Literature review on mathematical and phylodynamic modelling of mpox outbreaks in men who have sex with men populations

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Table of Contents

Plain Language Summary

Mpox, previously 'monkeypox', is a smallpox-like disease caused by the mpox virus (MPXV) that causes symptoms including rashes, fever and skin lesions. It is spread primarily through close (including sexual) contact with infected individuals. During the 2022-2023 international mpox outbreak and on August 2024, the WHO declared mpox as a public health emergency of international concern. Mpox outbreaks outside Africa have disproportionally affected men who have sex with men (MSM) populations, with >98% of mpox cases being reported in MSM.

To better understand mpox, researchers have employed mathematical modeling and phylodynamic analyses. In the former category, researchers use mathematical models to construct scenarios and simulations of mpox spread and investigate which public health interventions are efficient to prevent spread. In the latter, phylodynamic analyses combine information about viral evolution and genetic changes with epidemiological data about viral transmission to understand how the virus evolves and is transmitted through populations.

Here, after thoroughly and systematically searching the available literature, we conducted a review of 35 studies. Of these, 20 described mathematical modeling of mpox outbreaks in MSM populations and 15 described phylodynamic analyses of mpox. Our goal was to determine which public health interventions were effective in preventing or controlling mpox outbreaks and to identify gaps in literature.

After analyzing and synthesizing the results of these studies, we found that despite differences in populations, model types, phylodynamic analysis techniques and mathematical models used, studies agreed with each other in terms of interventions to control mpox spread, proposing combinations of the following four kinds of interventions that were deemed most effective. The most recommended intervention was vaccination, especially targeted towards high-risk groups such as MSM and people living with HIV. Several studies suggested that behavior change, such as reduced sexual contact rate and increased condom usage is important to stop transmission, as is surveillance and timely detection of cases through contact tracing. Finally, all phylodynamic analysis studies highlighted that genomic surveillance of MPXV to monitor viral evolution is important to prevent outbreaks by new strains.

Based on these findings, we formulated a four-point strategy of public health interventions including vaccination of high-risk populations, genomic and epidemiological surveillance and education campaigns to facilitate behavior change. Based on our findings, this combination of interventions should be enough to achieve outbreak control.

We also identified several gaps in research that limit our understanding of mpox. Most studies focused on a specific mpox strain (IIb) that was responsible for the 2022-2023 outbreak. However, the current 2024 outbreak was caused by strain I.b. Thus, we cannot fully say if the findings of these studies can be generalized to this new outbreak.

The 2024 outbreak has made it clear that mpox is still a serious issue in public health. MSM populations are still at high risk for contracting and transmitting the virus. Our study provides information to guide public health authorities into making informed choices about implementing interventions to prevent and control outbreaks.

Abstract

Background: Mpox, previously known as 'monkeypox' poses a significant concern for public health, especially among men who have sex with men (MSM) communities. This was emphasized by the 2022-2023 international mpox outbreak, in which >98% of cases globally were MSM. Given the status of MSM as a high-risk group for mpox transmission, targeted interventions are necessary.

Objective: We aimed to conduct a literature review and evidence synthesis of studies describing mathematical modeling of mpox outbreaks in MSM populations and phylodynamic analyses of mpox. Our aim was to identify the most effective interventions for limiting outbreak spread and to locate potential gaps in the literature.

Methods: After conducting a systematic and thorough search of the available literature, 35 studies that fulfilled the search criteria were selected. We extracted data about the types of models and analyses used, sources of data, and the principal results of the studies and which interventions the authors recommended.

Results: We found that despite the variety in model types, phylodynamic analyses methods, data sources and techniques used, there was a distinct trend in recommended interventions. Most studies recommended vaccination (especially targeted towards high-risk groups), behavior changes (such as condom use and reduction in sexual contacts), enhanced genomic surveillance to track viral evolution, and surveillance and timely detection of cases via contact tracing. We identified

several gaps in the literature pertaining to studies focusing only on MPXV clade IIb. This limits the generalizability of their results, especially in the wake of the August 2024 outbreak which was caused by clade I.b.

Conclusion: Mpox has transitioned from a zoonotic to a human-to-human transmitted disease. Our study highlights the importance of MSM being included in public health strategies against mpox. Such strategies should include interventions such as the ones mentioned above to control the outbreak. The gaps we identified should be addressed by future research to improve knowledge of mpox transmission dynamics and assure outbreak preparedness.

Background and introduction

Mpox, in the past referred to as 'monkeypox' is a zoonotic disease similar to smallpox. It is caused by the mpox virus (MPXV), a virus belonging to the Poxviridae family of the Orthopoxvirus genus[1,2]. The symptoms caused by the disease include rashes, respiratory distress, gastrointestinal, oral and throat ulcers, headache, fever, inflammation of the lymph nodes and skin lesions[4]. In humans, the disease is primarily transmitted through close physical contact with an infected person[1]. Routes of infection include physical contact with infected individuals, e.g., during sexual intercourse, but can also occur via respiratory droplets or contaminated objects e.g., clothing or bedding[5].

Two distinct clades of MPXV can be distinguished. These clades are designated as clade I, stemming from DRC and Central Africa and clade II originating from West Africa. Clade II was later subdivided into clades IIa and IIb. There also exist sub-lineages for each clade, such as B.I, a clade IIb sub-lineage associated with the 2022 epidemic [2,46]. The disease is endemic in West African countries, but starting in 2022, several cases of MPX clade II infection were reported in countries outside Africa. This eventually escalated into an international outbreak, with mpox cases reported in more than 100 countries[1,2,3]. In June 2022, the WHO declared the mpox outbreak a Public Health Emergency of International Concern (PHEIC). By January 2023, a total of 84.716 confirmed cases and 80 deaths had been reported globally. Public health authorities responded by implementing contact tracing of cases, information campaigns to raise public awareness of the outbreak, and vaccination strategies to curb the epidemic[1,2,3].

A key epidemiologic characteristic of the outbreak was that most of the cases were reported in men and specifically in the subgroup of men who have sex with men (MSM)[1,2,3,4]. As the study by Lu et al (2023) reported, 98% of mpox cases were detected in MSM populations and were associated with sexual contact[3]. This agrees

with other studies, which indicated that high risk behaviors often observed in MSM sexual networks, such as multiple partners, unprotected sexual contact, group-sex etc., were risk factors for being infected with mpox, and thus MSM constituted a high-risk group due to these high-risk behaviors. It should also be noted that 41% of mpox cases reported co-infection with HIV, which could be due to increased susceptibility due to HIV-induced immunosuppression[2,3].

In May 2023, WHO declared that the mpox outbreak no longer constituted a PHEIC. Monitoring and surveillance continued, with a WHO mpox global risk assessment in July 2024 declaring that while the reported cases globally had been drastically reduced since 2022-2023, the overall risk for gay, bisexual, and other MSM was classified as moderate and that the ongoing outbreak primarily affected MSM[6]. There have been concerns that the 2022-2023 outbreak might cause MPXV to become endemic outside of Africa and that development of pandemic preparedness strategies and continued surveillance are required to prevent future mpox outbreaks[4]. Since MSM were the group most affected by the recent mpox outbreak, strategies and protocols for outbreak prevention should take the MSM population into account[4,6].

Due to each disease's unique transmission dynamics, both population-wide and in subgroups like MSM, it is necessary to use advanced analytical tools to effectively manage outbreaks. Two commonly employed strategies for outbreak forecast and assessment of prevention measures are mathematical modeling of infectious diseases and phylodynamic analyses. These strategies facilitate understanding of the spread of infectious diseases and the trends and dynamics of the outbreak, which in turn contribute to more well-informed and effective strategies for outbreak prevention and management[8,11].

Mathematical modeling of infectious diseases

To predict the course of future mpox outbreaks, researchers have used mathematical modeling to simulate outbreaks in various settings. Mathematical models are usually built by fitting algorithms to surveillance data with the aim of gaining insight into the dynamics and spread of an outbreak to more effectively guide public health surveillance and decisions[7]. There is a large variety of mathematical model types, such as agent-based models, network models, deterministic compartmental Susceptible-Infected-Recovered (SIR) models and others, as seen in figure 1, each with their own characteristics and parameters[8].

