Review

A Review of Epidemiological Modeling Studies on Monkeypox

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ABSTRACT

Between 2022 and 2025, nearly 130,000 confirmed monkeypox (mpox) cases, including over 280 deaths, were reported to the World Health Organization (WHO) from 130 countries and territories, prompting the WHO to declare it a public health emergency of international concern on two occasions. Hence, to enable a scientific approach to prevention and control, transmission dynamics through mathematical modeling must be elucidated. Through a comprehensive literature review on the modeling of mpox transmission dynamics, this study indicates that existing research primarily extends the susceptible-infectious-recovered (SIR) modeling framework and largely focuses on the 2022 global outbreak. The analysis revealed significant variations in mpox virulence, particularly dependent on the subtypes, and variations according to the descending order of clades: Ib>Ia>IIa>IIb. Interpersonal transmission capacity was notably higher for clade II than for clade I, highlighting geographical disparities, with the highest transmission capacity in the Americas, moderate in Europe and Oceania, and the lowest in Asia. In contrast, Africa maintained consistently low but non-declining transmission levels. Furthermore, the study confirmed significant co-infection patterns between mpox and sexually transmitted diseases, such as Human Immunodeficiency Virus (HIV) and syphilis, along with evidence of synergistic transmission interactions among multiple pathogens. This study provides crucial modeling evidence for mpox regulation. By quantifying high-risk populations, evaluating intervention effectiveness, and identifying the risks associated with subtypes and geographic areas, this study offers a comprehensive reference for understanding the interface between model complexity and practical application. These advancements have enhanced the strategic focus and precision of public health responses during outbreaks.

Monkeypox (mpox) is a zoonotic infectious disease caused by the monkeypox virus (MPXV), with clinical manifestations similar to those of smallpox but with lower incidence and mortality (*1*). MPXV is classified into clades I (formerly the Central African or Congo Basin clade, subdivided into Ia and Ib) and II (formerly the West African clade, subdivided into IIa and IIb). Transmission occurs via direct contact with infectious lesions, body fluids, respiratory droplets, or contaminated fomites (*2*). From 1970 to 2017, mpox was endemic primarily in Central and West Africa, predominantly via animal-to-human transmission. Sporadic cases in non-endemic regions were largely related to travel or animal importation (*3*–*4*). However, human-to-human transmission has increased following the 2017 Nigerian outbreak (*5*). In May 2022, a large global outbreak occurred, spreading primarily through sexual contact networks (*6*), with cases reported among men who have sex with men (MSM).

The epidemiological modeling framework for mpox has evolved over the decades, with research on transmission dynamics among humans and between humans and animals, forming a relatively complete theoretical system. This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews guidelines (*7*). The literature search covered the China National Knowledge Infrastructure (CNKI), Web of Science, and PubMed for the period spanning 3 years following the global spread of mpox in 2022 (2022–2025). The focus was on the literature employing mathematical modeling methods to study the transmission dynamics models of orthopoxvirus (mpox) among humans or between humans and animals. The searches were conducted on December 25, 2025, using keywords including "mpox," "Ia/Ib/IIa/IIb," "dynamic" and "model." "Monkeypox" was also included as a keyword for the 2022 publications to account for the WHO nomenclature change in November 2022. This study did not include

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gray literature, and all analyses were based on published peer-reviewed academic literature. No geographic or language restrictions were applied.

The systematic search yielded 11,824 relevant records. After deduplication, 5,479 duplicate records were removed. The remaining records were independently screened by two reviewers in a two-round process and discrepancies were resolved by consensus. The first round, based on title and abstract review assessing the application of mathematical compartmental models, identified 122 articles for full-text assessment. During the second round of full-text screening, 39 articles that did not analyze the epidemic transmission potential and 4 dissertations were excluded. Ultimately, 79 studies were included in the systematic review of compartmental structures, parameter settings, and dynamic characteristics of the models (Figure 1).

