

Mpox: genomic insights and public health implications

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Mpox: genomic insights and public health implications

The emergence of monkeypox (mpox), formerly known as monkeypox virus (MPXV), as a global public health threat has profoundly transformed our understanding of orthopoxviruses, highlighting critical gaps in surveillance, control strategies, and basic virological knowledge. Historically considered a rare zoonotic disease, mpox was primarily confined to the rainforest regions of central and West Africa, with the first human case identified in 1970 in the Democratic Republic of Congo (DRC) [1,2]. For decades, outbreaks were sporadic and mostly associated with animal-to-human transmission. However, the global outbreak of 2022 marked a decisive turning point in the epidemiological landscape, revealing an unexpected ability of the virus to sustain human-to-human (H2H) transmission in several nonendemic areas. This development has highlighted a fundamental shift in the interaction between MPXV and the human host, as persistent interhuman transmission—previously thought biologically unlikely—has been observed in all viral clades [3]. This paradigm shift challenges previous assumptions about the limited transmissibility of the virus and underscores the need to revise current models of public health response. Given the growing epidemic potential of mpox, especially in light of these new transmission dynamics, it is essential to gain a thorough understanding of its virological evolution. In this context, we conducted an evolutionary analysis based on genomic data of all available sequences of MPXV, offering new insights into the pathogenicity of the virus and its future adaptive potential.

Factors driving epidemic potential

The potential for mpox to spread epidemically is determined by a complex interplay of factors, including interhuman transmission mechanisms, virus evolution, population immunity levels, and various social determinants of health. Comparing mpox with other viruses responsible for significant outbreaks, such as SARS-CoV-2, reveals substantial differences in transmission dynamics. While COVID-19 demonstrated the devastating impact of highly efficient airborne transmission, mpox highlights how even zoonotic viruses with more specific transmission requirements can

sustain significant interhuman transmission under favorable conditions [2]. Unlike SARS-CoV-2, which is transmitted primarily through respiratory droplets and aerosols, the transmission of mpox usually occurs through close physical contact with infected skin lesions, body fluids, or contaminated materials. Respiratory transmission can occur during prolonged face-to-face contact, and potential short-range aerosol transmission, although less efficient, has also been documented [4]. The baseline reproduction number (R_0) for mpox Clade IIb generally ranges between 0.6 and 1.0, with lower values in the general population and higher values in networks with frequent close contacts, particularly among men who have sex with men (MSM). In these settings, R_0 often exceeds 1, allowing sustained transmission, whereas in non-MSM populations it tends to remain below 1 unless there are high rates of secondary transmission [5]. These values contrast with the R_0 of ancestral SARS-CoV-2, estimated to be between 2 and 3 [6], suggesting that mpox outbreaks, while posing a serious threat, are generally more circumscribed and manageable through targeted public health interventions.

Sexual transmission played a key role in the 2022 global epidemic, particularly in the spread of Clade IIb [7]. However, transmission is not limited to sexual contact. Non-sexual routes, such as household contact—especially in children during Clade I outbreaks—contact with contaminated materials (fomites), and transmission in healthcare settings where control measures are inadequate, have all been documented [4,8]. Heterosexual transmission has also been reported, particularly during Clade Ib outbreaks [9]. Despite these different modes of transmission, current evidence suggests limited community-wide spread *via* nonsexual routes in nonendemic settings. Consequently, risk assessments for the general population remain low in regions such as the United States and the EU/EEA [8].

Finally, behavioral and social factors further influence the transmission dynamics of mpox. Networks with a high frequency of sexual activity, social events, or gatherings that encourage close contact can accelerate the spread. In addition, the stigma associated with the disease can be a barrier to early diagnosis, seeking medical

treatment, and taking preventive measures, thus hindering containment efforts [10].

At the genomic level, there is a clear separation, as is well known, between the two clades currently in circulation (Figure 1): Clade I and Clade II.