One of the advantages of mathematical models is that by employing them, researchers can quantify the impact of various interventions in various settings

during an outbreak. Furthermore, by appropriately configuring the model's parameters one can determine the course of the outbreak if another intervention or if no intervention was introduced[9]. It is also possible to estimate various outbreak parameters, such as the basic reproduction number R0 (average number of secondary cases generated by introducing a primary case into a completely susceptible population) , the effective reproduction number Re (number of novel infections caused by a case in a population where some individuals aren't susceptible), the final size of the epidemic, and the amount of vaccine coverage needed for elimination[10,15]. Thus, these models are invaluable in forecasting the trend of an epidemic, estimating the transmission parameters and in developing a preparedness plan for combating emerging outbreaks[11].

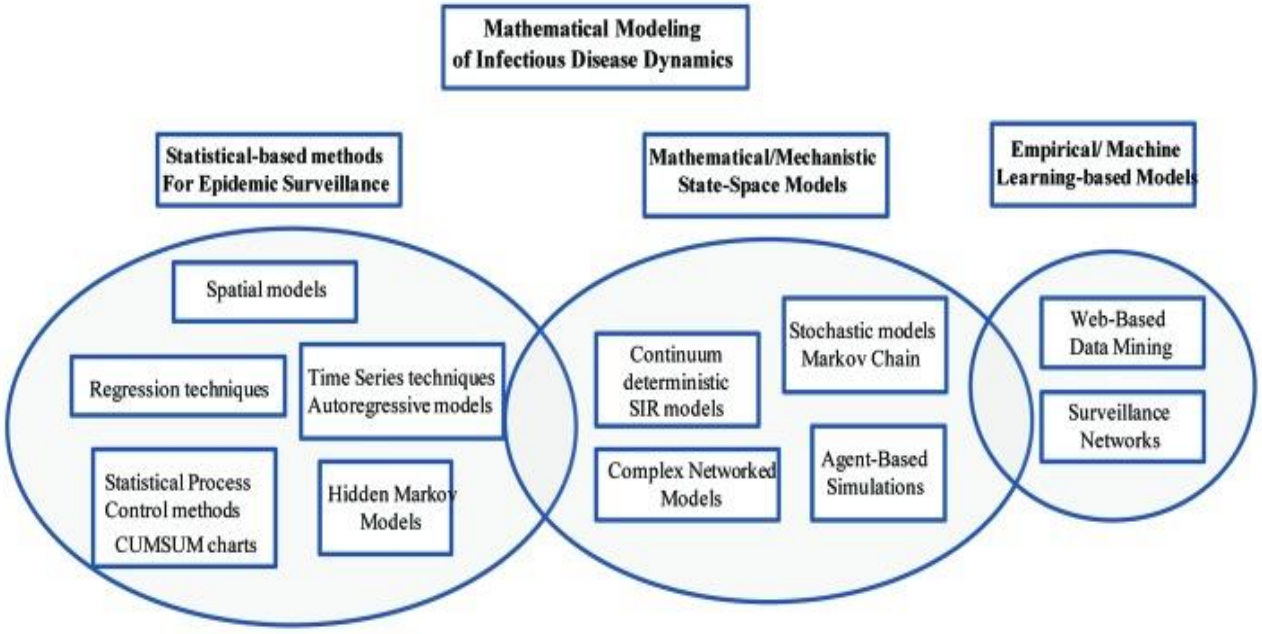

Figure 1: Overview of mathematical model types[8]

Phylodynamic analysis of infectious diseases

Phylodynamics, as defined by Rife et al (2017) is the study of the interactions between epidemiological and pathogen evolutionary processes within and among population[11]. Simply put, it is the integration of traditional epidemiological methods with more novel phylogenetic methods, with the aim of associating a pathogen's evolutionary history and genetic diversity with surveillance data to make inferences about the pathogen's dynamics[12]. It is possible, provided that enough pathogen evolution history and genetic diversity data and information about the host population are available, to estimate the transmission dynamics and parameters of the outbreak such as the basic reproduction number R0 or the effective population

size through Bayesian phylogenetic reconstruction or even identify potential risk factors for the pathogen's spread[12,13,14]. By employing these techniques to infer outbreak parameters, researchers can understand relationships between pathogen evolution and spatiotemporal distribution among populations or transmission among networks. Thus, is it possible to develop strategies for outbreak containment using phylodynamic analyses[12,13,14].

Objectives and aims of this study

The aim of this study is to answer the following research question: "What mathematical models and phylodynamic analyses for mpox outbreaks in MSM populations have been developed in the wake of the 2022-2023 mpox global outbreak?"

The study objective is to conduct a review of the available literature on mathematical models and phylodynamic analyses of mpox outbreaks in MSM populations. We aim to compile and synthesize eligible articles to identify which interventions have been found to be effective in the scenario described above and identify any potential gaps in literature.

Based on the results of our review, we also aim to provide recommendations for public health strategies for controlling mpox outbreaks in MSM populations, and recommendations for future research. The information gleaned by our study will contribute to the better understanding of mpox transmission dynamics in MSM communities and enable public health authorities to make better informed decisions in their efforts to control and prevent future outbreaks.

Methods and Materials

Search Strategy

To locate as much eligible literature as possible we conducted a comprehensive search across multiple academic databases. We conducted our search primarily within Pubmed, Scopus and Web of Science. We selected these databases due to their extensive coverage of scientific articles containing epidemiological and medical research. In the case of phylodynamic analyses of mpox articles, we expanded the search to Google Scholar due to the small number of results from the other databases, which led to the inclusion of several more relevant studies.

For our search strategy we employed several MeSH terms consisting of combinations of specific keywords (e.g., "mpox") and Boolean operators (e.g., "AND"). These terms were tested across the previously mentioned databases to ensure our search captured all studies relevant to the research question.

To locate articles detailing mathematical modeling of mpox outbreaks in MSM populations, we used "mpox" AND "mathematical" AND "modeling" AND "MSM" as our primary search terms. For articles describing phylodynamic analyses of mpox outbreaks in MSM populations, the MeSH terms used were "mpox" AND "phylodynamic". We limited our search to studies published between 2022 and 2024, to capture the period during and after the 2022-2023 international mpox outbreak. We only included articles that were published in English. For additional details concerning the selection of MeSH terms, consult the supplementary material.

We did not consider expanding the search to grey literature due to concerns over quality and eligibility. This may have caused us to miss a portion of articles that could be relevant to our research question, a limitation to our study that we deemed was acceptable given the number of results we already had.

We also included several pre-prints of articles pending publication in our selection. While this has the benefit of including several relevant studies that offer additional information about our topic, the caveat was that since those articles had not been peer-reviewed yet, one should be careful when making recommendations for public health interventions based on their results. We exercised caution when discussing the results of these articles. The results of these studies were interpreted together with the results of the fully peer-reviewed articles to ensure the robustness of our conclusions.

Inclusion and exclusion criteria

To ensure that all articles we included were relevant to the topic and to guarantee the quality of the articles, we applied several specific inclusion and exclusion criteria during each step of the search and screening process.

We only included studies if their main topic was mathematical modeling of mpox outbreaks in MSM populations or phylodynamic analyses of mpox and evaluated different interventions for controlling mpox outbreaks or offered insight into mpox transmission dynamics. Studies that included both MSM and non-MSM populations were included only if the main focus was on MSM populations.

We excluded all cases where studies focused on non-MSM populations, did not give detailed information about the mathematical models or phylodynamic analyses the researchers employed, or were published in a language other than English. We chose these criteria to be able to make correct inferences from the results of the articles, even though it may have led to the exclusion of potentially relevant content.

Screening process

There were two stages in the screening process. In the first stage all titles and abstracts of studies identified using the search strategy were reviewed to assess their relevance to this study's research question. Any duplicate articles were excluded from the rest of the analysis.

In the second stage, we assessed the articles for eligibility based on the inclusion and exclusion criteria described above through full-text reviews. Articles were deemed suitable for inclusion if they fulfilled all the inclusion criteria mentioned above. After irrelevant and unsuitable articles were excluded, the remaining were selected for final inclusion in the literature review. When a study met the criteria for inclusion, a review of the full text of the corresponding article was conducted. Both stages are summarized in figures 2 and 3. These figures provide a visual synopsis of the key highlights of the study selection process for mathematical modeling and phylodynamic analysis articles, respectively.

