Monkeypox: A review of epidemiological modelling studies and how modelling has led to mechanistic insight

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Monkeypox: A review of epidemiological modelling studies and how modelling has led to mechanistic insight

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Abstract

Human monkeypox virus (mpox) is a viral zoonosis belonging to the Orthopoxvirus genus of the Poxviridae family that presents with similar symptoms as seen previously in human smallpox patients. mpox is a growing concern internationally with over 80000 cases in non-endemic countries as of December 2022. In this review, we briefly cover the history and origins of mpox and describe its basic virology, noting key differences in mpox viral fitness traits pre and post-2022. We then summarize and critique current knowledge from epidemiological mathematical models, within-host models, and between-host transmission models. We distinguish between models that focus on immunity from vaccination, as well as geography, climatic variables, and animal models. We report various epidemiological parameters, such as the reproduction number R_0, in a condensed format for ease of comparison between studies. We focus specifically on how mathematical modelling studies have led to novel mechanistic insight into Monkeypox transmission and pathogenesis. As mpox continues to emerge and is predicted to continue to form subsequent peaks in many historically non-endemic countries, mpox mathematical modelling studies can provide rapid actionable insight into viral dynamics to guide public health measures and mitigation strategies.

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1 Introduction

Orthopoxviruses are a genus of viruses that include variola, vaccinia, cowpox, and monkeypox (mpox) viruses. Smallpox, a highly pathogenic orthopoxvirus, is estimated to have killed over 300 million people worldwide and was eradicated in 1977 due to an international vaccine campaign led by the World Health Organization (WHO). mpox, which clinically presents similar to smallpox, is endemic to multiple African countries, including Benin, Cameroon, the Central African Republic, the Democratic Republic of the Congo, Gabon, Ivory Coast, Liberia, Nigeria, the Republic of the Congo, Sierra Leone, and South Sudan [1].

mpox transmission in non-endemic regions is typically short-lived and geographically contained [2]. However, the increased prevalence in humans since the 1980s, which has been linked to a decrease in vaccine immunity and an increase in viral fitness traits, has led mpox to be recognized as a significant burgeoning human threat [2]. Throughout the year 2022, WHO reported multiple international mpox outbreaks in 20 non-endemic European countries, the United States of America, Canada, Mexico, and much of South America [3]. From May to June 2022, these cases totalled 780 [4]. By July 28th of 2022, the Centers for Disease Control and Prevention (CDC) reported 4907 cases in the United States, with cumulative cases in non-endemic countries reaching over 20800 confirmed, and by December, total cumulative cases numbered over 80,000 in non-endemic countries [4]. A heatmap of global cumulative case counts for the 2022 epidemic (as of November 17, 2022) is shown in Figure 1. We also include a heatmap of case counts normalized by total country population as shown in Figure 2. In June of 2022, the drastic increase in mpox cases in non-endemic countries led WHO to declare the overall risk of further transmission as 'moderate' globally and 'high' in the European region; it is hypothesized mpox mutated to find a new niche in tightly connected sexual networks [5]. mpox presents a burgeoning public health threat to non-endemic regions, where such countries, such as the United Kingdom, have already responded by purchasing large amounts of smallpox vaccines for public

dissemination.

Mathematical modelling has been used extensively to understand epidemics and inform intervention strategies [6, 7]. Modelling of in-host pathogen dynamics has proven critical towards furthering our understanding of many pathogens such as HIV, HCV, HBV, HSV, influenza, pneumococcus, and SARS-CoV-2 as well as aiding the development of vaccine therapies [8–16]. This review focuses on the current epidemiological understanding of mpox from a modelling perspective and how modelling studies lead to mechanistic insight into viral fitness and transmission traits. We first begin by briefly covering the history and origins of mpox (Section 2), and then describe the current basic knowledge of biology and clinical presentation of human mpox in Section 3. We then review and critique population-level modelling studies, distinguishing between studies focused on endemic and non-endemic regions, those considering prior immunity from smallpox vaccines, and animal models. We summarize both pre and post-2022 modelling parameters, such as the reproduction number, force of infection, incubation and recovery rates, in Table 1.

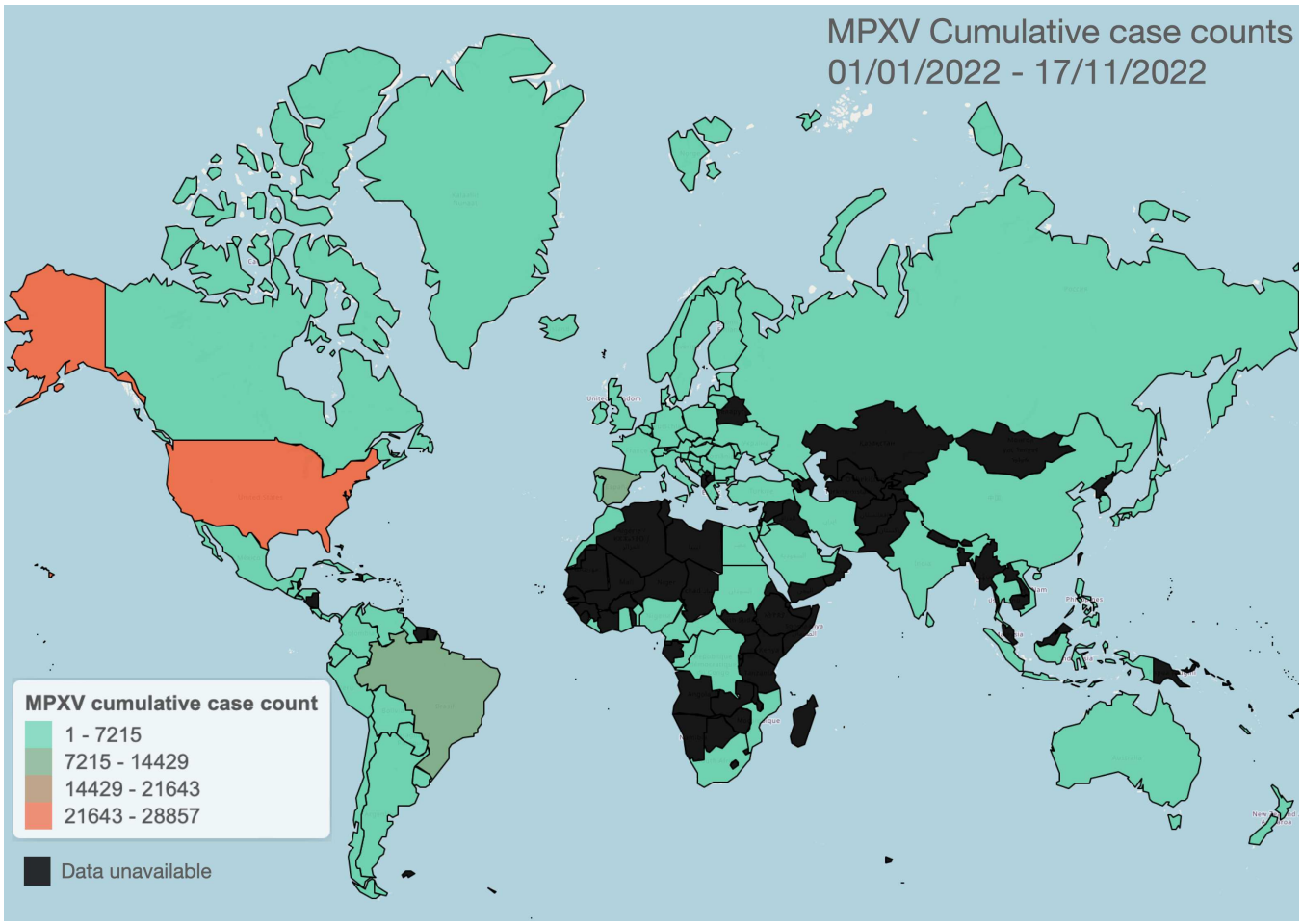

Figure 1: Cumulative mpox cases for the 2022 epidemic from January 1, 2022, through November 17, 2022. Heatmap constructed from publically available WHO data (ref. [3], accessed on November 17th, 2022).

