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Mpox virus clade evolution and epidemiology in Africa: a systematic review of genetic variability and clinical impact

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Systematic Review

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Abstract

Background: The Mpox virus (MPXV), formerly known as monkeypox virus, is re-emerging in endemic and non-endemic regions, driven in part by divergent genetic lineages: Clade 1 and Clade 2.
Objective: This systematic review synthesizes current evidence on the genomic variability of MPXV in Africa and its relationship to clinical severity, transmission dynamics, and outbreak patterns.

Methods: Following PRISMA guidelines, we searched Semantic Scholar, PubMed, Google Scholar, and other relevant databases to identify studies comparing Clade 1 and Clade 2. Data extraction included mutation profiling, outbreak size, and transmission dynamics.

Results: Eleven studies met inclusion criteria. Clade 1, predominant in Central and East Africa, exhibits key deletions in virulence genes (D14L, complement control protein) and high mortality rates (up to 10%). Clade 2, prevalent in West Africa and globally, shows extensive APOBEC3-type mutations, frameshifts, and tandem repeats, with milder disease and enhanced human-to-human transmission.

Conclusion: Genetic differences in virulence and immune evasion genes fundamentally influence outbreak characteristics across Mpox clades. Improved genomic surveillance is critical for public health preparedness.

Introduction

The monkeypox virus (MPXV), now referred to as mpox virus, is a double-stranded DNA virus belonging to the *Orthopoxvirus* genus within the *Poxviridae* family. It is the etiologic agent of a zoonotic disease historically confined to regions of Central and West Africa. However, mpox has recently emerged as a global health concern following an outbreak that, as of mid-2023, had resulted in over 28,700 confirmed cases across 93 countries (Lucero-Obusan et al., 2023). The outbreak, which began in May 2022, simultaneously affected both endemic and non-endemic countries, prompting the World Health Organization (WHO) to declare it a Public Health Emergency of International Concern on July 23, 2022 (Thieme et al., 2023). Subsequently, the United States Department of Health and Human Services declared it a national public health emergency on August 4, 2022 (Lucero-Obusan et al., 2023). The Africa Centers for Disease Control and Prevention (ACDC) declared it a Public Health Emergency of Continental Security (PHECS), on August 13, 2024, owing to 160% increase in the spread of the virus across the continent, with the aim of fostering regional coordination and resource mobilization to curb pandemic (Ndembi et al., 2024, Zumla et al., 2025).

Although mpox was previously endemic only to specific ecological niches in Central and West Africa, recent outbreaks have demonstrated the virus's capacity to spread internationally. This expansion underscores the urgent need for a deeper understanding of the virus's virological properties, transmission mechanisms, and clinical characteristics (Altun et al., 2023; Okwor et al., 2023). In the Democratic Republic of the Congo (DRC), the epidemic continues to exhibit two distinct patterns. In traditional endemic zones, transmission remains largely zoonotic, driven by Clade 1a (Kinganda-

Lusamaki et al., 2024). In contrast, the global outbreak has been attributed to human-to-human transmission of a newly designated Clade 2b, with no confirmed zoonotic links (Okwor et al., 2023).

The changing epidemiology of mpox, particularly its emergence in non-endemic regions and among new risk populations, highlights the importance of integrated molecular surveillance. Such surveillance can enable real-time tracking of lineage evolution, supporting timely and targeted public health responses, especially in Africa where both Clades 1 and 2 circulate (Durski et al., 2018). Strengthening laboratory diagnostics, case detection, and infection control protocols remain essential to curtail transmission. Furthermore, addressing knowledge gaps in the ecology and epidemiology of MPXV is vital for designing effective preventive and containment strategies.(1)(2)

Recent research has concentrated on identifying the genetic and epidemiological distinctions between Clade 1 and Clade 2, which are co-circulating in different geographical and socio-ecological contexts. Genomic studies have revealed key differences in virulence genes, including deletions in D14L and the complement control protein (CCP), both of which may influence immune evasion and viral fitness (Kumar et al., 2024). Additionally, both clades exhibit evidence of adaptation to human transmission, marked by APOBEC3-type mutations that drive accelerated evolution and intra-clade diversification (Vakaniaki et al., 2024).

Clade 1 and Clade 2 differ by approximately 0.5% of their genomic sequences. Despite this modest divergence, the clades show significant differences in transmissibility, pathogenicity, and geographic prevalence. Clade 1 is associated with a mortality rate of up to 10%, while Clade 2 is characterized by a lower mortality rate of approximately 4% (Karagoz et al., 2023). Structural differences in open reading frames (ORFs) due to gene deletions and fragmentation contribute to these phenotypic differences (Kaler et al., 2022).