As seen in figure 2, we identified 55 articles (44 + 11 preprints) for mathematical modeling of mpox outbreaks in MSM communities. After excluding 20 duplicate articles, the remaining 35 were selected for full text reviews. Fifteen articles were deemed to be unsuitable during full text review and were excluded. The final selection included 17 full text articles and 3 preprints for a total of 20 articles. All preprints were accessed via the preprint repository Medrxiv.

Figure 3 presents the article selection process for the articles detailing phylodynamic analyses of mpox outbreaks. A total of 145 articles (139 full text + 6 preprints) were identified. We excluded 23 duplicate articles and selected 119 for review of eligibility. The final selection, after the exclusions, consisted of 12 full text articles and 3 preprints, totaling 15 articles.

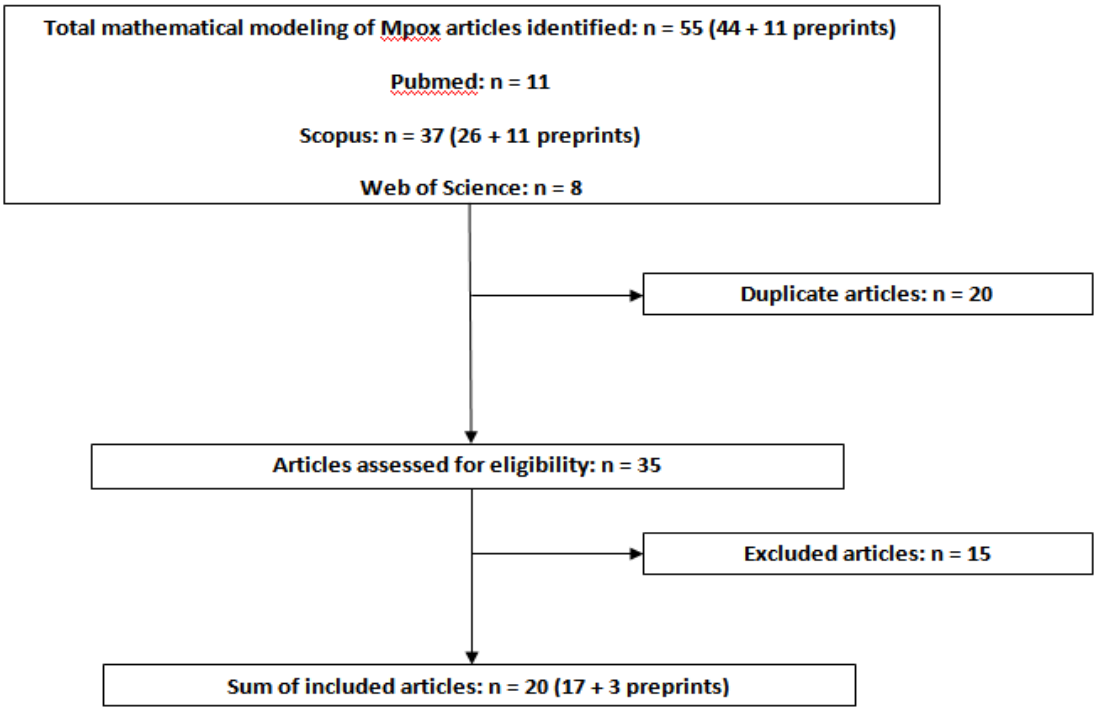

Figure 2: Mathematical modeling of mpox outbreaks in MSM article inclusion flowchart

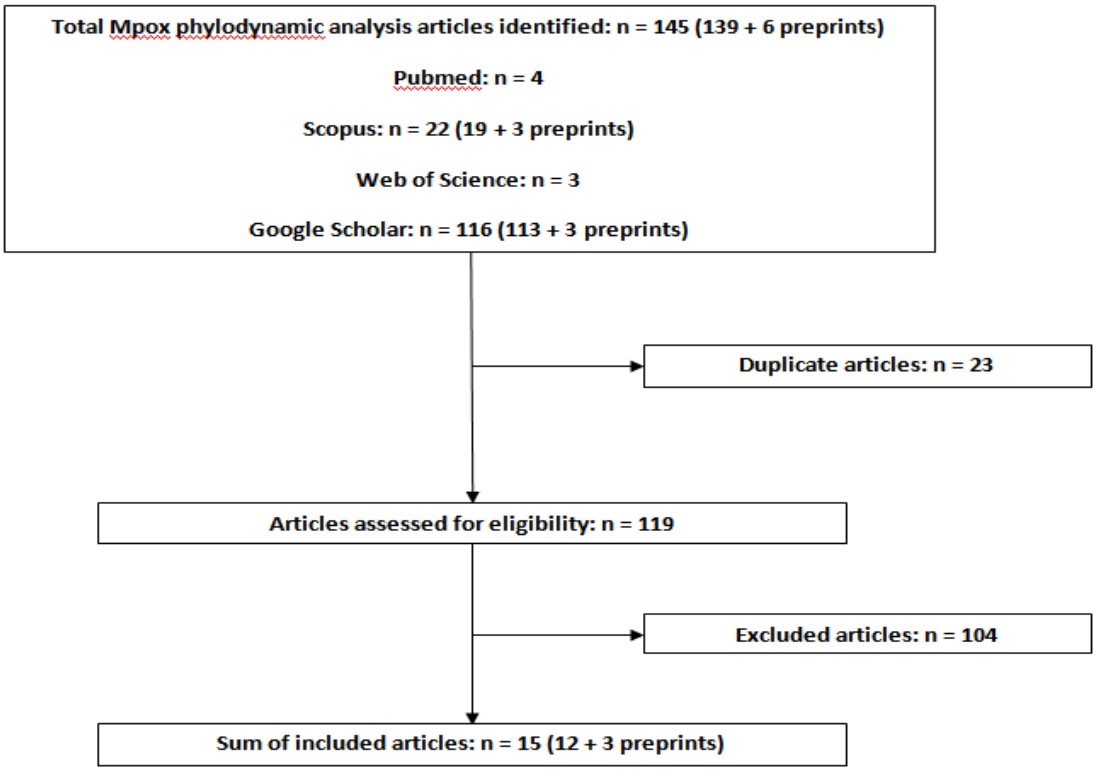

Figure 3: Phylodynamic analysis of mpox outbreaks in MSM article inclusion flowchart

Data extraction

Once article selection was completed, we started extracting the required data from each of the studies to compare their results. We specifically extracted data that provided information on the key parameters of mathematical models and phylodynamic analyses and their results and conclusions.

For mathematical modeling studies we extracted data on the type of model used in the study (e.g. agent-based, compartmental SEIR, others), the country, territory or region of the data used in the model, whether the model was built using simulated or actual epidemiological data, whether the model was fitted to the data, the assumptions the researchers made when constructing the model, which interventions were included in the model (e.g. vaccination, behavior change, etc.) and which interventions were deemed to be effective based on the scenarios the model was applied to.

For articles detailing phylodynamic analyses of mpox, we focused on extracting data on the type of phylodynamic model used (e.g. Bayesian, phylogeographic etc.), genetic and epidemiological data on viral strains analyzed (e.g. MPX clade IIa, IIb etc.), characteristics about where the study was conducted or data collection took place, key outcomes of the analyses and which interventions were recommended by the authors.

Results

Once article search and data extraction had been completed, a total of 35 studies were selected for analysis. These included 20 (17 full-text, 3 preprint) studies that focused on mathematical modeling of mpox outbreaks in MSM population and 15 (12 full-text, 3 preprint) studies about phylodynamic analyses of mpox outbreaks. In this section we present the key characteristics of these studies and their principal findings.

Mathematical modeling studies (full text)

All information concerning the articles detailed in this section can be found in tables 1 and 2, which contain the characteristics of the models and the modeled and recommended interventions of the models, respectively. Unless explicitly mentioned otherwise, all models focused on MSM populations.

There was a total of 20 studies (17 full-text and 3 preprint) in this section. The majority (n=13, 65%) of models were deterministic or stochastic compartmental SIR type models, based on differential equations, sometimes with extensions such as additional compartments for quarantine or mortality. We also included 2 studies that developed network models. The rest of the models (n = 5) belonged to other types such as agent-based, microsimulation and others. Most of the models (n = 15, 75%) used actual data, while the rest (n = 5, 25%) used simulated data. Similarly, most of the models (n = 15, 75%) were fitted to real world data while only 5 (25%) weren't. For a complete list of model characteristics, consult table 1 or supplementary data table S1.