The phylogenomic reconstruction confirms their common origin dating back in time, as well as the presence of parallel evolution, which over the years has led to the diversification of two lineages with distinct characteristics, both at the genomic level and in terms of fitness. Clade I, previously referred to as the Central African (Congo Basin) clade, and Clade II, formerly known as the West African clade, differ in their impact and transmission [11]. Clade I is associated with more severe disease and higher transmissibility, exhibiting a case fatality rate (CFR) above 10%, while Clade II has a CFR of less than 1% [12]. The virus has been identified in animal hosts such as rodents and non-human primates. Clade II was first identified during outbreaks in Nigeria, Singapore, the UK, and the US between 2017 and 2019, and it is responsible for the rapid global spread observed in 2022 [13]. The genetic structure between the two clades is clearly defined and based on the topology and the presence or absence of subgroups, different evolutionary rates and speeds are evident. Clade I is more adapted to its region of origin and does not show the presence of further lineages within it, except for the subdivision into two subclades, a and b. The Clade Ib is of recent origin, first isolated in August 2024 [14], when it presented the first extra-African case with a higher

fitness performance compared to the original strain (former Clade I, now Clade 1a).

As shown in Figure 2A, the phylogenomic reconstruction suggests differing evolutionary rates between the two subclades, inferred from branch lengths: subclade 1a, the older lineage, appears more conserved and slow evolving, whereas the more recent subclade shows a faster and more variable evolutionary pattern. For what Clade II is concerned, the phylogenomic reconstruction (Figure 2B) reveals a substantial genetic variability following the onset of the international outbreak. The branching patterns, color-coded by country of origin, display a complex genomic structure characterized by the emergence and co-circulation of multiple viral lineages. The marked horizontal divergence of branches and the higher frequency of bifurcations suggest an ongoing and rapid evolutionary dynamic in comparison with Clade I, with the progressive accumulation of mutations contributing to lineage diversification. The coexistence of both short and extended branches reflects heterogeneous substitution rates among different subgroups, potentially driven by varying epidemiological and transmission dynamics across geographic regions. Additionally, the non-random clustering of similarly colored tips within specific clades points to localized transmission chains, while the intermixing of diverse colors within other clusters implies multiple independent introductions and international dissemination events. Overall, the tree topology reflects a high degree of evolutionary