The geographical distribution of these clades aligns with observed clinical and epidemiological trends. Clade 1 predominates in Central and East Africa, particularly in countries such as the DRC and Kenya (Langat et al., 2024), whereas Clade 2 is predominantly found in West Africa and was the causative agent of the 2022–2023 global outbreak (Anjorin et al., 2024). These clade-specific characteristics are further reflected in clinical severity and transmission dynamics. Clade 1 infections are more likely to cause severe systemic illness and higher case fatality rates (Americo et al., 2022), while Clade 2 infections tend to present with milder symptoms but exhibit higher person-to-person transmission potential (Anjorin et al., 2024).

Outbreak magnitude has also varied substantially between clades. Clade 1 outbreaks in the DRC are typically localized, involving hundreds of cases (Vakaniaki et al., 2024), while Clade 2b has been responsible for a global epidemic with over 85,600 confirmed cases (Anjorin et al., 2024). These patterns are supported by robust genomic, epidemiological, and phylogenetic data that link specific mutations to clinical outcomes and transmission routes (Molteni et al., 2023).

Mpox continues to spread via both animal-to-human (zoonotic) and human-to-human routes. Although long-range airborne transmission has not been confirmed, close contact remains the primary mode of spread (Gupta et al., 2023). The evolving nature of mpox epidemiology—including shifts in age distribution, risk groups, and geographical spread—emphasizes the need for continuous monitoring and adaptive public health responses (Satapathy et al., 2024).

This systematic review synthesized the current knowledge on the genetic variability and clinical impacts of MPXV clades circulating in Africa. Specifically, it investigated the evolutionary dynamics of the virus, its regional epidemiology, and the phenotypic consequences of genomic diversity. Understanding these clade-specific differences is essential for informing public health interventions, optimizing clinical management, and guiding future research priorities. By integrating findings across molecular, clinical, and epidemiological domains, this review offers valuable insights for shaping national and global strategies to mitigate the threat posed by mpox.

Methods

This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A structured search was conducted using the Semantic Scholar corpus, PubMed, and Google Scholar. We used the query: "How does the genetic variability of Mpox influence its outbreak in Africa, comparing Clade 1 with Clade 2?" We retrieved 50 papers from Semantic Scholar Corpus, 38 papers from PubMed, and 176 papers from Google Scholar, as the most relevant to the query.

Study Selection

Inclusion Criteria:

- Studies reporting genetic sequence data for MPXV
- African geographic focus (Clade 1 or Clade 2)
- Comparative clade/genomic analyses
- Reports linking molecular data to clinical or epidemiological outcomes

Exclusion Criteria:

- Laboratory-adapted strain studies without natural outbreak data
- Purely descriptive clinical reports with no genomic analysis

Data Extraction:

From each included study, we extracted: (1) study design; (2) geographic location; (3) sequencing and phylogenetic methods; (4) clade identification and mutations; (5) outbreak size and severity metrics (Table 1).

Results

Eleven studies were included (5 focused on Clade 1, 3 on Clade 2, and 3 comparative). Most studies used whole-genome or Illumina sequencing with phylogenetic analysis. Table 1 summarizes key findings.

Table 1
Summary of Included Studies by Clade, Region, and Genomic Features

Study	Design	Geographic Focus	Clade	Key Findings
Vakaniaki et al. (2024)	Outbreak, genomic, phylogenetic	Kamituga, DRC	Clade Ib	APOBEC3, 1kb deletion, sexual transmission
Masirika et al. (2024)	Outbreak, genomic, phylogenetic	South Kivu, DRC	Clade I (subgroup VI)	D14L deletion, mutational hotspots
Langat et al. (2024)	Genomic, phylogenetic	Kenya	Clade Ib	SNPs, high child mortality
Americo et al. (2022)	Animal model study	Africa	Clades 1, 2a, 2b.1	Clade 1 more virulent than 2b.1
Anjorin et al. (2024)	Systematic review	Nigeria, global	Clade IIb	85,600 + cases, H3L mutations
Kumar et al. (2024)	Genomic comparison	Africa, global	Clade Ib, IIb	D14L & CCP deletions, B22R changes
Desingu et al. (2023)	Genomic analysis	Nigeria, multi-country	Clade IIb	Frameshifts, APOBEC3-type mutations
Molteni et al. (2023)	Phylogenetic study	West Africa, DRC	Multiple	Positive selection, immune genes
Chen et al. (2005)	Genomic analysis	West Africa, DRC	Clade I, II	Virulence comparison, D14L
Likos et al. (2005)	Outbreak, genomic	USA, DRC	Clade I, II	Clinical/genomic clade differences
Americo et al. (2022)	Animal model	Congo Basin, West Africa	Clades 1, 2a, 2b.1	Virulence ranking: 1 > 2a > 2b.1

Genetic Variability Analysis

The analysis of genetic variability revealed deletions in the D14L gene and complement control protein of both Clade 1 and Clade 2, with deletions previously thought to be exclusive to Clade 2 now also found in Clade 1 (Table 2).