Ajmal et al (2024)[16] developed two agent-based models using simulated data with parameters drawn from the UK NATSAL-3 survey to simulate an mpox outbreak in an artificial population. The models were not fitted to real world data. We only analyzed the second model, which focused on MSM populations. They incorporated different scenarios like super-spreader events, imported cases and vaccination strategies. They assumed heterogeneous sexual mixing, concurrency in short term partnerships, 85% vaccine efficacy and permanent immunity post recovery. They found that by vaccinating high risk MSM individuals, the effective reproduction number was reduced from 1.69 to 0.19, therefore signaling the end of the outbreak.

Al-Raeei et al (2023)[17] made an extension to the basic SIR model, adding a compartment for mortality. The model was built using actual data from the United States and Spain and was fit to real world data using specialized techniques. The authors did not model any intervention, instead focusing on making estimations for the basic reproduction number R0 and how herd immunity might be achieved. They assumed constant infection, recovery, and mortality rates. They concluded that to achieve herd immunity to stop disease spread, immunization thresholds of 35.52% for the USA and 30.99% for Spain had to be reached.

Betti et al (2023)[18] constructed a pair formation model with recovery using actual case data from the 2022-2023 mpox outbreak. The model was fit using data from Canada and global data, as reported by the government of Canada. No interventions were modeled. Their assumptions were monogamous pairings and no public health interventions. It was reported that the model reflected outbreak patterns better than a traditional SIR model, since it considered pair formation and dissolution dynamics. The authors recommended that measures to monitor and prevent spread be taken to avoid multiple waves of infection in case of stoppage of public health interventions after the initial infection wave has passed.

A SEIR model with a quarantine compartment was developed by Bragazzi et al (2023)[19] using actual data from Canada and fitted using Bayesian inference methods. They modeled several kinds of behavior changes as response to the outbreak such as

increased condom use and reduction or complete abstinence from sexual encounters. They concluded that, assuming that a high-risk MSM population was the driving force of the outbreak and that high and low risk groups had different transmission dynamics, reduction in sexual encounters was more effective than increased condom uses or complete abstinence.

The same team published another study (Bragazzi et al, 2024) [20] in which they constructed a SEIR model with quarantine using actual data reported from 16 countries including USA, Canada and others, and fitted it to real world data with Bayesian inference. Their aim wasn't to model interventions but to quantify R0 and the amount of underestimation of mpox cases in MSM communities, assuming underreporting was caused by stigmatization towards MSM. They found that underestimation and R0 varied widely between countries and suggested that anti-stigma campaigns against MSM and enhanced surveillance were required to reduce underestimation.

Dimitrov et al (2023)[21] adapted a SEIR model for HIV spread that was previously developed and fitted using data from USA, Seattle. Their own parameters simulated a MSM population in the USA based on survey population statistics. They modeled various dose-sparing or fractional vaccination strategies to account for limited vaccine supply and compared them to full vaccination. It was reported that assuming a high risk MSM population and that fractional doses retained at least 40% of full dose effectiveness, one can expect meaningful benefit from using fractional vaccination to immunize a larger proportion of the high-risk population.

Endo et al (2022)[22] constructed a branching process transmission model fitted to UK data with data from the NATSAL survey. They focused on the heavy tailed distribution of numbers of sexual partnerships within MSM. This meant a small fraction of individuals had a much higher number of partners than the majority of the population. Early prevention and detection of such individuals were found to be crucial for controlling disease spread.

An individual based SEIR model using simulated data from Singapore, Hong Kong, and Sydney by Gan et al (2023)[23] found that pre-emptive or immediate vaccination was effective in controlling or preventing mpox outbreaks, even in heavily populated cities. The authors used simulated data based on previous studies of local sexual behavior and assumed that MSM communities had dense sexual networks with multiple super-spreader events.

A recent study by Guzzeta et al (2024)[24] reported another individual based model, built with actual reported data from Italy and fitted to Italian surveillance report data. The authors modeled behavior changes, contact tracing and vaccination. When constructing the model, they assumed that transmission happened primarily within

MSM sexual networks. They concluded that implementing a strategy of vaccinating high risk MSM alongside strict contact tracing led to a sharp decline in cases when combined with a spontaneous behavior change in the MSM community.

Murayama et al (2024)[25] had a similar topic to Gan et al (2023)[23]. They constructed a mathematical model that considered MSM sexual networks with heavy tailed degree distributions using actual data from multiple EU countries and the USA, and fitted it to global mpox outbreak data. They assumed that public health interventions and behavior change weren't the primary drivers of reduction in cases. Their results suggested that instead of interventions, infection-derived immunity could explain the observed reduction in cases. They also emphasized the importance of continued surveillance and sustaining population immunity by vaccinating individuals with high centrality.

Omame et al (2023)[26] focused on the effects of HIV on a mpox outbreak in the MSM population. Their SEIR model accounted for co-infection with HIV and incorporated both diseases' dynamics, with assumptions of increased susceptibility to mpox due to HIV, reduced HIV infectiousness due to ART (antiretroviral therapy, used to treat HIV), and sexual transmission as the primary infection route for both diseases. It was built using actual data from outbreaks in Canadian MSM populations but was not fitted to outbreak data. The modeled interventions were ART, condom use, and reduction in sexual contacts. The authors reported that behavior changes like condom use and less sexual contact in combination with ART must be employed to control mpox spread in HIV MSM populations.

Rabiu et al (2024)[27] developed a SEIR model with reported data from the USA and fitted it to outbreak data using Bayesian inference. They modeled condom use as a control strategy, based on previous literature stating that it was one of the best ways to contain spread of STIs. This strategy was found to be quite effective at reducing mpox transmission. The only assumption of their model was that sexual contact was the primary route of transmission.

Savinkina et al (2023)[28] proposed an entirely simulated scenario of a mpox outbreak in a fictional USA college campus. They constructed a stochastic SEIR model with a quarantine compartment using hypothetical cohort simulations with the assumptions of a high risk MSM population with a specific transmission rate, no movement between groups, specific recovery / isolation rates and a constant population size. They modeled quarantine, reactive and preemptive vaccination. From the results of their analysis, timely detection, isolation, and preemptive vaccination of high risk MSM individuals is paramount to preventing and controlling the outbreak.

The model by Shamier et al (2024)[29] was a stochastic SEIR model developed using actual seroprevalence data from The Netherlands and fitted to data from the 2022-2023 outbreak. The authors tested various interventions such as vaccination, reduction in sexual contacts and early diagnosis of infection, assuming population turnover, variable vaccine effective and seroprevalence levels and disassortative mixing in MSM sexual networks. Based on their results, they recommended that vaccination coverage and diagnostic capacity be maintained, detection and quarantine of confirmed cases become more expedient and increasing awareness of mpox among MSM populations to prevent future outbreaks.

Van Dijck et al (2023)[30] constructed a network model using simulated behavior data from Belgian MSM populations and calibrated it to high risk MSM behavioral data. They modeled contact isolation, pre and post exposure vaccination. They assumed varying transmission probabilities for each sexual encounter and that undiagnosed cases continued sexual contact. They found that pre-exposure vaccination of high risk MSM was more effective in reducing cases than post exposure vaccination. Contact tracing had beneficial effects in reducing epidemic size even if only a small number of contacts stopped their sexual activity.

In a study by Xiridou et al (2023)[31], a deterministic SEIR model was built using actual reported data from the Netherlands and fitted to the daily number of mpox cases during the 2022-2023 outbreak. The authors modeled several behavior adaptations including reduction in number of sexual partnerships, sexual abstinence, and vaccination. Unlike other models, they found that while behavioral changes accelerated the decline in cases, the infection-induced immunity among high-risk MSM was enough to cause waning of the outbreak even without other interventions. It must however be said that authors assumed assortative mixing in sexual networks and varying levels of sexual activity. They also considered the possibility of immunity due to different percentages of MSM having been vaccinated against smallpox in the past as a sensitivity analysis. However, as the authors state, the results were similar to that of the main analysis.