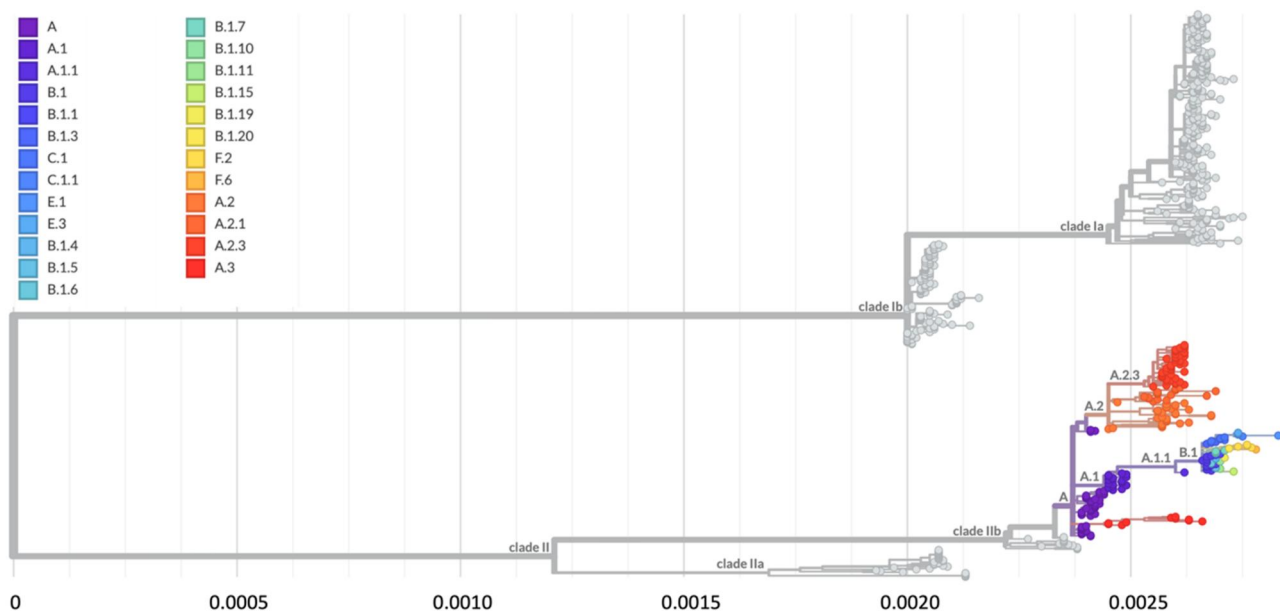


Figure 1. Phylogenomic analysis of all clades and lineages of MPXV sampled from 1958 and February 2025. Data have been downloaded from GISAID (available at <https://gisaid.org>), last updated on 2025-03-30. The analysis was conducted using the nextstrain/ncov tool from the GitHub repository (<https://github.com/nextstrain/ncov>). The figure was edited with GIMP 2.8 software (available at <https://www.gimp.org/downloads/oldstable/>).