COMPARTMENTAL MODEL STRUCTURE

Since Kermack and McKendrick introduced the classic susceptible-infectious-recovered (SIR) compartmental model in 1927 (*8*) and elucidated the threshold theory of infectious disease dynamics in 1932 (*9*), mathematical compartmental models have become essential tools for evaluating epidemic prevention and control strategies. The study of mpox transmission dynamics still employed the basic SIR model to depict the fundamental transmission process of the disease (*10*–*13*). Based on the natural history of mpox virus infection, most studies have introduced an exposed compartment E (exposed) to construct the susceptible-exposed-infectious-recovered (SEIR) model (*14*–*18*), whereas a few have incorporated an asymptomatic infectious compartment A into the

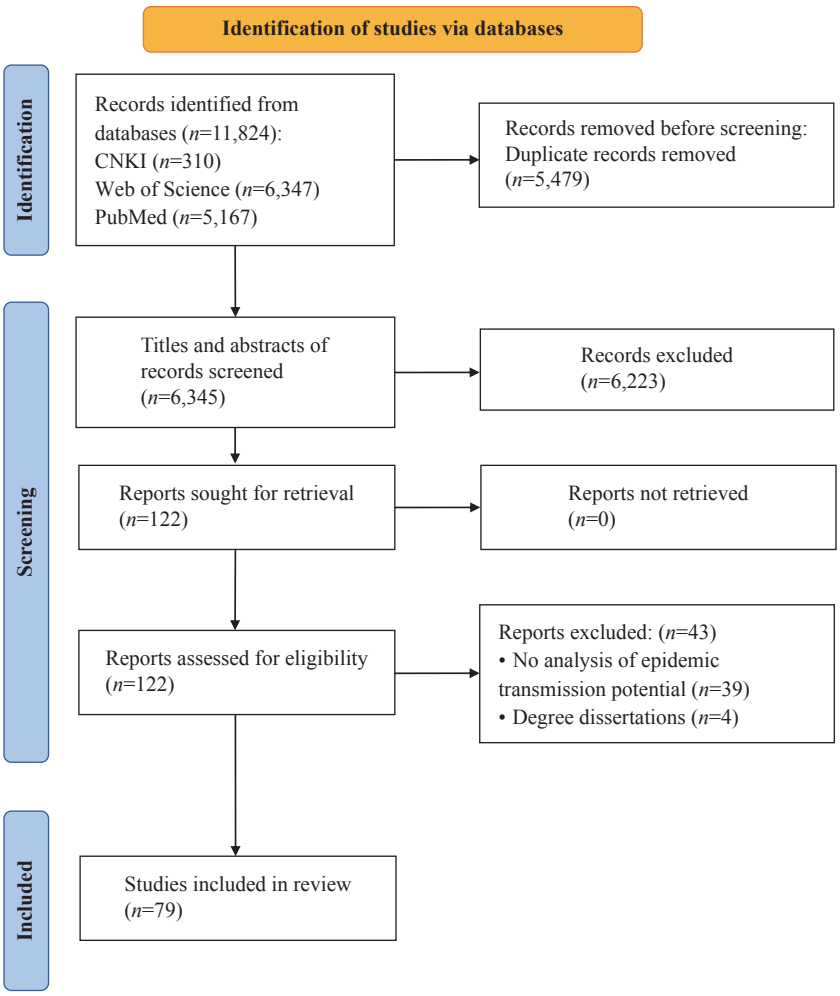


FIGURE 1. Flowchart of literature screening and selection results.
Abbreviation: CNKI=China National Knowledge Infrastructure.

model framework (*19*–*20*) as a possible state following the exposure period, thereby providing a more comprehensive representation of the clinical spectrum and transmission characteristics of mpox. Given the zoonotic nature of mpox, numerous models have also incorporated animal populations (e.g., rodent or murine species), typically with simplified compartmental structures, such as susceptible-infectious (SI) (*21*–*29*), susceptible-exposed-infectious (SEI) (*30*–*38*), SIR (*39*–*40*), and SEIR (*41*–*48*). To distinguish them from human compartments, animal compartments are often labeled with subscripts, such as m, r, or a. Infected animal compartments (I_m, I_r, and I_a) serve as sources of infection, participating in both transmission within susceptible animal populations (S_m, S_r, and S_a) and cross-species transmission to susceptible humans (S_h). A few models consider reverse transmission from infected humans (I_h) to susceptible animals (*25*,*34*,*44*,*46*,*49*). Through a systematic review of the relevant models, this study summarizes a schematic diagram of the mpox transmission patterns (Figure 2), revealing that the evolution of model frameworks has always been closely aligned with their transmission characteristics.