Finally, Yang et al (2023)[32] constructed a multi-group SEIR model using global outbreak data but focusing on 5 countries (UK, Spain, Portugal, Italy, and Germany). They used actual data to build their model and fitted it to global and country-specific data. The interventions evaluated were vaccination, early detection / treatment / isolation, and community-based prevention, assuming varying scenarios of contact rates, various levels of vaccination coverage and high-risk behaviors of MSM populations. They concluded that community-based prevention and control, specifically reducing rate of high-risk sexual contacts and increased use of protective measures were more effective in reducing transmission among high risk MSM populations instead of vaccination or early detection / treatment / isolation.

Mathematical modeling studies (preprints)

The following 3 studies were preprints and had not been peer-reviewed at the time of this study. Be cautious when interpreting their results and conclusions.

The first study was by Clay et al (2023)[33]. It detailed a dynamic network transmission model built with actual data from Washington D.C., USA and fitted to cumulative case data from there. The modeled interventions were vaccination and behavior change (reduction in sexual contact rate). The authors concluded that while vaccination prevented more cases than behavior change, a combination of the two interventions was the most effective. The authors assumed high transmissibility of MPX, varying vaccine effectiveness and that behavior adjustments would occur in response to the risk posed by the outbreak.

The second study was by Asakura et al (2024)[34]. The authors constructed a stochastic SEIR model using actual data from Japan and simulated data for 42 Asian countries. They then fitted the model to actual incidence data from Japan using Bayesian inference. They did not model any interventions, rather focusing on detecting risks of importation of cases and spread of the outbreak. Based on their results, they called for global cooperation and vaccination support for Asian LMIC countries to prevent such events. Assumptions were limited vaccine availability, heterogeneous sexual networks, and rates of sexual activity across the countries.

The third study was by Liang et al (2024)[35], in which the authors developed a microsimulation model using actual data from Los Angeles County, USA and fitted it to the county's surveillance data. They modeled several interventions such as reduction in sexual partnership rate and different vaccination scenarios (e.g., timing / magnitude / prioritization of HIV positive individuals) and concluded that by reducing the rate of sexual partnerships and implementing timely vaccination (especially for people with HIV) were most effective in reducing the number of cases. The authors' assumptions included higher disease transmission risk among people with HIV, vaccine effectiveness and sexual contact as the primary route of infection.

Table 1: Overview of characteristics of studies detailing mathematical modeling of mpox outbreaks within MSM populations

Model study	Model type	Country data	Simulated / actual data ?	Fitted?
Ajmal et al 2024[16]	Agent-based	UK (NATSAL-3 survey)	Simulated	No
Al-Raeei et al 2023[17]	SIR with mortality	USA, Spain	Actual	Yes
Betti et al 2023[18]	Pair formation SIR	Canada / global	Actual	Yes
Bragazzi et al 2023[19]	SEIR with quarantine	Canada	Actual	Yes
Bragazzi et al 2024[20]	SEIR with quarantine	16 countries (USA, Canada, Spain, others)	Actual	Yes
Dimitrov et al 2023[21]	SEIR	USA, Seattle	Simulated	No
Endo et al 2022[22]	Branching process	UK (NATSAL-3 survey)	Actual	Yes
Gan et al 2023[23]	Individual-based SEIR	Singapore, Hong Kong, Sydney	Simulated	No
Guzzetta et al 2024[24]	Individual-based	Italy	Actual	Yes
Murayama et al 2024[25]	Mathematical model	EU countries, USA, Canada, USA states	Actual	Yes
Omame et al 2024[26]	SEIR with HIV co-infection	Canada	Actual	No
Rabiu et al 2024[27]	SEIR	USA	Actual	Yes
Savinkina et al 2023[28]	Stochastic SEIR with quarantine	Simulated USA college campus	Simulated	No
Shamier et al 2024[29]	Stochastic SEIR	The Netherlands	Actual	Yes
Van Dijck et al 2023[30]	Network	Belgium	Simulated	Yes
Xiridou et al 2023[31]	SEIR	The Netherlands	Actual	Yes
Yang et al 2023[32]	SEIR	Global / 5 countries (UK, Spain, Portugal, Italy, Germany)	Actual	Yes
Clay et al 2023 [33](preprint)	Network	USA, Washington D.C.	Actual	Yes
Asakura et al 2024 [34](preprint)	Stochastic SEIR	Japan, 42 Asian countries	Actual (Japan), simulated (others)	Yes
Liang et al	Microsimulation	USA, Los Angeles county	Actual	Yes

2024 [35](preprint)				

Table 2: Overview of modeled and recommended interventions of studies detailing mathematical modeling of mpox outbreaks within MSM populations

Model study	Modeled intervention(s)	Recommended intervention(s)
Ajmal et al 2024[16]	Vaccination among HR MSM, superspreader events, imported cases	Vaccination of HR MSM
Al-Raeei et al 2023[17]	Herd immunity (no public health interventions)	Immunization to achieve herd immunity thresholds
Betti et al 2023[18]	None	Monitoring, suppressing spread to avoid multiple infection waves
Bragazzi et al 2023[19]	Sexual behavior change (reduction, abstinence, condom use)	Reduction in sexual contacts
Bragazzi et al 2024[20]	None	Enhanced surveillance, campaigns against stigmatization of MSM to reduce underestimation of cases
Dimitrov et al 2023[21]	Dose-sparing vaccination	Vaccination, even if fractional (if effectiveness >40%)
Endo et al 2022[22]	None	Early prevention, detection of high risk MSM
Gan et al 2023[23]	Pre emptive / immediate vaccination	High pre-emptive / immediate vaccination coverage, especially in heavily populated cities
Guzzetta et al 2024[24]	Contact /ring tracing, contact / ring vaccination, behavior changes	Contact tracing, HR MSM vaccination, behavior changes within MSM community
Murayama et al 2024[25]	None	Infection-derived immunity among HR MSM could naturally limit outbreak size, vaccination
Omame et al 2024[26]	HIV treatment with ART, condom use, reduction in sexual contacts	Behavior change (condom use, sexual contact reduction) combined with ART
Rabiu et al 2024[27]	Condom use	High compliance to condom uses or sexual abstinence, especially among MSM
Savinkina et al 2023[28]	Detection, quarantine, reactive / preemptive vaccination,	Timely detection and quarantine of cases, reactive and preemptive vaccination strategies
Shamier et al 2024[29]	Vaccination, early diagnosis, reduction in sexual partners	Vaccination to maintain immunity of at-risk population, sustained disease awareness, diagnostic capacity
Van Dijck et al 2023[30]	Contact tracing, pre-, and post-exposure vaccination	Pre-exposure vaccination of high-risk MSM, contact tracing
Xiridou et al	Sexual partner reduction, early	Infection-induced immunity and behavioral

2023[31]	abstinence, vaccination	adaptations
Yang et al 2023[32]	Early detection/treatment/isolation, vaccination, community-based prevention/control	Community based prevention / control (reduction in sexual contact rate, protective measures)
Clay et al 2023 [33]**(preprint)**	Behavioral change (reduction in sexual partnerships), vaccination	Vaccination and behavioral change
Asakura et al 2024 [34]**(preprint)**	None	Global cooperation and vaccination support for LMIC in Asia to prevent spread
Liang et al 2024 [35]**(preprint)**	Vaccination timing / magnitude scenarios, sexual partner reduction	Timely vaccination and early sexual partner reduction, prioritizing PWH for vaccination

Phylodynamic analysis studies (full text)

The following section contains the information extracted from the studies that described phylodynamic analyses of mpox. A summary of the characteristics and principal findings of the studies can be found in tables 3 and 4, respectively.

We included 15 studies in total in this section (12 full-text and 3 preprints). The majority of the models (n = 10, 67%) focused on MXPV clades IIa and IIb and their associated lineages and sublineages. Only 1 study (7%) focused on clade I. The remaining 4 studies (27%) analyzed all MPXV clades (I, IIa, and IIb). The type of analysis employed was more varied. Several studies used combinations of different analysis methods, which meant that one study could potentially be included in multiple categories. Most of the studies (n = 9) employed maximum-likelihood phylogenetic analysis. Four studies used Bayesian phylogeographic analysis. There were 12 studies that used other types of analysis methods. For a complete list of these characteristics, consult table 3 or supplementary data table S2.