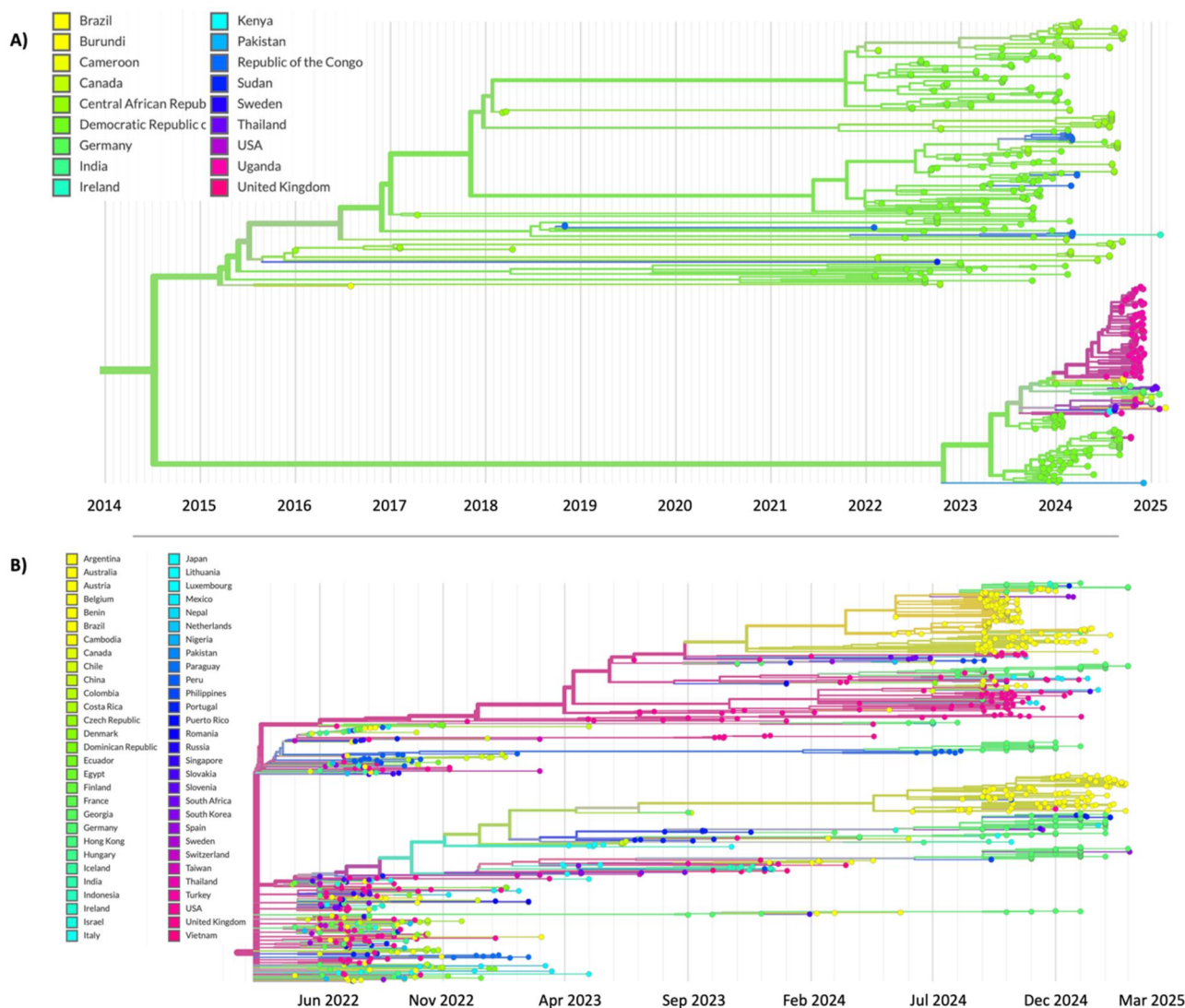


Figure 2. Phylogenomic analysis of clades I (A) and II (B) was performed individually. Genomes for Clade I were collected between January 2016 and February 2025, while genomes for Clade II were collected between October 2017 and March 2025. Data have been downloaded from GISAID (available at <https://gisaid.org>), last updated on 2025-04-01. In both cases, the analysis was conducted using the nextstrain/ncov tool from the GitHub repository (<https://github.com/nextstrain/ncov>). The figure was edited using GIMP 2.8 software (available at <https://www.gimp.org/downloads/oldstable/>).

plasticity, underscoring the virus's ability to adapt across diverse ecological and epidemiological contexts while maintaining efficient global spread. Among the subset of MPXV Clade II, the maximum level of genetic distance of 0.007 (± 0.0002), highlighting the overall genomic stability of the virus despite its global spread. This condition is in general quite normal for DNA viruses that typically evolve more slowly than RNA viruses, leading to weak or absent correlations between genetic divergence and sampling dates. MPXV indeed, lacks the high mutation rate characteristic of RNA viruses, which would otherwise support rapid evolutionary shifts.

This genomic conservation supports the long-term use of current law enforcement tools: the JYNNEOS vaccine, used against smallpox, has shown 66% efficacy

against mpox in real-world settings, while antivirals such as tecovirimat target conserved viral proteins, providing durable tools for outbreak management [15]. Additionally, waning population immunity following the cessation of smallpox vaccination [16], combined with inequities in vaccine access (with endemic African regions reporting <10% coverage [17]), heightens the risk of future spill-overs and sustained transmission.

Effectiveness of current counter measures

Currently, several countermeasures are taken to prevent and contain mpox outbreaks, including vaccination strategies, antiviral treatments, and public health interventions. Vaccination is a key tool in reducing the risk of

transmission. The JYNNEOS vaccine, based on a modified version of vaccinia virus Ankara (MVA), is licensed for use against mpox. Data collected during the outbreak caused by Clade IIb in 2022 indicate that two doses of the vaccine offer significant protection, with estimated efficacy between 66% and 90% [18], while a single dose showed efficacy around 75-78%. It is relevant to note that “breakthrough” infections in vaccinated individuals tend to occur in a milder form than in unvaccinated individuals [18]. Information on the efficacy of JYNNEOS against Clade I is currently more limited [19]. However, an unpublished CDC study conducted in the Democratic Republic of Congo (DRC), where Clade I circulation is high, reported only one confirmed case among 1,600 vaccinated healthcare workers [20], suggesting some degree of protection.

Current vaccination strategies focus on targeted protection of individuals at high risk of exposure, including close contacts of confirmed cases and healthcare workers. Pre-exposure prophylaxis (PrEP) is recommended for populations with increased exposure risk, while post-exposure prophylaxis (PEP) is advised for unvaccinated close contacts within 14 days of confirmed exposure [21]. Despite the availability of an effective vaccine, global access, and equitable distribution remain significant challenges. The World Health Organisation (WHO), in collaboration with international partners, has established mechanisms to allocate vaccine doses to countries most affected by mpox outbreaks, particularly in Africa [22,23]. A phased vaccination approach is commonly adopted, prioritizing the most vulnerable groups according to local epidemiological conditions [24]. Nonetheless, studies have reported low uptake of vaccination even among eligible individuals in some settings, highlighting the urgent need for more effective outreach strategies and improved accessibility to vaccines [25].