Table 2
Clade-Specific Genetic Markers

Genetic Feature	Clade 1 Characteristics	Clade 2 Characteristics	Clinical Significance
D14L gene	Deletion in Kamituga Clade I (subgroup VI); implicated in virulence	Deletion previously exclusive to Clade II	Loss may affect complement evasion, virulence
Complement control protein (CCP)	~ 1 kilobase pair deletion in Clade Ib (Kamituga); ~1141 base pair deletion in Clade Ib	Deletion previously exclusive to Clade II	May reduce immune evasion, alter virulence
B22R protein	Clade-specific amino acid changes in Clade Ib; mutational hotspots in Kamituga	Clade-specific changes in IIb	Host receptor binding, immunogenicity
H3L gene	8 point mutations (3 missense, 5 silent) in African strains	Mutations in West African clade (Nigerian subclade)	Envelope protein, viral attachment
Apolipoprotein B mRNA Editing Enzyme, Catalytic Polypeptide-like 3 (APOBEC3-type) mutations	Predominant in Clade Ib (Kamituga, Kenya); marker of human-to-human transmission	Extensive in Clade IIb (B.1 lineage)	Marker of adaptation to human transmission
Other mutational hotspots	C9L, I4L, L6R, A17L, A25R, A28L, B21R in Kamituga Clade I	Genomic gaps, frameshifts, tandem repeats in IIb	Various roles in morphogenesis, immune evasion

Clade specific changes in amino acids were reported in the B22R protein in both clades. Point mutations were found in the H3L gene of both clades. The APOBEC3-type mutations were predominant or extensive in both clades (Clade 1: Kamituga, Kenya; Clade 2: IIb/B.1 lineage) and are associated with adaptation to human-to-human transmission. Clade 1 showed mutational hotspots in B22R and several other genes; Clade 2 showed genomic gaps, frameshifts, and tandem repeats. Among the studies included, we did not find mention of any genetic features exclusive to only one clade; all features analyzed had changes reported in both clades, with some previously thought to be clade-specific now found in both.

Clinical and Epidemiological Effects

We identified multiple distinct findings for Clade 1 and Clade 2 across the clinical parameters, as summarized in Table 3. The studies reviewed showed that Clade 1 (Central/East Africa), has higher virulence and severity, with high mortality and severe disease, including high child mortality and greater virulence in animal models. Clade 2 (West Africa/global) is associated with lower mortality and milder disease, with Clade IIb linked to the global outbreak.

In addition, we found evidence of sexual contact, heterosexual and community spread, and APOBEC3-driven human-to-human transmission routes for Clade 1. Clade 2 was associated with enhanced person-to-person transmission, global spread (especially via Clade IIb), and animal-to-human transmission in earlier outbreaks. Clade 1 affects adolescents, young adults, sex workers, and a broad age range including children. Clade 2 historically affected children, while recent outbreaks involve men who have sex with men and travelers. The outbreak size of Clade 1 outbreaks was localized, with two outbreaks exceeding 100 cases. Clade 2 was associated with a large global outbreak with over 85,000 cases. APOBEC3 mutations, sexual and community spread, and high child mortality were reported for Clade 1. Clade 2 was characterized by enhanced transmissibility and global spread.

Table 3
Virulence Comparison

Clinical Parameter	Clade 1 Impact	Clade 2 Impact	Regional Distribution
Virulence (mortality, severity)	High mortality (up to 10%); severe disease; high child mortality in Democratic Republic of Congo; most virulent in animal models	Lower mortality; milder disease; Clade IIb associated with g lobal outbreak	Clade 1: Central/East Africa (Democratic Republic of Congo, Kenya); Clade 2: West Africa, global
Transmission routes	Sexual contact (29% sex workers in Kamituga); heterosexual and community spread; APOBEC3 mutations indicate human-to-human	Enhanced person-to-person in West African clade; g lobal spread via Clade IIb; animal-to-human in earlier outbreaks	Clade 1: Democratic Republic of Congo, Kenya; Clade 2: Nigeria, multi-country
Key populations	Adolescents, young adults, sex workers; broad age range including children	Historically children; recent outbreaks involve men who have sex with men, travelers	Clade 1: Democratic Republic of Congo, Kenya; Clade 2: Nigeria, Global
Outbreak size	Kamituga: 241 suspected, 108 confirmed (Oct 2023–Jan 2024); over 200 in Masirika	Over 85,600 cases globally (2022–2023)	Clade 1: localized; Clade 2: global
Transmission evidence	APOBEC3 mutations, sexual/community spread, high child mortality	Enhanced transmissibility in West African clade, global spread	Clade 1: Democratic Republic of Congo, Kenya; Clade 2: global