Alankunle et al (2024)[36] fitted a Bayesian phylogenetic model to analyze various MPXV strains including Clades I, IIa, and IIb. They focused on the B.I lineage that was linked to the 2022-2023 mpox outbreak. They found that MPXV's genome undergone numerous mutations driven by mutations in the APOBEC3 enzyme which led to the virus' accelerated evolution. The B.I lineage emerged in 2016 and was cryptically transmitted undetected until the 2022-2023 outbreak. They proposed a combination of genomic surveillance of viral evolution with a One Health approach to integrate human, animal, and environmental health to prevent future outbreaks.

Borges et al (2023)[37] constructed a time-discrete SEIR model to the 2022-2023 mpox outbreak Portuguese MSM case data using a daily time step and fitted it in a Bayesian framework to study transmission dynamics and used a phylogenetic tree to identify outbreak subclusters. They focused on the B.I lineage and its sublineages. They found that this lineage was heavily disseminated amongst MSM sexual networks, facilitated by superspreader events and (re-)introductions from international sources. Based on their evidence, they suggested interventions such as public health messaging, behavioral changes, contact tracing and vaccination of high-risk groups alongside genomic surveillance to contain future outbreaks.

Another study based in Portugal, but also Belgium, by Giorgi et al (2023)[38], used a phylogenetic tree analysis to study MPXV Clade II (West African) during the 2022-2023 outbreak. They highlighted that the strains from Belgium and Portugal are remarkably like each other and descended from MPXV Clade II. They suggested continued genomic surveillance and urged development of novel vaccines for mpox.

In a study from Gomez-Sanchez et al (2023)[39], maximum likelihood phylogenetic analysis was used on mpox cases in Mexico. 880 isolates from MPXV clades I, IIa and IIb were analyzed. It was revealed that MPXV was introduced into Mexico on multiple occasions, from countries such as the UK, Portugal, and Canada. This was followed by local transmission. The authors suggest continued genomic surveillance to monitor viral evolution and adaptation, especially in endemic and high-risk regions and targeted interventions to prevent outbreak spread.

Guan et al (2023)[40] used Bayesian phylogeographic analysis and maximum likelihood phylogenetic analysis to analyze 567 MPXV genomes from around the globe. They identified clades I, IIa and IIb contributed to the 2022-2023 global mpox outbreak and that the virus used north America to spread from Africa to other continents like Europe and Asia. They suggested continued global genomic surveillance of mpox evolution and monitoring of viral spread.

Luna et al (2022)[41] was like Guan et al (2023)[40] in that the authors also used maximum likelihood phylogenetic analysis on 337 MPXV genomes from various countries, focusing on the B.I lineage. They concluded that B.I lineage emerged in Europe around March 2022, with a rapid evolution driven by APOBEC3 enzyme mutations. These mutations caused adaptation to human-to-human transmission and had a critical role in viral spread, especially in MSM networks. The authors suggested enhanced genomic surveillance to track MPXV genomic changes.

O'Toole et al (2023)[42] developed a dual process phylogenetic molecular clock and used it to analyze MPXV strains within clade IIb, especially lineage B.I, focusing on APOBEC3 mutations. It was found that MPXV had been circulating in human populations since 2016, driven by APOBEC3 mutations that led the virus to shift to

human-to-human transmission. The authors highlighted the need for public health messaging and global surveillance, especially in countries where MPXV is endemic.

Paredes et al (2024)[43] used Bayesian phylogeographic and phylodynamic models to study 1004 MPXV genomes from around the globe, focusing on Clade IIb and high-risk populations, particularly MSM. They concluded that the 2022-2023 epidemic was driven by rapid and under detected local transmission and that viral introductions after the initial spread had negligible effect. They stressed that behavioral changes in high-risk groups, especially MSM were more effective in stopping transmission than travel restrictions or vaccination. They suggested that rapid detection, behavioral changes, and swift public health interventions in high-risk groups including MSM could be enough to stop disease spread.

Schuele et al (2024)[44] used phylogenetic analysis on 158 MPXV genomes from The Netherlands. All belonged to clade IIb and lineage B.I. They identified 14 sublineages and concluded that there were multiple viral introductions in The Netherlands, followed by rapid local spread. MPXV also had an exceedingly high evolutionary rate. They recommended continued genomic surveillance and suggested that interventions such as behavior change, infection or vaccine induced immunity and education, especially in MSM communities could decrease the number of mpox cases.

Sun et al (2023)[45] reported maximum likelihood phylogenetic analysis of 525 MPXV genomes from various countries. They identified MPXV clades I (Congo basin) and II (West African) and noted that clade II showed increased transmissibility during the 2022-2023 outbreak, especially in the USA, Peru, and Brazil. They highlighted a risk for MPXV importation from African countries to other countries like UK, Spain, Germany and suggested enhanced global surveillance and targeted interventions like contact tracing, detection, and vaccination in MPXV endemic countries.

Vakaniaki et al (2024)[46] focused on a mpox outbreak in the Democratic Republic of the Congo during 2023-2024. They analyzed 22 MPXV genomes using maximum likelihood phylogenetic analysis and identified a novel clade I lineage designated I.b that was circulating since September 2023. They observed the virus had sustained human to human transmission in the region. Because of this, they called for urgent intensified local surveillance and targeted vaccination for high-risk populations like sex workers, and enhanced community engagement and monitoring to prevent spread of the virus to neighboring countries.

Vazquez et al (2024)[47] used maximum likelihood phylogenetic analysis on 30 MPXV genomes from Paraguay taken from male patients aged 21-47. A portion (37%) were HIV positive. All strains belonged to lineage IIb. They identified 3 distinct clades, which suggested multiple independent viral introductions had taken place. They

traced the origin of the mpox outbreak to Brazil, followed by local transmission and spread in the region. They recommended increased genomic surveillance at international borders to prevent cross-border transmission.

Phylodynamic analysis studies (preprints)

The studies in this section had not been peer-reviewed at the time of this study. Exercise caution when interpreting their results.

Djuicy et al (2024)[48] employed a variety of methods including Bayesian phylogeographic analysis, maximum-likelihood phylogenetic analysis and a BEAST coalescent model to analyze 14 MPXV clade IIB.I and IIB.II genomes from Cameroon and Nigeria, with a focus on the border regions. The results of their study showed that ongoing mpox outbreak in Cameroon was driven by zoonotic, instead of human-to-human transmission of clade IIB.I and that cross-border transmission between Nigeria and Cameroon had taken place. The authors suggested enhanced surveillance, especially in cross border regions, to prevent zoonotic spillover and cross-border transmission events.

Similarly, Parker et al (2024)[49] used Bayesian phylogeographic analysis, maximum-likelihood phylogenetic analysis and a BEAST coalescent model to analyze 112 MPXV genomes from Nigeria. They focused on clade IIb and lineage hMPXV-I. They found that this lineage emerged in Rivers State, which was the primary source of viral dissemination, around July 2014 in Nigeria and was cryptically transmitted until 2017. APOBEC3 enzyme mutations were responsible for increased viral evolution rate. They suggested enhanced surveillance and diagnostic capacities, especially in Rivers State and targeted public health interventions to resolve the Nigerian mpox epidemic.

Pekar et al (2024)[50] used Bayesian phylogeographic and Maximum-likelihood phylogenetic analysis to analyze 757 MPXV genomes from New York City, USA. Most of them were linked to Clade IIB and lineage B.I. They concluded that the 2022-2023 mpox outbreak in New York City was primarily driven by heavily tailed sexual networks among MSM, which facilitated the rapid spread but also decline of the outbreak, as depletion of susceptible high-risk individuals took place. They recommended vaccination of high-risk populations, including MSM, in combination with genomic and epidemiological surveillance to prevent future outbreaks.