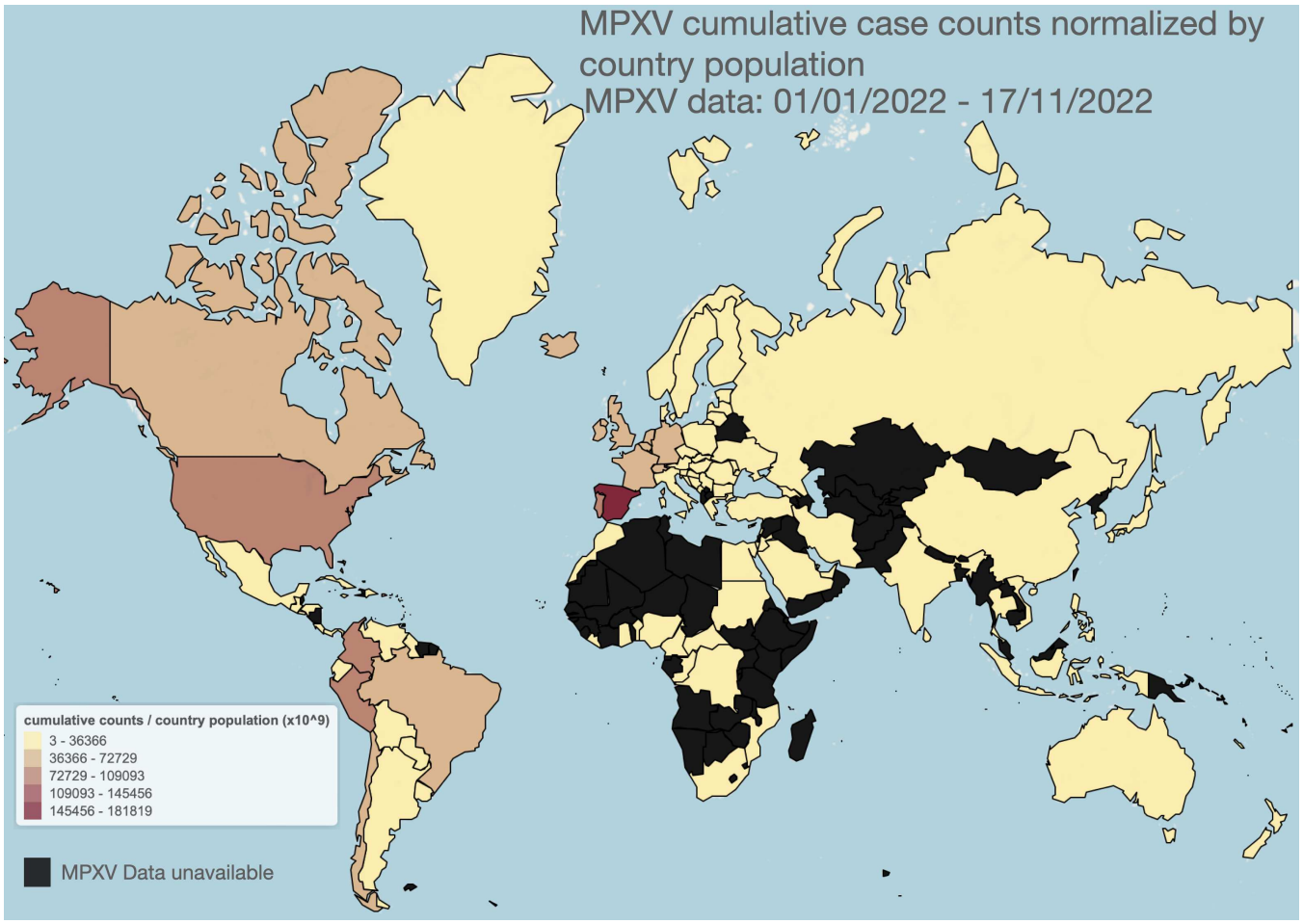

Figure 2: Cumulative mpox cases for the 2022 epidemic from January 1, 2022, through November 17, 2022, normalized by country total population. Heatmap constructed from publically available WHO data (ref. [3], accessed on November 17th, 2022). Country population data accessed from WolframAlpha Knowledgebase on November 29th, 2022.

2 History and Ecology of mpox

A pox-like disease was first reported in 1959 in cynomolgus monkeys and was thus coined 'monkeypox' [17]. Upon its discovery, mpox virus particles were noted to have similar structural features as known orthopoxviruses; rectangular with diameter 200-250 μm [17]. It was further observed to present similarly to variola-vaccinia viruses with a similar serological relationship [17], as well as leads to the formation of intracytoplasmic eosinophilic inclusions, small whitish lesions, and was found to pass serially in rabbit skin [18]. mpox and smallpox would continue to be monitored by the WHO in non-human primates to determine if an animal reservoir existed throughout the 1960s and 1970s. In

the 1960s, 4 mpox outbreaks were recorded in animals with no recorded infections in humans [18–20]. Believed to be caused by two imported ant eaters, the 1966 zoo outbreak reported by Peters has a particularly high mortality. Despite containment procedures, mpox spread to nearby enclosures, resulting in 23 animal infections and 11 total deaths, including the deaths of 6 out of 10 infected orangutans [20].

2.1 Effect of reservoirs and wildlife control measures

A report by the WHO in 1968 concluded that mpox transmission between monkeys is 'infrequent' and that most likely another animal reservoir existed [18]. A definitive mpox virus reservoir host is still unknown and under study. Currently, giant-pouched rats, rope squirrels, and African dormice are posited as the most likely candidates [21, 22]. Throughout the 1980s, the animal-animal spread was found with particular prevalence in squirrels of the *Funisciurus anerythrus* species, where it was shown they sustain mpox viral transmission in areas near human settlements [23]. Squirrel mpox-related death rates and recovery rates were later found to be approximately 17.5 and 12 days, respectively [24] (see Table 1). During the 2022 global mpox outbreak, it was discovered that human-to-dog transmission is possible, thus raising concerns about further dog-to-dog and dog-to-human transmission [25]. Culling, the reduction in wild animal populations through selective slaughter, has been employed as a method for wildlife reservoir management and to mitigate the potential of further animal-to-human transmission [26]. For example, culling has been employed recently during the SARS-CoV-2 pandemic to mitigate further animal-to-animal transmission amongst farmed minks [27]. Culling to prevent further mpox spread has been explored through transmission modelling approaches, where it has been found to be ineffective and can lead to the counter-productive outcome of increasing mpox infection. This is because culling results in the sudden removal of mature animals with immunity replaced with juvenile, more susceptible animals, thus increasing the probability of outbreaks [28].

