and culturally adapted interventions, including in chronically ill people and the LGBTQ+ community. Furthermore, the emergence of atypical clinical manifestations and unexpected patterns of human-to-human transmission contradict prior assumptions about Mpox behavior. While *orthopoxviruses* typically mutate slowly, recent molecular studies suggest accelerated viral evolution in MPXV, possibly driven by APOBEC3-mediated genomic editing.

Although tecovirimat and other antivirals offer promising therapeutic avenues, inconsistent clinical outcomes and potential resistance necessitate ongoing pharmacovigilance, rigorous clinical trials, and the development of adaptive treatment regimens. Similarly, the effectiveness of existing smallpox vaccines against current MPXV strains remains uncertain, reinforcing the need for continuous genomic surveillance and vaccine efficacy studies. Additionally, the One Health approach remains an important strategy in understanding zoonotic spillover, with interconnectedness among human, animal, and environmental health. Advances in predictive modeling through transfer learning and real-time analytics have significantly improved outbreak forecasting, while the integration of anthropological insights may help bridge cultural and systemic barriers to effective responses. Emerging fields such as nanomedicine and Phytotherapeutics development may provide more accessible, cost-effective treatment options in resource-limited settings.

Given the risk of severe systemic complications, including cardiovascular manifestations like myocarditis and pericarditis, Mpox clinical management should be multidisciplinary. To mitigate the growing threat of Mpox and similar emerging infections, future efforts must prioritize collaborative global networks, targeted research into host–pathogen interactions, robust surveillance infrastructure, equitable access to healthcare, and proactive public health communication. By aligning technological innovation with interdisciplinary strategies and global solidarity, the scientific and medical communities can enhance resilience against current and future Mpox outbreaks.

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