The evidence base we found was relatively strong for recent Clade 1/Ib outbreaks in the Democratic Republic of Congo and Kenya, with detailed genomic and epidemiological data available in the included

studies. Animal model findings support higher virulence of Clade 1, but their generalizability to human outbreaks was limited. Older studies use less precise clade nomenclature and lack comprehensive molecular data.

Discussion

A comprehensive synthesis of current literature on MPXV genomic variability reveals consistent evolutionary patterns with significant implications for public health preparedness and outbreak control. Drawing on eleven peer-reviewed studies employing diverse methodological approaches, the review revealed a strong emphasis on molecular analyses: eight studies utilized whole-genome sequencing and phylogenetic inference, five incorporated outbreak investigations, and four included epidemiological surveys. This methodological predominance of genomics underscores the growing recognition of molecular epidemiology as a central tool for understanding MPXV evolution, transmission, and adaptation to human hosts.

Clade structure and geographic distribution

MPXV is a zoonotic orthopoxvirus characterized by substantial genetic diversity, classically grouped into two major clades—Clade 1 and Clade 2—each displaying distinct geographic, epidemiological, and clinical profiles. Clade 1, formerly known as the Central African or Congo Basin clade, predominates in Central and East Africa, particularly in the Democratic Republic of Congo (DRC) and Kenya. This clade is consistently associated with higher virulence, increased transmissibility, and elevated case-fatality rates relative to Clade 2 (Langat et al., 2024). Its persistence in these regions reflects favorable ecological conditions for zoonotic spillover, sustained human-to-human transmission, and structural challenges such as limited diagnostic capacity, weak surveillance systems, and constrained healthcare infrastructure.

In contrast, Clade 2 (formerly the West African clade) has historically circulated in West African countries such as Nigeria, Liberia, and Sierra Leone and has been associated with milder clinical disease and lower mortality. Notably, Clade 2 has been responsible for recent international outbreaks, signifying a major epidemiological shift. The 2022–2023 global mpox outbreak, which affected multiple non-endemic regions across Europe, the Americas, and Asia, was genetically linked to Clade 2 lineages (Anjorin et al., 2024). This expansion highlights the adaptive potential of Clade 2 and reinforces the importance of genomic surveillance for tracking viral dissemination across globalized human networks.

Comparative virulence, transmission, and outbreak dynamics

Marked differences exist between MPXV clades in terms of virulence, transmission dynamics, and outbreak scale, with important implications for global health responses. Clade 1 remains substantially more virulent, with reported mortality rates reaching up to 10%, particularly among children and other

vulnerable populations. Clinical presentations frequently include severe dermatological manifestations, hemorrhagic lesions, and systemic complications (Langat et al., 2024). Consequently, Clade 1 continues to impose a heavy public health burden in endemic regions, where zoonotic exposure and household transmission remain common.

Conversely, Clade 2 demonstrates enhanced capacity for sustained human-to-human transmission and has driven large-scale outbreaks beyond Africa. Despite its broader geographic reach, Clade 2 infections are typically associated with milder disease and significantly lower fatality rates (Anjorin et al., 2024). The 2022–2023 outbreak resulted in more than 85,600 reported cases globally, illustrating the virus's pandemic potential when introduced into highly connected populations (Vakaniaki et al., 2024).

Outbreak characteristics differ further by clade: Clade 1 outbreaks have historically been localized, often confined to rural or peri-urban settings with limited access to healthcare and typically involving hundreds of cases. In contrast, Clade 2 outbreaks have shown extensive international spread affecting diverse demographic groups. Importantly, recent data suggest convergence in transmission routes. For example, an outbreak in Kamituga, DRC, identified 29% of cases among sex workers, highlighting an increasing role of sexual contact in Clade 1 transmission (Vakaniaki et al., 2024). This convergence complicates risk communication and necessitates culturally appropriate, context-specific public health interventions.

Genomic determinants of virulence and adaptation

Across studies, genetic variability in virulence-associated and immune-evasion genes emerges as a central determinant of observed epidemiological and clinical differences between clades. Key genes—including *D14L*, complement control protein (CCP), *B22R*, and *H3L*—consistently differentiate clades and are implicated in viral entry, immune modulation, and tissue tropism. While their molecular functions are well described, direct genotype-phenotype correlations remain largely inferential, highlighting an important gap between genomic data and clinical outcomes (Vakaniaki et al., 2024).