2.2 Transmission between humans

The first human mpox case was reported in 1970 in a 9-month-old baby in the Democratic Republic of Congo [29]. A study of 155 mpox cases in west and central Africa from 1970-1983 estimated only 20% of cases to spread from human-to-human contact, where human mpox cases were primarily suspected to occur from contact with monkeys and squirrels [30]. The human-to-human transmission was noted to "stop spontaneously", with attack rates suspected to be 15% amongst smallpox-unvaccinated households and 0.4% amongst vaccinated [30], comparably less than smallpox attack rates amongst the unvaccinated which ranged from 33% to 88% [31–33]. A study conducted in Zaire between 1980 and 1984 of 214 patients with human mpox found attack rates for household contacts of 7.2% amongst unvaccinated and 0.9% amongst vaccinated [34]. In this study, 13% of cases were found amongst vaccinated individuals leading to the hypothesis that the immunity gained from smallpox vaccination was waning [34], and

further raised a concern that the virus may later become endemic [30].

The low attack rates of mpox and the unchanging secondary attack rates throughout the 1970s through early 1980s amongst the unvaccinated supported the decision from the Global Commission to cease the smallpox vaccination program in Central African countries where mpox was now considered endemic [35]. Multiple self-contained mpox outbreaks were documented through the early 2000s. Of note, a major outbreak in Nigeria began in September 2017 and ultimately led to 228 suspected cases [36]. Human mpox infections in the 2017 Nigeria outbreak were predominantly male, and the outbreak was ultimately considered contained [36]. The 2003 mpox outbreak in the USA appeared to be particularly severe in children, where one-fifth of pediatric patients developed serious complications resulting in intensive medical intervention and 5 out of 10 pediatric patients were admitted to the ICU [37]. For a detailed review of all pre-2018 human mpox outbreaks, we refer to ref. [2].

The 2022 international emergence of human-human transmission of mpox in multiple non-endemic countries constitutes a significant shift in viral prevalence.

3 Pathogenesis, clinical presentation, and longitudinal within-host dynamics of mpox

The incubation period of human mpox can range from 5-21 days [38], with a typical incubation period of 7-17 days, followed by a prodromal period of 1-4 days [39]. Clinical characteristics of mpox are similar to that of smallpox: enlarged lymph nodes and a rash period that lasts 14-28 days. Distinct from smallpox, mpox often presents with cervical or inguinal lymphadenopathy suggesting that the immune response to mpox differs from that of smallpox [39]. A detailed list of clinical characteristics, including changes in mpox epidemiology as a function of time, is described in the article by Wilson *et al.* [39].

A study on non-human primates longitudinally tracked viral shedding and cytokines from both intrabronchial exposure (i.b.) and intravenous inoculation (i.v.) of mpox [40]. Through tracking mpox viral features over a 36-day window, they found that the time to mean day of lesion exposure increases as a function of decreasing mpox dosage. They further found peak viral load to vary significantly between nasal and oral swabs. Recent clinical human studies in France and Spain have longitudinally tracked cohorts of people over 14 and 57 days [41,42]. These studies compare mpox viral load between HIV+ and HIV- individuals and find mpox cycle threshold (Ct) values to decrease significantly for both categories of individuals [41,42], and further conclude transmission of mpox to primarily occur through direct body contact rather than through a respiratory route or bodily fluids [41].

Serological features that inform us about immune responses can also be used by within-host modelling studies to reveal mechanistic insight into viral traits as well as vaccine dynamics. Interferon gamma (IFNg) is a cytokine known

to play a pivotal role in host defence against pathogens [43,44], and is often used to model within-host inflammatory responses and infer cellular-mediated immunity [15, 16]. Immunity from smallpox vaccination has been shown to elicit IFNg, cytotoxic T cell, and neutralizing protein responses in humans that can last over 20 years [45]. mpox cross-protective immunity from the smallpox vaccine is known to occur [38], with efficacy waning at an approximate rate of 1.29%/yr [46]. Prairie dogs vaccinated with the smallpox vaccine and then challenged with mpox were found to mount a significant humoral response. Further, vaccinated humans were found to mount strong cellular and humoral responses as shown in longitudinal data over a 32-day study period [47]. IFNg has been shown to play an important role in protection against mpox in mice, whereby inactivation of the IFNg receptor led to increased sensitivity to mpox [48]. Earl *et al.* [48] also report viral titres as a function of time in various major organs, where lungs were found to contain the highest PFU/g for all time points. They also track six cytokines, including IFNg and IL6, as a function of time after injection and find a strong IFNg response in BALB/c mice but not in other types of mice [48]. Interestingly, orthopoxvirus has been shown to suppress IFN production and to further possess a multiple-gene system to resist to IFN [49]. mpox has been found to suppress T cell activation by triggering a state of T cell nonresponsiveness [50]; thus, a within-host model of mpox should take into account CD4 and CD8 suppression dynamics. These longitudinal data serve as a useful starting point for a within-host modelling study of mpox and can be utilized to guide model predictive power and determine practical identifiability in estimated parameters. Such modelling studies for mpox are currently lacking in the literature. Lum [38] provides an in-depth review of the clinical immune features of mpox. We spend the remainder of the review covering modelling efforts to understand the epidemiological population spread of mpox in human-human, animal-animal, animal-human, and human-animal scenarios. We further cover modelling studies incorporating climate variables, therapeutic strategies (from smallpox vaccine waning and future vaccination outcomes), contact tracing and isolation measures.

4 Population-level epidemiological models

4.1 SIR/SEIR with no immunity

Compartmental modelling techniques have been used extensively to describe the population spread of infectious diseases. Among infectious disease models, the most fundamental and classic model is the Susceptible-Infected-Recovered (**SIR**) compartmental model developed by Kermack and McKendrick [51]. In the SIR model, the total population is divided into three subgroups based on the disease status: susceptible (S), infected (I), and recovered (R). **S** represents the subgroup that has not yet but may be infected by the disease, **I** stands for the subgroup that has been infected and can transmit the disease, and **R** represents the subgroup that has been recovered from the infected disease. Two parameters are used in the SIR model, the effective contact rate (β) and the recovery rate

(γ). β affects the transition from $S \to I$, and γ affects the transition from $I \to R$, and the total population, N, is conserved through time $N_n(t) = S_n(t) + I_n(t) + R_n(t)$. An example schematic of the SIR model with is shown in Figure 4b.

The epidemiological model framework for mpox has been established over the past few decades, and many models capturing human-human, and animal-human interactions have been explored [52]. Jezek *et al.* [53] constructed a stochastic model using the Monte Carlo method to simulate the chain of human-to-human transmission of mpox. The model has been validated and applied to understand the transmission potential of mpox in unvaccinated populations [53]. Bhunu & Mushayabasa [54] presented a basic SIR compartmental model to examine the transmission dynamics of mpox between humans and non-humans, and Betti *et al.* [55] present a SIR model with additional pair-formation dynamics to account for transmission via prolonged close contact between individuals.