To better capture the complexities of transmission, several studies have extended model frameworks by incorporating population heterogeneity and dynamic control measures. Spatial and demographic heterogeneity are addressed by expanding compartments with subscript i, representing either different countries to model the effect of cross-border mobility on epidemic spread (*50*–*51*) or different age groups to analyze variations in disease prevalence across age structure (*13*,*52*–*53*). Furthermore, given the high incidence of mpox among MSM, some models further stratify them based on sex or sexual behavior risk, dividing it into male (subscript m) and female (subscript f) groups (*54*) or into high-risk (subscript h) and low-risk (subscript l) groups (*50*,*55*–*60*), to construct coupled multi-group models. Vaccination, the most frequently considered intervention, is typically modeled before exposure. This is achieved by establishing dedicated compartments for vaccinated (V) or protected (P) (*60*–*64*) or by further subdividing the susceptible population into vaccinated (S_v) and unvaccinated (S_u) subgroups (*65*), representing the transition from susceptible to an immune state. Regarding the sequence of vaccination and isolation, some studies have also incorporated a post-exposure vaccination compartment (Q_v) (*50*). Models vary in their assumptions regarding vaccine-induced immunity, ranging from complete protection

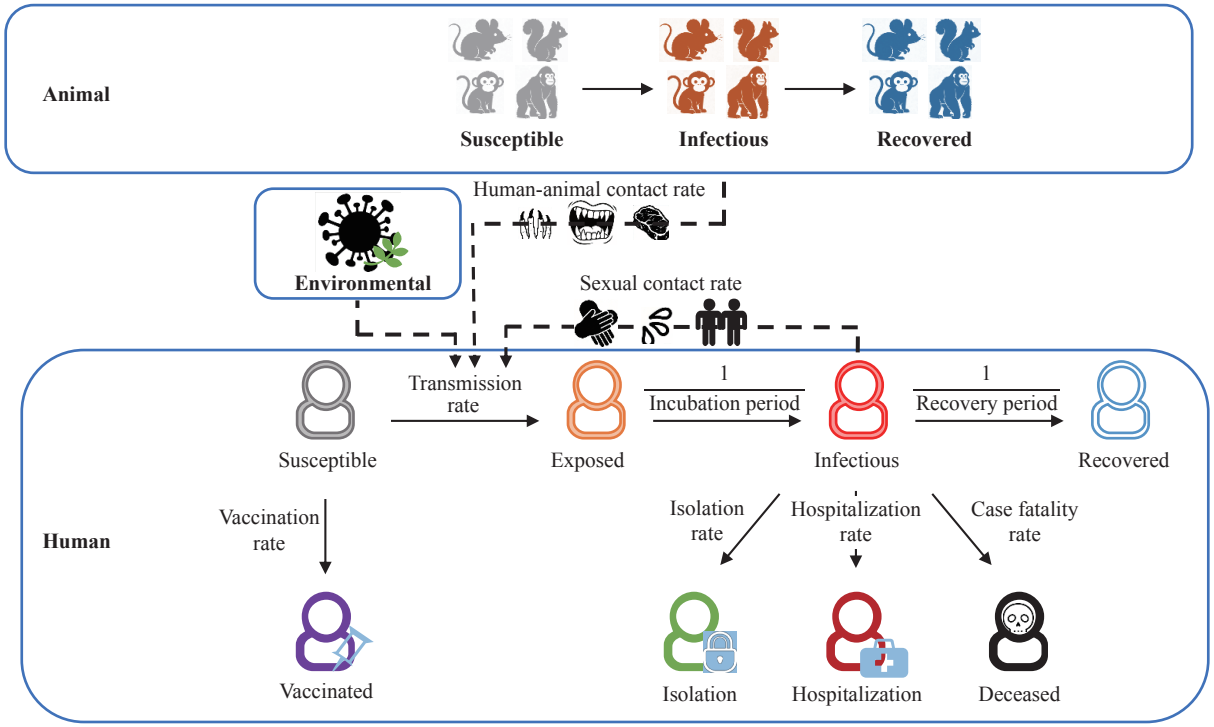


FIGURE 2. Schematic diagram of the conceptual framework and key components for mpox transmission dynamics modeling.
Abbreviation: mpox=monkeypox.

(57,63–64,66) to accounting for breakthrough infections (19,50,52,58–60,67–68) and waning immunity (18,21). Furthermore, isolation (Q) (19,38,50,56,60–62,69–71) or hospitalization (H) (60,68) compartments are included to manage symptomatic cases; a deceased compartment (D) (41,62–64,67,72) captures mortality outcomes; and an environmental contamination compartment (C) (73–74) simulates pathogen persistence, dissemination in the environment, and its role as a potential source of infection.

Owing to the temporal overlap of the mpox outbreak with the coronavirus disease 2019 (COVID-19) pandemic in 2022, some current modeling studies include analyses of the transmission dynamics of mpox co-infection with COVID-19 (75). Moreover, given that the epidemiological characteristics of mpox is primarily transmitted through sexual contact, co-infection with sexually transmitted pathogens such as HIV (54,76–79) and *Treponema pallidum* (80) has also become a significant focus of modeling research. Among these, models of mpox and HIV co-infection are relatively more common. These models typically construct three parallel transmission chains: monkeypox virus-only infection, HIV-only infection, and co-infection with both pathogens, with the susceptible population generally treated as a unified group. Common compartments