Recent genomic analyses have challenged earlier assumptions of strict clade-specific genomic features. Notably, deletions in *D14L* and CCP—previously considered exclusive to Clade 2—have been identified in Clade Ib isolates, including a ~ 1141 bp deletion (Kumar et al., 2024). These findings suggest shared evolutionary pressures or convergent adaptation, potentially related to complement system evasion, and underscore the dynamic nature of MPXV evolution.

Clade-specific amino acid substitutions are particularly prominent in *B22R*, a receptor-binding protein involved in viral entry. Approximately 19% of clade-defining substitutions occur within this protein family (MPXV_gp17), which is highly immunogenic and may influence host specificity and transmission efficiency (Kumar et al., 2024). These features make *B22R* a promising target for diagnostics and vaccine development.

H3L as a determinant of pathogenicity and therapeutic target

The *H3L* gene plays a multifaceted role in MPXV biology, influencing viral entry, host adaptation, immune recognition, and pathogenicity. It encodes a surface membrane protein essential for virus-host cell attachment and exhibits high immunogenic potential, making it a candidate antigen for vaccine development (Giorgi et al., 2024).

Beyond entry, *H3L* has been implicated in organ-specific pathogenic effects. Experimental studies have shown that H3L activates interleukin-1 alpha (IL1A), induces inflammatory pathways, and binds directly to cardiac gene promoters, leading to epigenetic dysregulation and cardiac injury in vitro and in vivo (Chen et al., 2024). These findings identify *H3L* and IL1A as potential therapeutic targets and reveal a novel mechanism of MPXV-associated tissue damage beyond classical dermatologic disease.

APOBEC3-driven mutagenesis and viral evolution

APOBEC3-associated mutational signatures are increasingly recognized as hallmarks of MPXV adaptation to sustained human transmission. These host cytidine deaminases introduce characteristic G-to-A and C-to-T substitutions that now account for 8–13% of mutations in recent MPXV genomes, particularly in Clade IIb lineages associated with global outbreaks (O'Toole et al., 2023; Vakaniaki et al., 2024). This pattern reflects a transition from sporadic zoonotic introductions to prolonged circulation within human populations.

APOBEC3-mediated mutations contribute disproportionately to mutational hotspots in genes involved in virion morphogenesis and immune evasion, especially within the variable terminal regions of the genome (Masirika et al., 2024). Structural genes such as *OPG004*, *OPG074*, and *OPG192*, as well as ankyrin repeat proteins, are under strong positive selection and may influence virion assembly, antigen presentation, and antibody evasion (O'Toole et al., 2022).

Immune evasion genes—including *J2L*, *C9L*, *C15L*, *A47R*, and *B21R*—also harbor functionally relevant mutations. These alterations may modulate cytokine signaling, T-cell activation, and Toll-like receptor pathways, collectively reducing host immune effectiveness (Chen et al., 2023; Li et al., 2023). Additionally, gene loss and rearrangements in terminal regions may streamline viral replication or facilitate immune escape, further enhancing fitness in human hosts (Sharma et al., 2023).

Public health implications and study limitations

The accumulation of mutations affecting morphogenesis and immune evasion has direct implications for disease severity, transmission efficiency, and vaccine effectiveness. For instance, mutations in *B21R*, a major surface antigen, may reduce neutralizing antibody binding, potentially diminishing the protective efficacy of smallpox-derived vaccines (Planas et al., 2022). Continuous genomic surveillance is therefore essential to detect emerging variants with altered virulence or immune escape potential.

Despite these insights, several limitations constrain current understanding. Some included studies were accessible only as abstracts, geographic representation was skewed toward Central Africa—particularly the DRC and Congo Basin—and findings from animal models may not fully translate to human infection (Americo et al., 2022). Limited sequencing capacity and inconsistent nomenclature across studies further restrict resolution of clade diversity (Molteni et al., 2023).

Collectively, the evidence highlights a complex and evolving MPXV genomic landscape in which overlapping mutations and deletions blur traditional clade distinctions. Both structural proteins (e.g., *B22R*, *H3L*) and immune evasion factors (e.g., *D14L*, CCP) contribute to viral fitness across diverse ecological and epidemiological contexts. While Clade 1 remains more clinically severe, Clade 2's capacity for rapid global spread presents an equally significant public health challenge. Tailoring surveillance, prevention, and intervention strategies to clade-specific risks—while strengthening sequencing capacity and data sharing, particularly in Africa—will be critical to effective mpox control and preparedness.