We summarize parameters determined by mpox epidemiological modelling studies in Table 1. For the non-human population, mpox parameters are found to be: $2yr^{-1}$ for the rate of recruitment for susceptibles, a natural death rate of $1.5yr^{-1}$, the death rate due to mpox is given as $0.4yr^{-1}$, and the rate of immunity is given as $0.6yr^{-1}$ [56]. Pre-2022, for the human population, mpox parameters were found to be: $0.029yr^{-1}$ for recruitment rate of susceptibles, a natural death rate of $0.02yr^{-1}$, death rate due to mpox of $0.1 - 0.17yr^{-1}$, and permanent immunity rate of $0.83 - 0.9yr^{-1}$ [56]. Disease-free and endemic equilibrium and the corresponding stability analysis were conducted in the literature. The animal-only endemic equilibrium is globally asymptotically stable when $R_{0_n} > 1$ and $R_{0_h} < 1$. The endemic equilibrium where mpox infections exist in both the human and non-human populations was shown to be locally asymptotically stable when $R_{0_h} > 1$, but close to 1 [56].

4.2 Models with vaccination

The SIR model often oversimplifies complex disease transmission dynamics. For example, the SIR model does not consider the incubation duration between when an individual is exposed to a disease and when that individual becomes infected. We refer to Tolles & Luong (2020) [57] who highlight limitations of the traditional SIR model, including that it results in often over-simplified assumptions about the population dynamics. Thus, most epidemiological work involves SIR-inspired models with more mathematical complexity to account for complex population dynamics. The Susceptible-Exposed-Infected-Recovered (**SEIR**) model has been widely used to study infectious disease dynamics. In the SEIR model, an exposed compartment (E) is added to the fundamental SIR model, representing individuals who are exposed but have not yet been contagious, such that they experience an incubation period. Mitigation strategies such as vaccination can also be considered. For example, Osman and Adamu [58] developed an SVEIR model (including a vaccinated component) that accounts for a varied incubation period and individual vaccination status. Usman *et al.* [58] study the effectiveness of vaccination on the spread of mpox between people in Nigeria.

They found that adequate vaccination and treatment policies could dramatically reduce the spread of mpox among humans. Based on mpox parameters pre-year 2017, they conclude that an increase in vaccination control parameters leads to a decrease in the basic reproduction number. Emeka *et al.* [59] also incorporate a vaccine compartment in a population of mpox-susceptible individuals and generally find that mpox outbreaks do not occur in populations of vaccinated individuals.

Building on the work of Usman & Adamu [58], Bankuru *et al.* [22] introduced a simplified SIR model of the mpox dynamics, providing closed-form formulas for equilibrium states of this disease dynamics, allowing for direct calculations of the semi-endemic equilibrium (Figure 3). They showed there exists a semi-endemic equilibrium in which there is no infection in the squirrel population, where the disease still persists in the human population. They found that the optimal vaccination rate amongst humans is about 0.04 vaccine/year, meaning that individuals should be advised to vaccinate approximately once every 25 years. They also found the optimal vaccination rate is about 10 times more sensitive to parameters related to animal hosts than to a corresponding parameter related to humans, thus concluding that more precise information about reservoir hosts is needed [22].

As countries such as the UK are purchasing large quantities of vaccines for public dissemination, given that vaccine efficacy has been found to drop at a rate of 1.29% per year [46], mathematical modelling studies such as that done by Bankuru *et al.* [22] can be used to inform vaccination rates, as well as how much of a proportion of the population needs to be vaccinated to achieve herd immunity. Another important factor explored by Bankuru *et al.* [22] is the cost of vaccination. Where cost here is defined in a game-theoretic sense, the cost of not vaccinating is given by the product of the cost of infection with the probability of becoming infected. In Fig 3, we include plots of cost as a function of vaccination rate when the human-human transmission rate is high, where Bankuru *et al.* [22] find that the overall cost of vaccinating is much lower than compared to not-vaccinating for most epidemic scenarios.

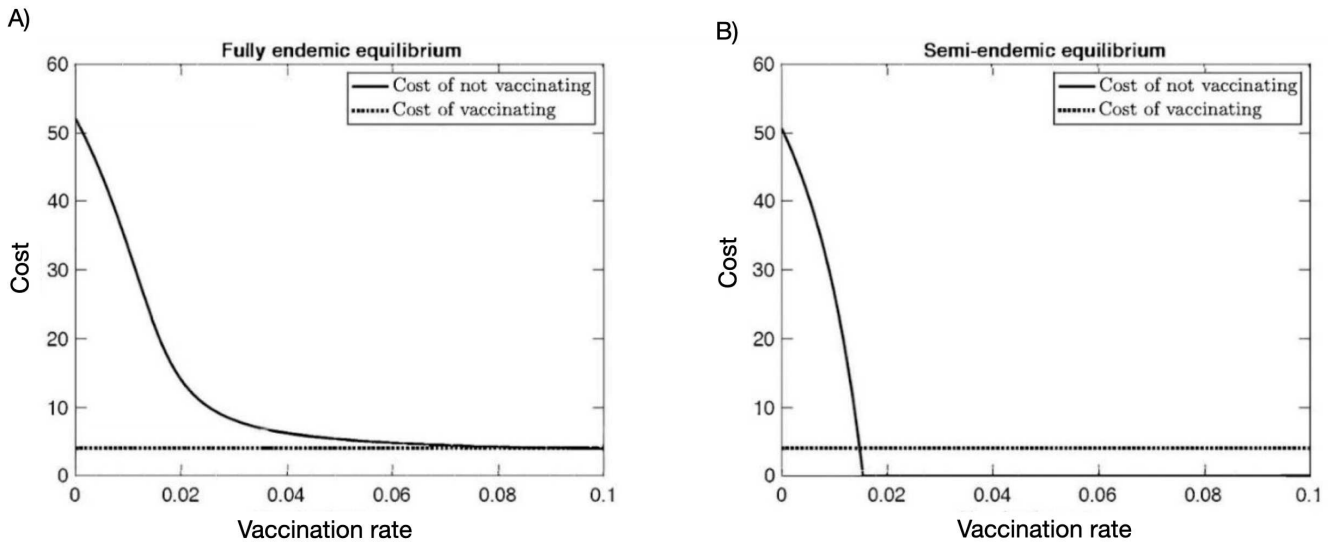

Figure 3: Costs vs. vaccination rate with a high rate of the effective human-to-human transmission ($\beta_{hh} = 60$). A) Fully endemic equilibrium and B) Semi-endemic equilibrium. Reprinted by permission from PeerJ from ref. [22]. Copyright 2020.

A combination of historical data and epidemiological modelling was used to estimate the basic reproduction number, R_0, of mpox in the Democratic Republic of the Congo during 1966-1984 to be between 1.46 and 2.17 [60], significantly less than smallpox which had an estimated R_0 range of 3.2-6.9 [61, 62]. Due to the lasting immunity from the smallpox vaccine, mpox was deemed not self-sustainable in human populations in the DRC from 1980-1984 [60]. Estimates show that the immunity from smallpox vaccination against mpox may have already fallen to 60% in non-endemic countries by 2011 [60], which corresponds to R in the range of 1.10-2.40. Hence, mpox has had increasing potential to become an epidemic in humans in historically non-endemic countries.