Antiviral treatments represent another important component of the mpox response. Tecovirimat (TPOXX), an antiviral targeting conserved proteins across orthopox viruses, has been employed in mpox management [26]. However, results from two randomized clinical trials—PALM007, which focused on Clade I mpox in the Democratic Republic of the Congo, and STOMP, which investigated Clade II mpox—indicate that although tecoviratis safe, it does not significantly reduce the time to resolution of skin lesions in patients with mild to moderate disease [27]. As a result, its use is now recommended primarily for individuals with severe disease or those who are immunocompromised, through an

Expanded Access Investigational New Drug (EA-IND) protocol managed by the CDC [28]. Preliminary data from the PALM007 trial also revealed lower mortality among hospitalized patients receiving supportive care, regardless of tecovirimat administration [29]. Furthermore, a recent Morbidity and Mortality Weekly Report (MMWR) documented an outbreak of mpox cases caused by a TPOXX-resistant variant in five U.S. states between October 2023 and February 2024. This outbreak involved 18 individuals who had not previously received treatment with tecovirimat, raising concerns about the emergence of antiviral resistance [30].

Future risk assessment and projections

Several epidemiological models and projections have been developed to assess the potential for future mpox epidemics, considering various transmission scenarios and geographical regions.

A recent study employing time series analysis techniques, including ARIMA models and Join Point Regression, forecasted mpox outbreak trends in Africa’s most affected countries (Nigeria, Democratic Republic of Congo, Central African Republic, and South Africa) from August 2023 to October 2024. The analysis revealed significant regional disparities, with the Democratic Republic of Congo bearing the highest burden of cases [31]. A model developed for the Netherlands suggests that future outbreaks among MSM remain a possibility due to declining immunity within this high-risk group; however, the model also indicates that preventive vaccination and behavioral adaptations could significantly reduce the number of cases. The introduction of a sub-clade with even higher transmissibility could lead to a substantial increase in the overall case burden [32]. A SEIR model applied to the 2023 mpox wave in Portugal indicated that transmission was highly sensitive to sexual behavior, with even slight increases in high-risk sexual activity potentially triggering new waves of infection [33]. A two-layer network model focusing on the 2022-2023 outbreak in the United States emphasized the significant role of behavioral changes, rather than solely vaccination, in slowing the spread of the mpox virus [34]. Modeling efforts by the CDC suggest that close-contact transmission within and between households in the US is unlikely to result in large Clade I mpox outbreaks, with most household clusters expected to involve ten or fewer cases and minimal spread between households [35]. A compartmental model constructed to assess potential mpox transmission dynamics in 37

Asian cities indicated that large-scale outbreaks could occur in territories with high proportions of sexually active individuals at risk or low immunity from smallpox vaccines, with the size of outbreaks increasing linearly with the number of initial exposures; the model also projected that non-pharmaceutical interventions such as isolation and quarantine could significantly alleviate potential outbreaks [36]. A global prediction model utilizing a modified SEIR approach demonstrated good accuracy in predicting the 2022 mpox epidemic, and simulations indicated that vaccination could effectively reduce the number of infected individuals [37].

These diverse modeling approaches highlight the complexity of predicting future mpox trends, which are influenced by a multitude of interacting factors, including transmission dynamics, behavioral responses, the effectiveness and uptake of vaccination, and the ongoing evolution of the virus with the emergence of new clades. While some models suggest a potential for future outbreaks, particularly if immunity levels decline or more transmissible variants become dominant, others indicate a current downward trend in certain geographical areas. The emergence of Clade Ib, with its reported increased transmissibility, introduces a significant element of uncertainty into these projections, underscoring the need for continued monitoring and refinement of predictive models as new epidemiological and genomic data become available.