Conclusion

Genomic variability plays a key role in the diverse epidemiological patterns of Mpox across Africa. The emergence of shared mutations between clades underscores the evolutionary dynamics of MPXV and the need for continuous surveillance, particularly in under-sequenced African regions. Different genetic markers in Mpox Clades 1 and 2 create distinct African outbreak patterns, where Clade 1's gene deletions cause severe outcomes while Clade 2's mutations result in milder disease. There are significant differences between Mpox virus Clade 1 and Clade 2, with important implications for public health response and disease management. Genetic analysis has revealed distinctive patterns of variation, including deletion. The clear demarcation in geographical distribution and pathogenicity between Clade 1 and Clade 2 of the mpox virus necessitates clade-specific public health strategies, including diagnostics, vaccination, and outbreak response protocols tailored to the unique characteristics of each lineage. Ongoing genomic surveillance and integration of molecular and epidemiological data are essential for tracking emerging lineages and informing public health responses.

Abbreviations

ACDC Africa Centre for Disease Control and Prevention

APOBEC3 Apolipoprotein B mRNA Editing Enzyme, Catalytic Polypeptide-like 3

CCP Compliment control protein

DRC Democratic Republic of Congo

IL1A Interleukin-1 alpha

MPXV Mpox virus

MSM Men who have sex with men

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PHECS Public Health Emergency of Continental Security

Declarations

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Not applicable

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Not applicable

Availability of data and materials:

Data is available on reasonable request to the corresponding author**.**

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TNY conceptualize and design the study, data analysis and interpretation, and manuscript development, IMT data retrieval, analysis, and interpretation, UST data analysis and manuscript review, MMS data retrieval, analysis, and interpretation, NNI data retrieval, analysis, and interpretation, OIO data retrieval, analysis, and interpretation, and AIA data retrieval, analysis, interpretation, manuscript review, and mentorship.