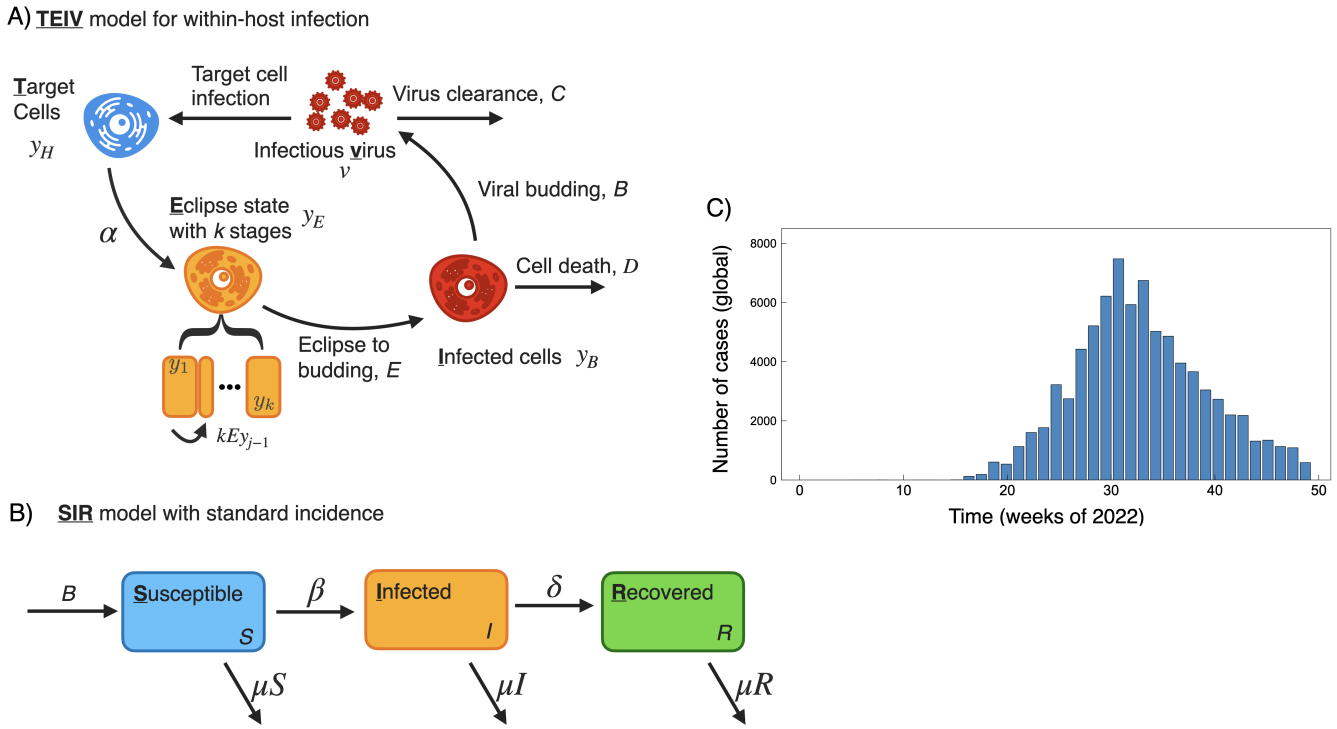

Figure 4: A) Schematic of a basic TEIV model. B) Schematic of basic SIR model with standard incidence, as used to model mpox dynamics for the 2022 pandemic [55]. C) Global mpox cases as a function of weeks in 2022. Data accessed from publically available WHO data (ref. [3], accessed on November 17th, 2022).

4.3 Epidemiological modelling studies on the 2022 global outbreak

Population-level human-to-human models of mpox spread throughout the 2022 epidemic have been based on SIR and SEIR frameworks. These novel modelling studies (discussed in detail below), consider extensions to consider public health mitigation strategies (e.g. quarantine and vaccines), contact tracing, and sexual mixing models. For reference, the current scenario of global cumulative mpox cases by country is shown in Figure 1, and with cases normalized by country population shown in Figure 2. We further include the current global trend as a function of time for 2022, as shown in Figure 4c.

The increase in cases from the 2022 mpox global outbreak has been shown to be strongly associated with close intimate sexual contact [41]. 2022 mpox spread has been predominantly transmitted between men who have sex with men, with one study of 528 diagnosed infections finding 98% of infected persons to be gay or bisexual males [63]. Data-driven individual-level and population-level modelling studies can be used to outline the importance of public health policies and various mitigation strategies. For example, the model presented by Betti *et al.* [55] presents a

novel framework that includes pair-formation (accounting for prolonged close contact between people) to describe mpox transmission. They show their pair-formation model captures population trends in data with an estimated R_0 of 2.3, and they further predict the occurrence of future waves of infection. Similarly, Bragazzi *et al.* [**?**] develop a SEIQR model that includes the sexual behaviour of high-risk individuals and find that R_0 amongst the high-risk population to be $\sim$1.5, whereas amongst the low-risk population to be as low as 0.007 [**?**]. Bisanzio *et al.* [64] utilize a recently developed individual-based modelling framework [65] whereby they simulate the spread of mpox in a network of 50 million susceptible individuals distributed across N cells to represent a population density characteristic of a typical European country of land mass similar to France or Spain. With spread amongst the population driven by an SEIR model, Bisanzio *et al.* [64] predict mpox outbreaks lasting 23-37 weeks where mitigation strategies such as contact tracing with isolation followed by vaccination could reduce the median duration of an mpox outbreak by as much as 75%. Another network model by Van Dijck*et al.* [66] explores the ramifications of undiagnosed mpox and contact tracing and predicts that if 10% mpox contact abstains from sexual activity, this would result in a 35% reduction in cases. A contact tracing study on the transmission dynamics in the UK predicted the epidemic peak to occur in early July of 2022 and further found that a significant number of cases were caused by pre-symptomatic transmission, and determined a mean incubation period of 8.5 days [67]. Mingione *et al.* [68] apply the generalized logistic curve to country-wide data from the top 10 non-endemic countries experiencing mpox outbreaks and find agreement with the literature that containment of the outbreak is feasible over the short term if mitigation strategies are employed. The population modelling studies of the 2022 global outbreak thus all agree, based on current data on mpox trends, that the outbreaks occurring in non-endemic countries are generally under control and on a declining trend. This is supported by the current global trend in cases; a histogram of global case counts up to November 29th of 2022 is shown in Figure 4c. A summary of 2022 mpox mathematical modelling population parameters is provided in Table 1.

Epidemiological modelling studies are important for policy-decision makers when deciding which mitigation strategy, or control measures (such as isolation and lockdown measures), to employ. Predictive modelling for future mpox peaks will be important in aiding policy decision-makers. Orthopoxvirus, such as smallpox, are known to transmit via a respiratory route [69]; at this time, however, a respiratory mode of transmission is not found to play a major role in the 2022 outbreak [41, 42]. Mitigation strategies, such as vaccination, should be taken to reduce population infectivity and further reduce the probability of allowing a more virulent and transmissive mpox strain to emerge. Predictive modelling for future mpox peaks will play an important factor in aiding policy decision-makers. For example, based on Canadian mpox trends, there are predicted to be further peaks occurring on an approximately annual basis [55]. Yuan *et al.* consider an SEIR model whereby the population is divided into high and low risk and focus their study on mass gathering scenarios [70]. They find that a broad vaccination campaign is less effective

in curbing the spread of mpox than compared to contact tracing, isolation and vaccination of close contacts. They further posit that the ring vaccination strategy may be inadequate in preventing an outbreak from occurring; however, it does still result in fewer case counts [70]. They follow up their work with a study to consider the mpox threat to the low-risk population if viral transmissibilities increases [71]. They conclude that isolation, contact tracing, and quarantine are key mitigation strategies to prevent infection in the event of increased viral transmission into low-risk populations [71].