include individuals infected only with mpox (I_m), individuals infected only with HIV (I_h), individuals infected with HIV receiving antiretroviral therapy (ART) (I_h^T), and individuals co-infected with both viruses (I_{mh} and co-infected individuals receiving ART, I_{mh}^T). As the classification of infections expands, the compartmental structure and dimensionality of the models increase significantly. Although this better reflects real-world complexity, it also significantly increases the difficulty of analyzing model dynamics.

MODEL PARAMETERIZATION

As core parameters of compartmental models, the values of the transmission rate coefficient (β), latency period, and recovery period vary depending on the study context, population structure, and transmission routes. Global data indicate an average human-to-human transmission rate of approximately 0.09 per day (64). The rate is significantly higher in high-risk populations, predominantly among MSM (50,55,58,67–68,75), with a per-sexual contact transmission rate of 0.24/day in Canada (56) and 0.34/day in the United States of America (USA) (81) in 2022. In contrast, the non-sexual contact rate in low-risk populations is only about one-thousandth of the sexual contact rate (82), and the estimated β value for the environmental transmission route is as low as 7.70×10^{-8} (73). The average incubation period is primarily considered as 8.5 (11,51,56,58) and 13 (50,64) days. Africa Centers for Disease Control and Prevention supports an average of 13 days (64), whereas Western countries adopt a mean of 8.5 days (51,56,58), possibly reflecting regional differences in population immunity. The prodromal period lasts 1–4 days (11,83–84); though asymptomatic, the mean infectiousness coefficient is between 0.25 and 0.51 (82).

For recovery, without isolation, untreated infected individuals have a mean recovery period of 21 days (20,50,56,60,63–64,74), with no significant differences in recovery rates across populations (81). The weekly recovery rate is 1.4×10^{-3} for both children/adolescents and adults (13) and similar for symptomatic and asymptomatic cases (20,56,64). Vaccination shortens recovery (20,25,61,67,74), and pre-exposure coverage of 20%–50% in high-risk populations yields major control benefits (28,61). Two-dose recipients recover approximately 30% faster (85), whereas vaccine waning rates range from 3.17×10^{-3} to 2.04×10^{-2} per day (19). Protection lasts approximately 5 years for a single dose and approximately 10 years for two doses, similar to natural immunity (67). However, modeling evidence confirms that residual immunity from historical smallpox vaccination alone is insufficient to prevent or contain mpox outbreaks (39). In fact, vaccination and isolation exhibit synergistic effects. Specifically, at ≤20% vaccination coverage, a 40% isolation rate is required to control transmission, whereas at 30% coverage, a 20% isolation rate remains effective (61).