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Figures

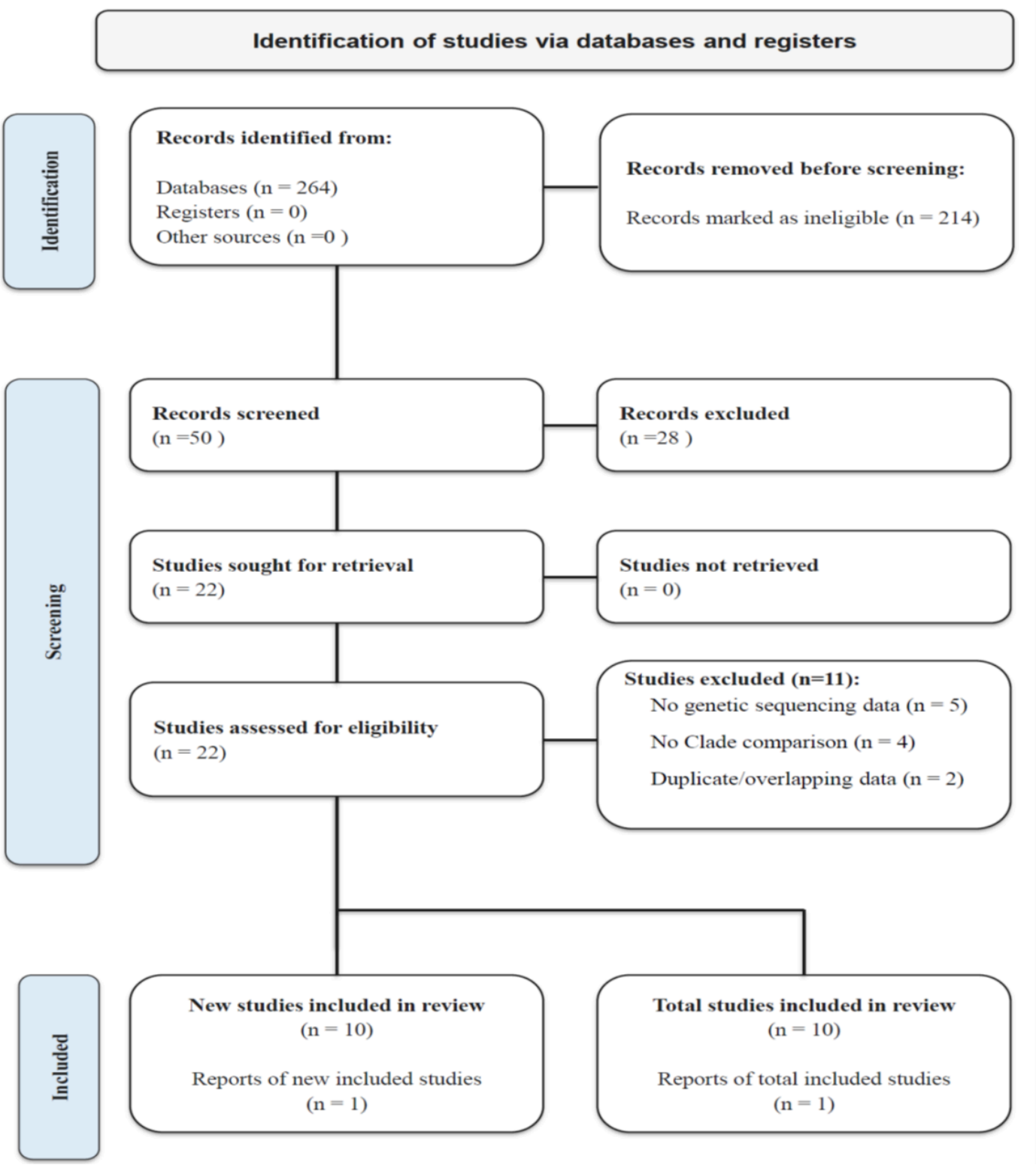


Figure 1

PRISMA Flowchart Diagram for the Study

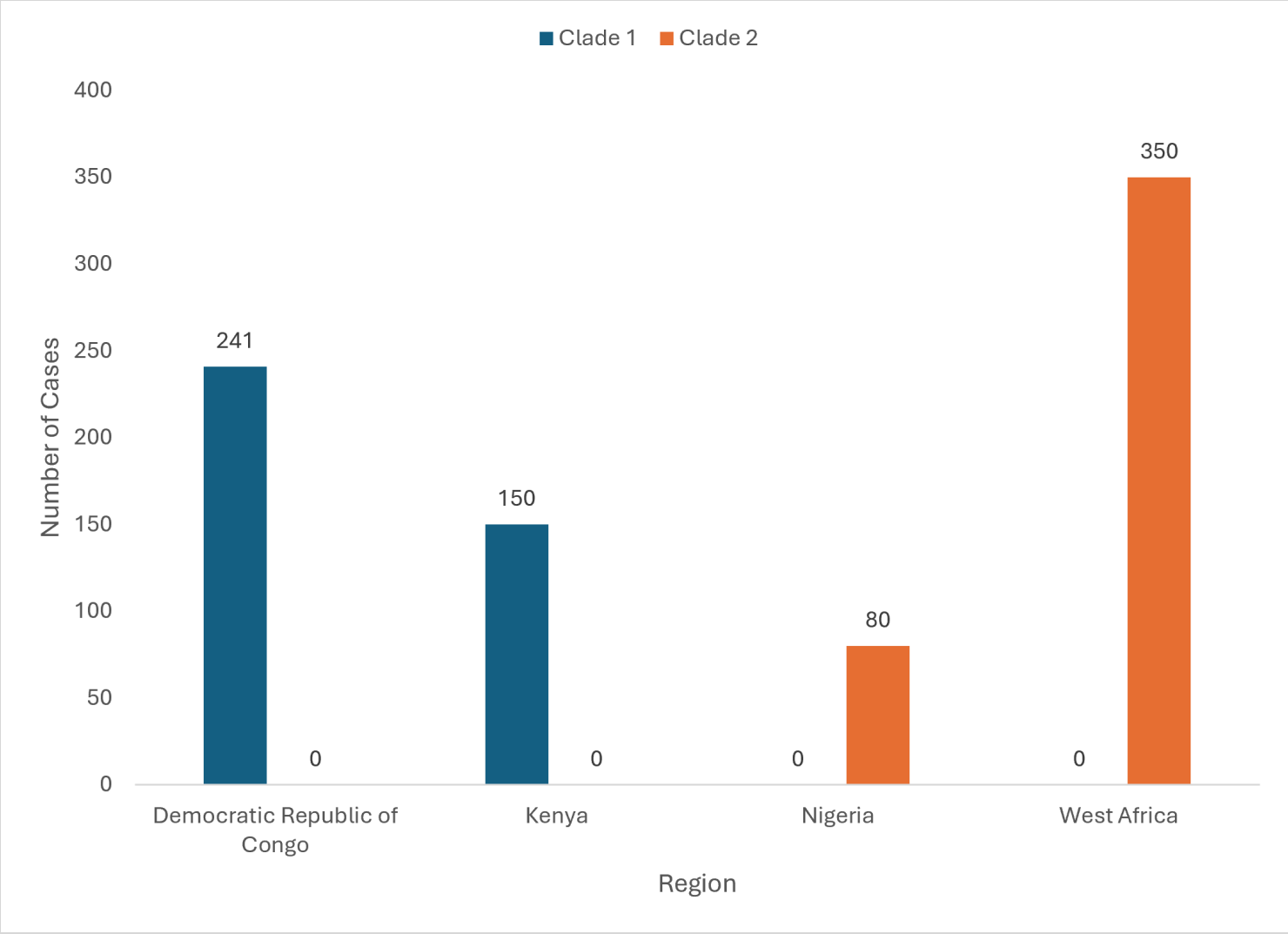