Currently, the 2022-mpox strain is predominantly spreading through close intimate contacts [41]. However, orthopoxviruses, such as smallpox, are known to transmit via a respiratory route [69]. Currently, a respiratory transmission mode is not found to play a major role in the 2022 outbreak [41, 42]. However, the concern that mpox could mutate to find a respiratory transmission route is warranted. The cost and benefits of mitigation strategies, including the details of how they can be disseminated to the public, can be readily explored through modelling studies. Such work can be used for the future spread of mpox transmission.

4.4 Immunity decline hypothesis

The recent 2022 re-emergence and recent outbreaks of mpox are still under investigation. One hypothesis for the increase in cases relates to the decline in population cross-immunity provided by the smallpox vaccine [72, 73]. In 1980, WHO declared the eradication of smallpox; soon afterwards, routine smallpox immunization ended worldwide [74]. Smallpox vaccine has proven to induce humoral and cell-mediated responses against orthopoxviruses [75, 76], creating a heterotypic immunity composed of a wide array of antigen receptors [77] and estimated to have an efficacy of 85% in preventing mpox infection in humans [60]. Thus, it has been suggested that younger generations not vaccinated against smallpox are vulnerable to mpox infection. This section will discuss the current evidence from mathematical models testing the declining immunity from vaccination in increasing susceptibility to mpox. Data from the Democratic Republic of the Congo (DRC) revealed that individuals born before the official vaccination cessation had a 5.21-fold lower risk of mpox infection than unvaccinated persons [72, 78]. Nguyen *et al.* [79] modelled the declining immunity in Nigeria, accounting for individual-level declining immunity at a rate of 1.29% per year, as well as country-wide declining immunity using weighted regional estimates of smallpox vaccination coverage. They found that with an increase in unvaccinated and immunologically naive population (90.7% of the total population in Nigeria in 2018), and together with the decline from 85% to 23.1% in efficacy from cross-immunity protection provided by smallpox vaccination, the overall population immunity was estimated to be only 2.2% as of 2018 [46]. We include a figure of their findings shown in Figure 5a.

The declining immunity from vaccination to smallpox represents an epidemiological threat by increasing the mpox reproduction number. The basic reproduction number, R_0, of any infectious disease is dynamic and depends on

many variables, including characteristics of the pathogen characteristics and the host. Grant *et al.* [60] modelled this relationship with data from the DRC. They determine an mpox reproduction number, R. R is given by $R = R_0(1-\epsilon p)$, where ϵ represents the vaccine efficacy, and p the vaccination coverage. They find R for mpox is increasing. Given a current immunity estimate (20%), this value could be higher than 2.5 [60]. We include a plot of their results for R as a function immunity in Fig 5b. The increase in attack rate over time may be evidence for the immunity decline hypothesis as well. mpox household attack rates amongst the unvaccinated and vaccinated were reported as 15% and 0.4%, respectively, in 1985 [30]. The 2013 outbreak in the DRC, which represented a 600-fold increase in annual infections, was found to have a household attack rate of 50%, where many people who contracted mpox were previous smallpox vaccine recipients [80].

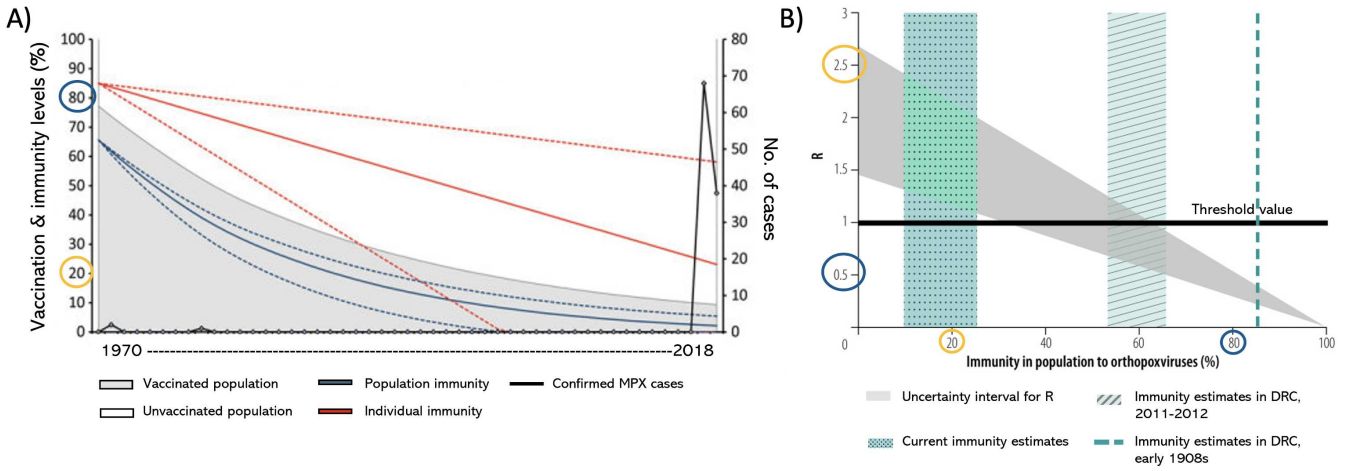

Figure 5: a) Visualization of the relationship between smallpox vaccination and cross-immunity conferred to mpox virus rates at a population (blue) and individual level (red) in Nigeria from 1970 to 2018. Reprinted by permission from Centers for Disease Control and Prevention from ref. [46]. Copyright 2021. b) Predicted change of the reproduction number R for MPX as a function of immunity in a population to orthopoxvirus species (provided by smallpox vaccine). Blue circles show a scenario where the vaccination percentage is high, most of the population presents high-level cross-immunity against orthopoxvirus species, and the mpox R value is low. Yellow circles show the scenario where vaccination and cross-immunity rates are low, and mpox R-value increases to >2.5. Reprinted by permission from the World Health Organization from ref. [60]. Copyright 2020.

The loss of immunity hypothesis is not mutually exclusive from other re-emergence theories, such as the increased exposure to wildlife, reservoir expansion, globalization, and mutations to mpox fitness traits. These factors represent critical barriers to consider for mpox spillover opportunity [81]. An increase in the mpox immune-naive population and the risk of exposure create a niche for continued mpox animal-to-human and human-to-human trans-

mission, longer chains of infection, and thus an opportunity for mutation in mpox viral transmission traits. Pre-2022, human-to-human transmission chains have been relatively short-lived, and stochastic models performed in the 1980s based on historical data found mpox to have a low probability to be established in human populations [53]. However, more recent models have shown that sustained human-to-human transmissions could favour pathogen evolution, creating a potential existence of semi-endemic or fully endemic equilibrium [60, 82].