For zoonotic diseases, the human-to-animal contact rate is a key parameter in models of initial outbreaks, areas with a clear animal exposure risk, or transmission chains traceable to animal contact (32-33,44–45,48). Its value varies according to regional habits, ecology, and host distribution. In endemic regions of Africa, where rural residents hunt, consume, or keep wild animals, the estimated human-to-animal contact rates are significantly higher than in non-endemic areas (34,44–45,48), ranging from 2.50×10^{-4} to 2.70×10^{-2} (33,40). The per-contact transmission probability from rodents to humans is 0.13 in the Democratic Republic

of the Congo (DRC) and as high as 0.85 in Nigeria (*45*). In contrast, outbreaks in Europe and North America are primarily driven by human-to-human transmission (*26*). During the 2022 outbreaks, the transmission rate associated with human-to-animal contact was 5.00×10^{-4} in Spain and 3.30×10^{-4} in Italy. Sensitivity analysis identified the animal-to-animal transmission rate and human-to-animal contact rate as critical parameters influencing R_0. Interventions targeting animal reservoirs and reducing human-to-animal contact rates could potentially reduce the number of infections by over 80% (*44*).

HIV and *T. pallidum*, as significant co-infecting pathogens in mpox transmission, influence mpox transmission dynamics primarily via susceptibility (*77*–*78*), infectiousness (*77*–*78*), and response to interventions (*77*), especially in high-risk populations such as MSM (*77*,*86*). Regarding susceptibility parameters, HIV-infected individuals have a susceptibility adjustment factor for mpox of 1.5, which has remained at 1.3, even for those receiving ART (*77*–*78*). Regarding the infectiousness parameters, the mpox infectiousness adjustment factor for HIV-infected individuals receiving ART is typically <1 (*54*,*77*), indicating that ART moderately reduces the transmission potential of co-infected individuals. Syphilis infection increases susceptibility to mpox to a lesser extent than HIV infection, with an adjustment factor typically set at 1.2. Regarding transmission dynamics, the basic transmission rate is approximately 6.50×10^{-2} for syphilis and approximately 2.01×10^{-1} for mpox. Co-infection with both pathogens exerts a synergistic effect, significantly enhancing the transmission potential compared with mono-infection (*87*). The selected parameter values reported in the literature are summarized in Table 1.

TRANSMISSION POTENTIAL

Transmissibility and virulence of mpox viruses vary by clade. Clade I, which is endemic to the Congo Basin, is characterized by high fatality rates (up to 10%) and zoonotic transmission with limited human-to-human spread (*88*). Subtypes Ia and Ib harbor a high proportion of apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like 3 (APOBEC3)-driven cells (68% and 72%, respectively), suggesting increased adaptability and transmission potential (*89*). Notably, since September 2023, the newly identified Ib subtype among sex workers in the DRC exhibited high fatality rates (approximately 5.3% overall and 8%–10% in children) (*90*–*93*), providing preliminary evidence of increased virulence and transmission efficiency. In contrast, clade II is predominantly

TABLE 1. Selected parameters for mpox compartmental models from the literature.