Figure 2

Mpox Outbreak Case Counts by Clade and Region

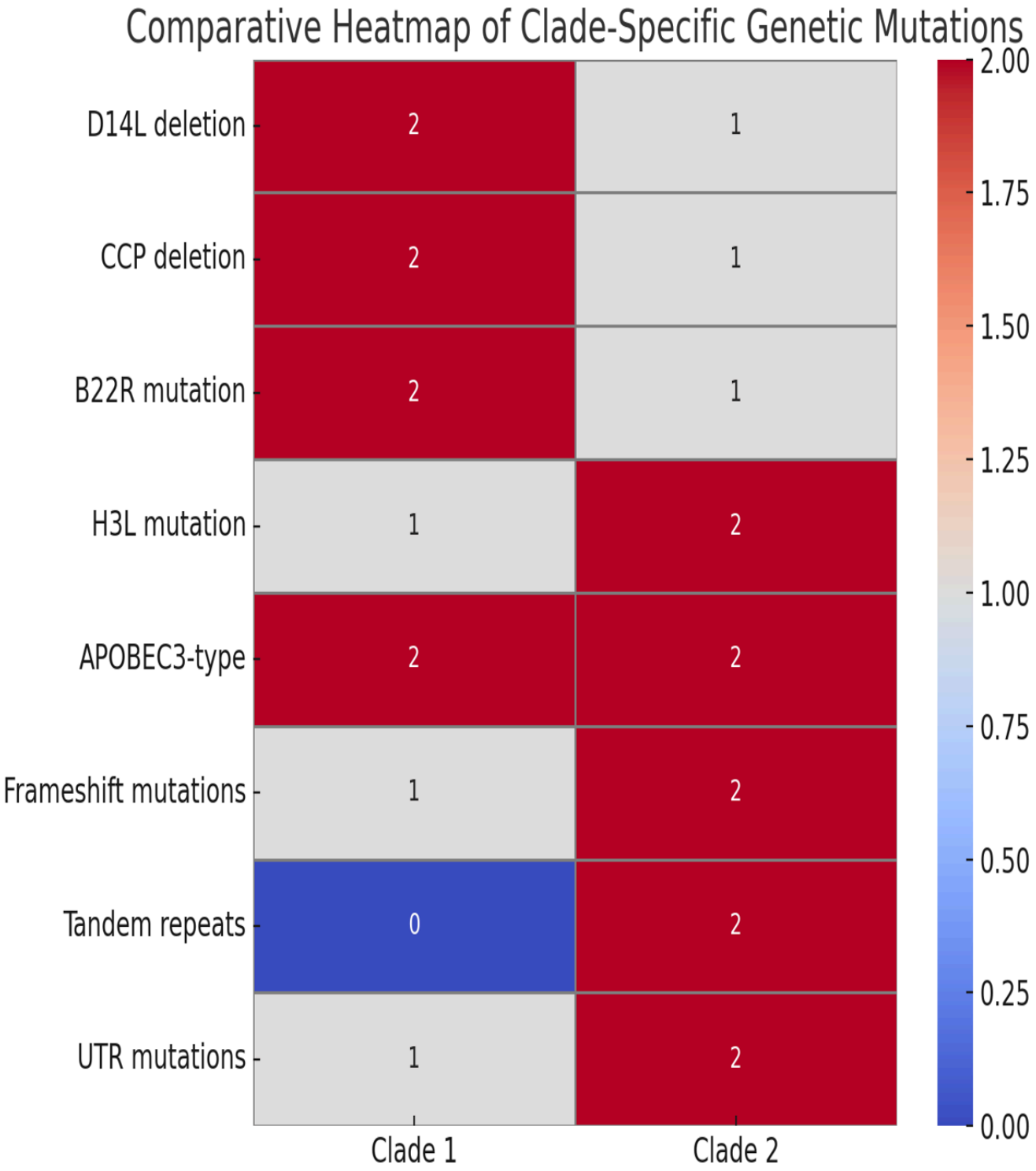


Figure 3

Comparative Heatmap of Clade-Specific Genetic Mutations