Table 3: Overview of characteristics of studies detailing phylodynamic analyses of mpox outbreaks

mpox phylodynamic analysis articles	Population	Strains	Model type
Alakunle et al 2024[36]	Global (focus on Africa, Europe, Americas)	MPXV (Clades I, IIa, IIb), focus on B.I lineage	Bayesian phylogenetic analysis, molecular clock estimation
Borges et al 2023[37]	Portugal MSM	B.I lineage and sublineages	SEIR with Bayesian framework
Giorgi et al 2023[38]	Portugal, Belgium	Clade II (West African)	Phylogenetic tree analysis
Gomez-Sanchez et al 2023[39]	Mexico	880 MPXV isolates (clades I, IIa, and Iib)	Maximum-likelihood phylogenetic analysis
Guan et al 2023[40]	Global	567 MPXV genomes (clades I, IIa, and Iib)	Maximum-likelihood phylogenetic analysis, Bayesian phylogeographic analysis
Luna et al 2022[41]	Global	337 MPXV genomes (focus on B.I lineage)	Maximum-likelihood phylogenetic analysis
O'Toole et al 2023[42]	Global	Clade IIb (focus on B.I lineage, APOBEC3 mutations)	Dual process phylogenetic molecular clock
Paredes et al 2024[43]	Global (focus on high-risk populations, MSM)	1,004 MPXV genomes (focus on clade IIb, MSM populations)	Bayesian phylodynamic model, phylogeographic analysis
Schuele et al 2024[44]	The Netherlands	158 MPXV Clade IIB B.I genomes	Phylogenetic analysis
Sun et al 2023[45]	Global	525 MPXV genomes (clades I and II)	Maximum-likelihood phylogenetic analysis
Vakaniaki et al 2024[46]	Eastern Democratic Republic of the Congo (2023-2024)	22 MPXV genomes (clade I)	Maximum-likelihood phylogenetic analysis
Vazquez et al 2024 [47]	Paraguay (males aged 21-47)	30 MPXV genomes (all B.I)	Maximum-likelihood phylogenetic analysis
Djuicy et al 2024 [48] (preprint)	Cameroon, Nigeria	14 MPXV genomes (clades IIB.I and IIB.II)	Bayesian phylogeographic analysis, maximum-

			likelihood phylogenetic analysis, BEAST coalescent model
Parker et al 2024 [49] (preprint)	Nigeria	112 MPXV genomes (focus on clade IIB.I, lineage hMPXV-I)	Bayesian phylogeographic analysis, maximum-likelihood phylogenetic analysis, BEAST coalescent model
Pekar et al 2024 [50] (preprint)	New York City (focus on MSM population)	757 MPXV genomes (NYC), most were Clade IIB and lineage B. I	Bayesian phylogeographic analysis, maximum-likelihood phylogenetic analysis

Table 4: Overview of key findings and recommended interventions of detailing phylodynamic analyses of mpox outbreaks

mpox phylodynamic analysis articles	Key findings	Recommended intervention
Alakunle et al 2024[36]	B.I lineage cryptic transmission since 2016, viral evolution due to APOBEC3 mutations	Genomic surveillance, One Health approach
Borges et al 2023[37]	High infection rate in sexual networks, superspreader events aided dissemination	Targeted public health messaging, contact tracing, vaccination of HR groups, behavioral changes, genomic surveillance
Giorgi et al 2023[38]	Outbreak derived from the West African clade	Genomic surveillance, novel vaccines
Gomez-Sanchez et al 2023[39]	Multiple MPXV introductions into Mexico, from the UK, Portugal, Canada	Genomic surveillance
Guan et al 2023[40]	MPXV spread from North America to other continents	Ongoing surveillance, monitoring to control spread
Luna et al 2022[41]	B.I lineage emerged in Europe around 2022, evolution driven by APOBEC3 enzyme	Enhanced genomic surveillance
O'Toole et al 2023[42]	MPXV circulating in humans since 2016, APOBEC3 enzyme activity led to rapid mutations, shift from zoonotic to human virus	Global surveillance, public health messaging, especially in MPXV endemic countries

Paredes et al 2024[43]	Significant early case underdetection, local behavioral changes were more effective than travel restrictions/vaccination, minor impact of viral introductions after initial dissemination	Rapid detection, behavioral changes, public health interventions in high-risk groups
Schuele et al 2024[44]	Multiple viral introductions into the Netherlands with rapid spread, ongoing viral evolution, adaptation	Genomic surveillance, education, vaccination, behavioral changes in MSM
Sun et al 2023[45]	Clade II increased transmissibility, significant risk of zoonotic transmission in Africa, elevated risk of importation to other countries from Africa	Enhanced global surveillance, contact tracing, detection, vaccination in MPXV endemic countries
Vakaniaki et al 2024[46]	Novel clade I lineage I.b, human-to-human transmission, outbreak began around September 2023	Intensified surveillance, enhanced community engagement, targeted vaccination for high-risk populations, monitoring to prevent spread
Vazquez et al 2024 [47]	Outbreak in Paraguay originated from Brazil, followed by local spread, presence of 3 clades indicates local transmission, multiple introductions	Enhanced genomic surveillance, particularly at international borders
Djuicy et al 2024 [48] **(preprint)**	Recent MPXV cases in Cameroon are driven by zoonotic, not human-to-human transmission of Clade IIB.I, evidence of cross-border viral spread	Enhanced genomic surveillance particularly in border regions to prevent cross-border and zoonotic transmission
Parker et al 2024 [49] **(preprint)**	hMPXV-I lineage emerged around 2014, circulating cryptically before 2017, Rivers State primary source of virus dissemination, significant evolutionary changes due to APOBEC3 mutations	Enhanced surveillance, diagnostic capacities, targeted public health interventions in high-risk areas, particularly in Rivers State
Pekar et al 2024 [50] **(preprint)**	NYC outbreak driven by MSM heavy-tailed sexual networks, leading to rapid spread and decline due to depletion of susceptible high-risk individuals	Targeted vaccination of high-risk populations, genomic and epidemiological surveillance to prevent future outbreaks

Data synthesis

After analyzing the results of the included studies, we identified several trends in the recommended interventions proposed by authors of both kinds of articles. The results of the data synthesis can be found in the supplementary data, tables S3, S4 and S5. It should be noted that articles that proposed more than one kind of intervention were included in all eligible categories. Due to this, a single study may appear in more than one category. In figure 3, studies that suggested combinations of interventions appear also as a separate category.

For mathematical modeling studies, as tables 2 and supplementary data table S3 show, most articles (n = 12) suggested vaccination, especially targeted towards high-risk groups and people living with HIV to achieve outbreak prevention / control. The second and third most popular interventions were behavior changes such as condom usage, reduced sexual contacts (n = 8) and epidemiological surveillance and detection of cases through methods such as contact tracing (n = 7). Three studies recommended that infection-induced immunity may be enough for outbreak control.

On the phylodynamic analysis articles category, we observed that the overwhelming majority (n=14) of articles recommended enhanced genomic surveillance of MPXV to detect viral evolution. The second most suggested intervention strategy was enhanced epidemiological surveillance and detection, proposed by 7 studies. We distinguish between epidemiological and genomic surveillance, as they typically focus on different data; whereas epidemiological surveillance tracks disease spread in populations, genomic surveillance tracks genetic changes within the virus. Six studies suggested vaccination and four studies suggested behavior changes as interventions. This data can be seen in tables 4 and supplementary data table S4.

We synthesized the recommendations of the two categories into one table, supplementary data table S5. We saw that again, most articles (n = 18) recommended vaccination, with articles suggesting genomic and epidemiological surveillance and detection (n = 14 for both categories respectively). The third largest category of interventions, suggested by 12 articles, was behavior changes. Finally, the same 3 articles recommended infection-induced immunity. A bar chart of recommended interventions can be seen in figure 4. For a complete list of which articles recommended which interventions consult tables 2 and 4 and supplementary data table S5.