A clustered epidemiological differential model developed by Ali *et al.* [83] took into account human behavioural dynamics such as vaccination and drug hesitancy, cooperation and mobility rate and showed how opination dynamics have a tremendous impact on fatality rates. Furthermore, models on voluntary vaccination have shown the potential control of mpox outbreaks in a semi-endemic equilibrium but not in a fully endemic one [22]. In an endemic equilibrium scenario, deterministic compartmental models showed that isolation of infected individuals, in combination with adequate treatment and vaccination, plays an essential role in the control and eradication of mpox [58, 84]. Vaccination remains a high-potential primary mpox mitigation strategy and should continue to be prioritized in endemic regions [72]. However, to achieve effective mpox management a combination of countermeasures needs to be considered. Novel mpox-specific vaccines [85, 86], treatments [87–89] and prophylaxis public health measures [83, 90, 91] are all under development to mitigate mpox spread.

Parameter	Definition	Units	Values (range) [ref.]
Epidemiological mpox parameters in humans			
R_0	Basic reproduction number	N/A	2.13(1.46-2.67) [60], 2.66 (international estimate)† [55], (1.5-4.3) (Canadian estimate)† [55], 1.5 (high risk pop.)† [92], 0.01(low risk pop.)† [92]
R_{vac}	Disease-free and vaccinated population reproduction number	N/A	0.32(0.22-0.4) [93]
β	Infection rate	Days^{-1}	1.68x10^{-4} (Canadian estimate) [55]†, 9.78x10^{-7}(International estimate) [55]†,
P_s	Transmission probability per sexual contact	N/A	0.24 [92]†
I	Incubation period	Days	(5-21) [22, 60], 8.5(6.6-10.9) [67]†, (10-14) [94]
P	Prodromal Period	Days	(1-4) [39], 2 [94]
σ	Timespan from the appearance of lesions to desquamation	Days	(14-28) [39], (22-24) [95]
d_h	Human death rate	Days^{-1}	3.12 [22]
D_{frac}	Human infection mortality percentage	%	(1-10) [1], (10-17, from 1970-1989) [94], 1.5 (1997) [94], <0.0005 [96]†
β_{hh}	human-human transmission rate	Days^{-1}	32.85 [22]
ρ_h	Human recovery rate	Days^{-1}	28.08 [22]
V_r	Optimal vaccination rate	vaccine/yr	0.04 [22]
V_{eff}	Cross-vaccine efficacy from smallpox vaccine	%	(80-95) [97]
V_{loss}	Vaccine efficacy loss	%/yr	1.29 [46]
Γ_2	Secondary attack rate: ratio of infected household members to total household members	%	15 (unvaccinated) [30], 0.4 (vaccinated) [30]
Γ_1	Primary attack rate: proportion of exposed susceptible population that become ill	%	7.2(unvaccinated) [34], 0.9(vaccinated) [34]
Animal transmission mpox infection parameters			
d_s	Squirrel mpox-related death rate	Days^{-1}	17.5 [24]
ρ_s	Squirrel recovery rate	Days^{-1}	12 [24]
β_{ss}	Squirrel-squirrel transmission rate	Days^{-1}	40 [22]
β_{sh}	Squirrel-human transmission rate	Days^{-1}	0.05 [22]

Table 1: Table of values listing epidemiological parameters for mpox viral dynamics from the literature. †These values are 2022 epidemic specific; all other values are determined from pre-2022 mpox outbreaks.

4.5 Climatic variables influencing mpox transmission

Climate change has altered human-environment systems [98]. The emergence and re-emergence of many infectious diseases are projected to increase due to the negative impact of climate change [99, 100]. Interactions between the three factors embodied in the epidemiological triangle (the virus (agent), the human (host), and the reservoir (environment) [101], have been found to contribute to mpox emergence and expansion. In addition to the decrease in herd immunity caused by the cessation of smallpox vaccination (discussed in detail in sections 4.2 and 4.4), climatic variables and human behaviour have created an ideal niche for mpox transmission [102, 103]. In this section, we discuss the current model-based evidence for mpox transmission, emphasizing the influence of climate factors.