Parameter	Units	Values	Reference
Human epidemiological parameters for mpox			
Human-to-human transmission rate	$Days^{-1}$	0.09 (international average value)	(*64*)
		0.24 (sexual, Canada)	(*56*)
		0.34 (sexual, USA)	(*81*)
Transmission rate coefficient	N/A	7.70×10^{-8} (environmental transmission)	(*73*)
		0.25–0.51	(*82*)
Incubation period	Days	8.5	(*11*,*51*,*56*,*58*)
		13 (average)	(*50*,*64*)
Prodromal period	Days	1–4	(*11*,*83*–*84*)
Recovery period	Days	21	(*20*,*50*,*56*–*60*,*63*–*64*,*74*)
Recovery rate	$Weeks^{-1}$	1.4×10^{-3}	(*13*)
Vaccine waning rate	$Days^{-1}$	3.17×10^{-3}–2.04×10^{-2}	(*19*)
Animal transmission mpox infection parameters			
Human-to-animal contact rate	N/A	2.50×10^{-4} –2.70×10^{-2}	(*33*,*40*)
Per-contact transmission probability	N/A	0.13 (DRC)	(*45*)
		0.85 (Nigeria)	(*45*)
Human-animal contact rate	N/A	5.00×10^{-4} (Spain)	(*26*)
		3.30×10^{-4} (Italy)	(*26*)

prevalent in West Africa, demonstrating higher human-to-human transmissibility and lower fatality rates of approximately 1% (*88*). Clade IIa, which shares approximately 95% nucleotide sequence homology with clade I, follows a zoonotic transmission pattern (*88*). Clade IIb, the primary subtype responsible for a global outbreak in 2022, combines high human transmissibility with relatively low virulence (*88*,*93*).

On May 7, 2022, the United Kingdom (UK) reported its first imported case, after which the outbreak rapidly spread to multiple countries in Europe and the Americas. During the early phase, transmission was most rapid in Europe, Oceania, North America, and Latin America, with the median basic reproduction number (R_0) reaching 7.02 (range 7.01–7.84). Asia and Africa recorded lower values of 3.68 and 1.61, respectively. After June 23, 2022, the transmission rates declined significantly in most regions except Africa. The median R_0 value in the medium- to high-risk countries dropped to 1.35. Geographically, R_0 remained at relatively high levels in Latin America and North America (4.13 and 3.51, respectively), followed by Oceania and Europe (1.67 and 1.35, respectively), whereas Asia recorded the lowest (0.70) (*51*). By December 2022, the cumulative number of cases in non-endemic countries exceeded 80,000. Transmission during this outbreak was primarily concentrated in the MSM population. A model based on this group was fitted with a global effective reproduction number (R_{eff}) of 3.11 (*57*).

Transmission in North America occurred significantly earlier in the outbreak. In Canada, R_0 was relatively high, at R_0=1.68 before May 6, 2022 (*57*), with an estimated annual value of 2.37 (*15*,*70*). R_0 for the high-risk, low-risk, and total populations were 1.464, 0.007, and 1.461, respectively. Intervention simulations targeting the high-risk group demonstrated that condom use and abstinence would require adherence rates of 25% and 10%, respectively, to block transmission (*56*,*70*), reducing R_{eff} to 0.69 after behavioral changes (*58*). In the USA, the concurrent R_0 was 3.28 (*15*,*81*), which was significantly higher than that of Canada, with R_0 of 3.88 and 0.39 for the high-risk and low-risk groups, respectively. A two-dose vaccination campaign targeting a high-risk population (71.8% of cases) could prevent approximately 21.2% of infections, whereas behavioral changes alone could prevent 15.4% of cases. This combination exhibited synergistic effects (*20*). Transmission intensity in Latin America was high. Colombia had the highest R_0 at 3.60, with approximately 25% of the actual cases reported on average (*70*). R_0 for Brazil, Peru, and Mexico are 2.61, 2.49, and 2.51, respectively (*15*). In Peru, reported cases were 96.3% male, with a mean age of 32.6 years. MSM accounted for 75.0% of the cases, and the HIV coinfection rate reached 55.6% (*94*).