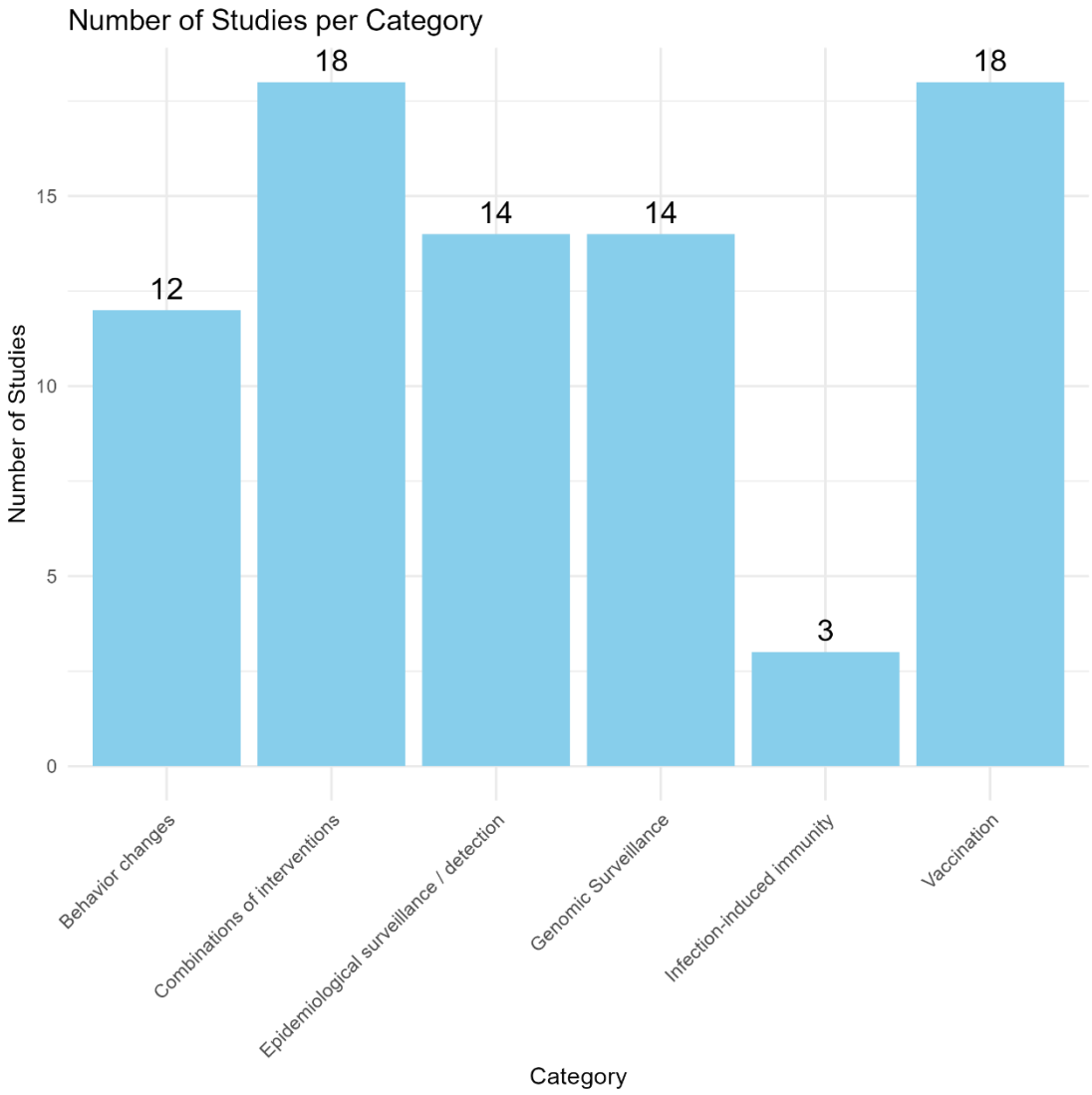

Figure 4: Bar chart of the recommended interventions of articles detailing mathematical models describing mpox outbreaks in MSM populations and of articles detailing phylodynamic analyses of mpox outbreaks

Discussion

The results we presented so far highlight how diverse and complex modeling and phylodynamic methods used to study outbreaks can be. Each study provided a unique perspective on effective interventions to control mpox outbreaks. The following section provides a synthesis of these findings, implications for public health interventions, commentary on gaps in literature and suggestions for future research.

Interpretation of findings

The majority of mathematical models (n = 13) were compartmental SIR, some with extensions (e.g additional compartments). Thus, we weren't able to make inferences about correlations between modeled interventions and model type.

A scoping review of mathematical modeling of mpox[51] suggested that a limitation of compartmental SEIR models might be that they cannot effectively capture the social and geographical dynamics and conditions of mpox transmission.

However, after comparing a variety of mathematical model types including SEIR, network, branching process and microsimulation models, we found that different models, developed using data from different countries, with different population parameters and assumptions came to similar conclusions. Across all modeling studies we reviewed, the most suggested intervention to control mpox outbreaks in MSM populations were vaccination, behavior change and timely detection of cases through surveillance.

This was reinforced by our findings in the phylodynamic analysis of mpox section. We found that these studies also suggested similar interventions to combat mpox outbreaks.

The fact that a sizeable number of studies, from different epidemiological fields, agreed on the interventions required against mpox outbreaks, suggests that these interventions are indeed effective. For additional commentary on the advantages and disadvantages of these interventions, consult the supplementary material.

Implications for public health

At the time of writing, 14/08/2024, WHO has once again declared an outbreak of mpox in the DRC and other African countries as a PHEIC[52]. Instead of Clade IIb, which was linked to the 2022-2023 international outbreak, the clade responsible for this outbreak is clade 1b. The study by Vakaniaki et al 2024[46], who were the ones to first identify this clade is included in our study.

Therefore, based on the suggestions by Vakaniaki et al, and the findings of our study, we propose that to suppress the spread of the outbreak before it spirals out of control, public health authorities should implement a four-point strategy based on the most prominent intervention types that were suggested by the articles we reviewed.

Firstly, importance should be given in targeted and pre-emptive vaccination of high-risk populations such as MSM, sex workers and people living with HIV. Secondly, information and awareness campaigns should be implemented to facilitate quick behavior change in the public and especially in high-risk groups. These campaigns should focus on the importance of condom usage and sexual contact reduction for the duration of the outbreak. Thirdly, surveillance and detection of cases should be as expedient as possible with the implementation of contact tracing and other methods of detection, especially at international border regions to prevent spread to other countries. Lastly, genomic surveillance of this MPXV clade should be enhanced to detect any possible mutations that would enable increased transmission or lethality.

Strengths and limitations of this study

To our knowledge, this is the first study to include both mathematical modeling and phylodynamic analyses articles and synthesize their findings to identify effective interventions against mpox spread. This variety in analysis methods adds to the credibility of our results. The systematic screening and data extraction processes and the number of databases searched and the articles we included (n = 35) add to the study's strength.

Our study isn't without limitations. We didn't expand our search to grey literature and articles not written in English, which may reduce generalizability. We included 5 preprints in our study selection, which at the time of writing hadn't been peer reviewed. While we took all necessary caution when interpreting their results, this is may limit the credibility of our findings. Finally, most of the studies focused on clade IIb. Thus, this limits the generalizability of the results to outbreaks caused by other clades.

Recommendations for future research

While the number of mathematical models describing mpox outbreaks is high, the number of studies reporting on phylodynamic analysis of mpox is smaller. While phylodynamics is a novel field of study, we would like to highlight its importance in understanding outbreak dynamics and estimating outbreak parameters to better prevent, and limit spread of outbreaks.

Additionally, we found almost no studies focused on MPXV clade I. This is understandable, as most instead focused on clade IIb, which was responsible for the

2022-2023 international mpox outbreak. However, with the advent of the recent clade 1b outbreak in Africa that was characterized as a PHEIC, we emphasize the need to focus on this clade to ensure generalizability of interventions.

Conclusion

In this study, we analyzed several articles of two different epidemiological fields that described interventions against spread of mpox outbreaks. We included 20 studies detailing mathematical modeling of mpox outbreaks in MSM populations and 15 studies describing phylodynamic analyses of mpox outbreaks.

We found that despite differences in methodology and characteristics, most of the studies recommended similar types of interventions to limit the spread of mpox outbreaks. These interventions include vaccination of high-risk groups such as MSM and people living with HIV, genomic surveillance of MPXV to detect viral evolution, facilitating behavior change in high-risk groups by encouraging condom usage and reduction in sexual contacts and epidemiological surveillance and detection of cases through contact tracing. Based on these results we formulated and proposed a four-point strategy to combat the emerging 2024 mpox outbreak in Africa.

Mpox has transitioned from a zoonotic to a human-to-human transmitted disease. This means that we must be able to effectively combat mpox outbreaks whenever and wherever they arise. Multiple studies have shown that MSM are a high-risk group for contacting the disease, and the group most disproportionally affected by it. Therefore, public health strategies must take MSM into account to better control mpox outbreaks, using combinations of the interventions the studies in our selection recommended.

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