Recommendations for epidemic preparedness and response

To effectively address potential epidemic risks related to mpox, a multilevel and integrated approach is essential. In light of the current epidemiological context and potential future developments, the following priority actions are recommended:

1. Strengthen monitoring systems, especially in endemic areas and countries affected by new outbreaks, to detect cases and variants early. Improve genomic sequencing to track virus evolution and identify any changes in transmissibility, virulence, or ability to evade immune response. Intensify monitoring of nonsexual transmission routes to gain a comprehensive view of how mpox is spread.
2. Invest in in-depth studies of the natural history of the disease, including animal reservoirs and transmission dynamics. Support the development of faster and more effective diagnostic tools, such as point-of-care tests.

Pursue research on safer and more effective antiviral therapies tailored to different viral clades. Evaluate new vaccine technologies, such as mRNA technologies, to respond rapidly to the emergence of new variants.

3. Develop and implement comprehensive preparedness and response plans, both nationally and globally, in line with WHO guidelines. Ensure equitable distribution of vaccines and treatment, with a focus on the most vulnerable populations and endemic areas. Apply targeted vaccination strategies to high-risk individuals, such as close contacts and health care workers. Disseminate clear, accessible, and culturally sensitive messages to increase awareness about mpox prevention, transmission, and symptoms, countering stigma and promoting equity. Strengthen health facilities and staff capacity for effective outbreak management, including contact tracing, case isolation, and infection control.
4. Take measures to reduce human-wildlife interactions in endemic areas to limit the risk of zoonotic transmission. Address social determinants of health, such as poverty, overcrowding, and limited access to health services, which increase vulnerability to the virus. Develop targeted interventions for specific risk groups, such as the MSM population, offering information, testing, vaccination, and care. Counter stigma and discrimination to promote early diagnosis and access to treatment.
5. Promote active collaboration among governments, health agencies, research institutions, and the private sector to share data, resources, and expertise. Support low- and middle-income countries in their preparedness and response efforts through technical and financial assistance.

Conclusion

The recent global emergence and spread of mpox have highlighted critical gaps in our understanding of orthopoxvirus evolution, transmission, and control. While historically considered a zoonosis with limited H2H transmissibility, mpox has demonstrated the capacity to sustain transmission chains under specific epidemiological conditions, particularly within high-contact networks. The comparative analysis of Clade I and Clade II viruses reveals significant differences in pathogenicity, transmissibility, and evolutionary dynamics, with Clade II exhibiting greater genomic plasticity and a broader global spread, albeit within the constraints imposed by its DNA-based replication machinery. Despite its relatively low mutation rate compared to RNA viruses, MPXV has

shown the potential to diversify and adapt, particularly in the context of Clade IIb, as evidenced by phylogenomic reconstructions. However, the overall genomic conservation of the virus supports the continued efficacy of existing medical countermeasures, including the JYNNEOS vaccine and antiviral therapies such as tecovirimat, which target conserved viral elements. In the face of ongoing transmission and the risk of future re-emergence, especially in regions with low vaccine coverage and high zoonotic exposure, a proactive and globally coordinated response is essential. Strengthening genomic surveillance, enhancing access to diagnostics and vaccines, investing in research, and addressing social and ecological determinants of transmission must be prioritized. These actions, combined with equitable public health strategies and strong international cooperation, will be crucial to mitigating the risk of mpox becoming a sustained global health threat or triggering future large-scale outbreaks.

All these efforts must be supported by continuous and comprehensive genomic surveillance, which remains essential for anticipating viral shifts, detecting emerging variants, monitoring evolutionary trends, and refining public health strategies over time.

Authors' contribution

Francesco Branda: Conceptualisation, Investigation, Writing—Original Draft, Writing—Review & Editing. **Massimo Ciccozzi:** Conceptualisation, Supervision, Validation, Writing—Original Draft, Writing—Review & Editing. **Fabio Scarpa:** Conceptualisation, Investigation, Data visualization, Data analysis, Writing—Original Draft, Writing—Review & Editing.

Disclosure statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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