Transmission in Europe fluctuated. During the initial 2022 outbreak, Spain's R_0 was 2.05 (*57*), increasing to 3.05 for the annual estimate (*15*). Germany's R_0 before May 6, 2022, was 3.21 (*15*), with the annual estimate rising to 3.57 (*57*). The annual R_0 estimates for France and the UK were 2.77 and 2.43, respectively (*15*), whereas Portugal's estimates were lower at 1.05 (*57*). In Africa, Uganda exhibited the highest R_0 at 2.51, followed by Rwanda and Burundi with 1.35 and 1.88 (*65*). In China, an analysis of 1,433 WHO-reported cases from April 3 to September 16, 2023, yielded an initial R_0 of 1.43 (*69*). Following the isolation interventions, R_{eff} decreased to 0.34 (*69*), indicating a transmission intensity lower than the global average.

DISCUSSION

Historically, mpox outbreaks have been largely confined to Africa. However, since the rapid global spread of subclade IIb began in May 2022, the construction of scientifically sound dynamic transmission models has become essential for understanding epidemic patterns and guiding prevention and control strategies. This study systematically reviews 79 publications, tracing the evolution of models from basic SIR/SEIR frameworks to multi-layered, heterogeneous structures incorporating sexual contact networks, cross-species transmission, and multi-pathogen co-infections. It also analyzes key parameters, as well as regional and population differences in transmission potential. The findings reveal a clear trade-off between virulence and transmissibility among viral subclades; while subclade IIb exhibited attenuated virulence, its human-to-human transmissibility was markedly enhanced. Geographically, apart from traditional endemic areas in Africa, the transmission intensity follows a gradient pattern of "Americas > Europe and Oceania > Asia." This distribution is closely associated with regional variations in sexual network density among MSM, the speed of vaccination coverage, and the intensity of public health responses. This work provides a methodological foundation for rapidly modeling and early warning of future mpox outbreaks and offers a

theoretical reference for the early response to potential "disease X" scenarios with similar transmission mechanisms.

During the literature search, different modeling approaches addressed the "what" or "why" questions. However, when the research question advanced to "how to control the outbreak" and "which interventions are most effective," the unique advantages of transmission dynamic models became evident. For instance, a modeling study of the 2022 New York City outbreak subdivided the population into five age groups and seven risk categories and concluded that targeted immunization of high-risk individuals aged 35–44 significantly enhances control effectiveness (*52*). This exemplifies the key distinction between dynamic transmission models and other modeling approaches. Their core value lies in their ability to quantitatively simulate the effects of different control measures, integrate the synergistic effects of multiple interventions such as vaccination, isolation, and behavioral change, and support the dynamic adjustment of strategy parameters as the epidemic evolves.

Although dynamic models hold irreplaceable value in strategy evaluation, existing studies have significant limitations. Some have focused on population stratification within a single region, which limits their ability to capture the complexities of the global spread of mpox, escalating geopolitical conflicts, and reduced international aid (*95*). The 2025 early-phase outbreak of the Ib subclade in China following imported cases (*96*) further underscores the urgent need to shift research from localized static analysis to cross-regional dynamic modeling. A Singapore modeling study demonstrated that dynamically adjusting border strategies based on prevalence rates in countries of origin could effectively reduce importation risk by approximately 21.8% (*14*), confirming the necessity and feasibility of cross-regional modeling. However, parameter estimation often relies on assumptions or literature values without clear justification, and insufficient surveillance, together with a lack of data standardization, may lead to systematic deviations between model predictions and reality (*6*).

In future research, the design of dynamic models must strike a balance between complexity and operability, thereby enhancing the accuracy and interpretability of parameters in real-world contexts through multi-model integration. It is essential to integrate multi-regional population mobility, intervention measures, and surveillance data to construct a dynamic framework that supports differentiated cross-border prevention and control and optimizes resource allocation, thereby strengthening model adaptability and decision-support capabilities in complex, real-world outbreak scenarios. Meanwhile, interdisciplinary research should explore collaborative modeling frameworks that protect data privacy, such as federated learning, and promote their validation and application in authentic clinical environments. For China, efforts should focus on conducting timely and prospective analyses using new data and emerging outbreaks, optimizing parameter settings based on local surveillance characteristics, and developing targeted analytical frameworks suitable for both outbreak emergency response and routine surveillance scenarios, thereby better supporting localized scientific prevention and control of the epidemic.

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