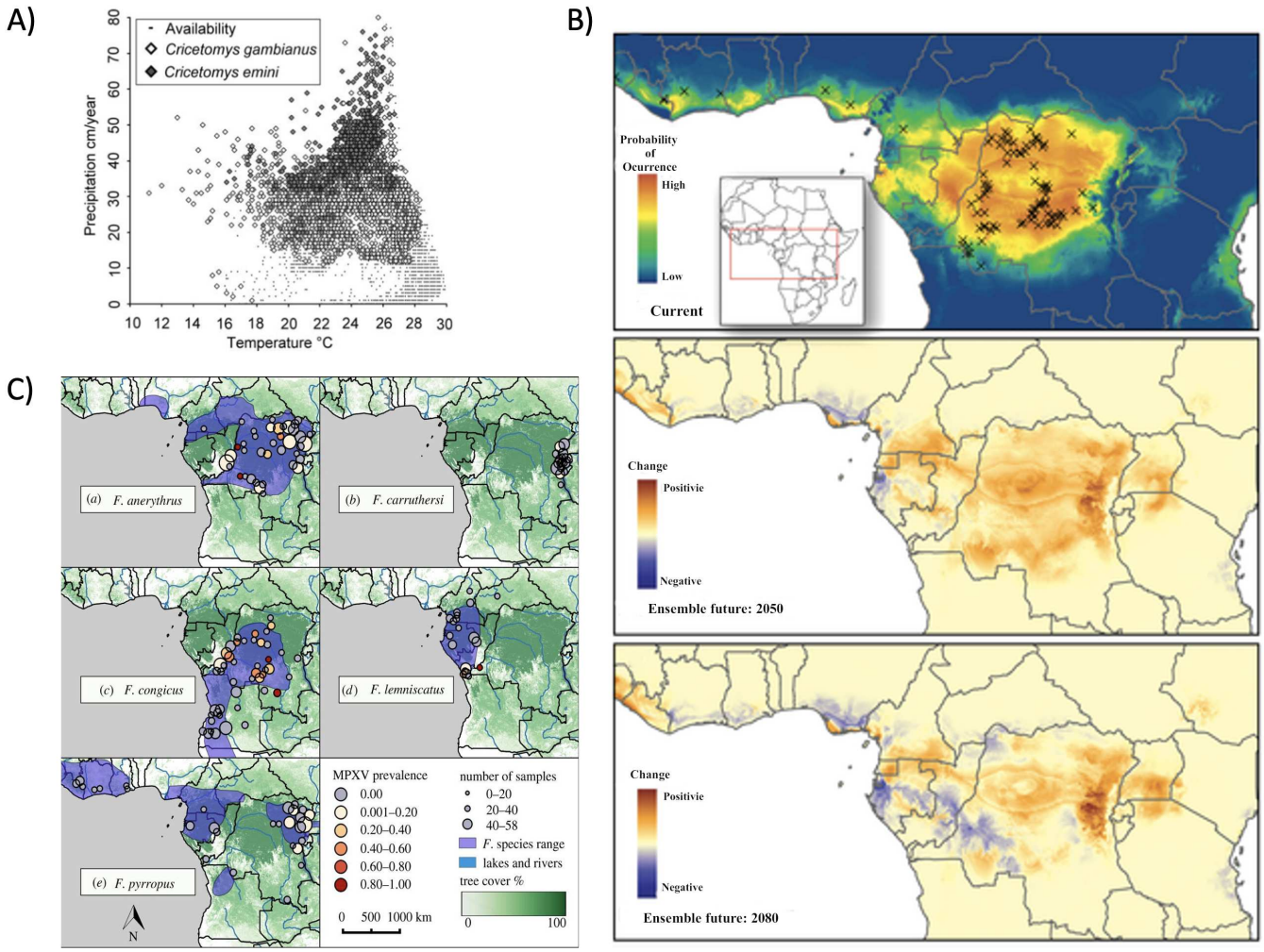

Figure 6: a) Two-dimensional representation (annual mean temperature and annual mean precipitation) of ecological niche models developed for two mpox reservoir species *cricetomys gambianus* (white diamonds) and *cricetomys emini* (gray diamonds) across tropical sub-Saharan Africa. Reprinted by permission from Oxford University Press from ref. [104]. Copyright 2006. b) Observed and predicted human mpox occurrence under present and future climate conditions with reservoir species as predictor variables in Central and Western Africa. The average projected change in occurrence probability for eight climate change scenarios for 2050 (middle) and 2080 (bottom). Reprinted and modified by permission from PLOS One from ref. [105]. Copyright 2013. c) mpox prevalence detected in dried museum specimens of potential mpox reservoir species, with an underlying layer representing tree cover, with darker greens corresponding to high cover percentages. Reprinted by permission from The Royal Society Publishing from ref. [106]. Copyright 2018.

The impact on human health from climate change is an emerging topic. Currently, there is a clear consensus

on the increase in adverse climate-related health outcomes such as food insecurity, heath-related mortality and morbidity, mental health damage, or injuries [98]. Impacts on health can include the impairment of the immune system due to direct or indirect effects of climate change.

There has been significant scientific interest in mpox spread within endemic African countries with particular attention to mpox biogeographic barriers [107]. Environmental conditions can define the spread and durability of pathogens outside their hosts. Survival models have shown that orthopoxviruses are high-virulence high-survival pathogens, which implies high durability outside their host [108]. Seasonal patterns of mpox outbreaks have been observed during the fall season and linked to deforestation and flooding [109]. Historical evidence suggests that dense and humid lowland tropical forests ecotones are the most favourable ecosystem for zoonotic transmission of mpox [106, 110].

Prior to the 2022 outbreak, mathematical models concluded that continued mpox human-human population spread required continued zoonotic reservoir exposure to maintain chains of transmission [35]. Therefore, much attention has been paid to mpox reservoirs, but there is no clear consensus on the natural or definitive reservoir as of the time of writing [102, 111]. It is known that environmental conditions can affect the transmission of mpox between animals [112]. Having an unknown primary reservoir for mpox limits a model's accuracy in prediction of the impact of climate variables on the animal-animal and animal-human dynamics [113]. Multivariate analyses of historical data have demonstrated that mpox can co-occur on several species in an unanticipated manner [106, 114]. Additionally, ecological niche modelling techniques have been used to model the climate and spatial distribution of mpox [104, 114, 115], where these modelling studies emphasized the critical role of ecosystem variation on reservoir distribution (shown in Figure 6).

Understanding mpox spatial ecology is essential to project future outbreaks under climate change conditions. Spatial and probabilistic models have been used to study mpox occurrence, particularly in Africa (see, for example, Figure 6c,b). Including climatic variables has been demonstrated to be critical in the spatial analysis of mpox at a local and regional scale [105, 116]. Climatic variables such as temperature and precipitation seasonality are reservoir species predictors, meaning that a small change in those variables could also change the reservoir dynamics and thus animal-human transmission probability [104, 105]. Furthermore, climatic and ecosystem variables can increase habitat suitability for potential mpox reservoirs and, by extension, more frequent wildlife-human contact [110, 114]. Other extreme weather events, such as droughts [117], can force carrying mpox species to move closer to human settlements [105]. Future research predicting shifts in reservoir species should also focus on how this dynamic is affected by environmental changes. We propose that models should include the viral dynamic considerations of interrupting or increasing wildlife-human frequency under climate change scenarios.

4.6 Towards a within-host model for mpox

The goal of within-host modelling is to represent the complex physiological processes of a disease, or therapeutic, within the body with mathematical models [7]. Within-host mathematical models are developed under biological principles and then fit longitudinal serological data to estimate various aspects of physiological dynamical outcomes. Modelling of in-host pathogen dynamics has proven critical towards furthering our understanding of HIV, HCV, HBV, HSV, influenza, and SARS-CoV-2 as well as aiding the development of vaccine therapies [8–12,14–16,118–120]. Following the development and fitting of a model to serological data, structural and practical identifiability methods are then employed to assess model reproducibility and reliability [121]. A basic example of a common within-host model is the TEIV (Target cell, Eclipse phase, Infected cells, Virus) model which is shown schematically in Figure 4a and given by

$$\text{Target cells}: \quad \frac{dy_T}{dt} = -\alpha y_T v \tag{1a}$$

$$\text{Eclipse stage 1}: \quad \frac{dy_1}{dt} = \alpha y_T v - kEy_1 \tag{1b}$$

$$\text{Eclipse stage 2...k}: \quad \frac{dy_j}{dt} = kEy_{j-1} - kEy_j, \quad j = 2...k \tag{1c}$$

$$\text{Budding}: \quad \frac{dy_B}{dt} = kEy_k - Dy_B \tag{1d}$$

$$\text{Infectious Virions}: \quad \frac{dv}{dt} = By_B - \alpha y_T v - Cv. \tag{1e}$$

$$\tag{1f}$$

Models based on the TEIV model have been used extensively to estimate within-host properties of disease dynamics thus contributing to our understanding of the disease progression at the within-host scale [12,119,122–128]. Models can inform and predict various aspects of disease dynamics. For example, SARS-CoV-2 viral load modelling has predicted median peak viral load to coincide with symptom onset [12].

At the time of writing, there is a notable gap in within-host mechanistic modelling studies of mpox; indeed, very few within-host modelling papers can be found for any orthopoxvirus. Ogunjimi *et al.* [129] model the CD4 trajectories of chickenpox patients appears to be the only current example of within-host modelling work of orthopoxvirus. The longitudinal studies outlined in the previous section provide detailed knowledge of mpox serological parameters required to fit into a typical TEIV model with immunity.

5 Concluding remarks and future outlooks

Mathematical epidemiological and within-host modelling is a methodology capable of rapidly-through cost-effective and non-invasive means-gaining actionable into population-level and within-host-level viral dynamics and therapeu-

tic responses. At the within-host level, mathematical modelling utilizes serology-based diagnostics to understand disease transmission dynamics, such as the viral reproduction number and viral load clearance and cell recovery, to understand the timescales of disease transmission. Such studies on mpox are lacking. At the population level, mathematical modelling leverages population-metrics such as contact tracing data, cumulative case counts, and wastewater surveillance to predict outbreak characteristics such as recovery rates, transmission, virulence, and reproduction numbers. Although the current mpox epidemic case counts are on the decline, models are currently predicting future waves to occur on an annual scale [55]. Thus, modelling efforts can be used to allocate public health resources to curb the future spread of infection, such as when and who to target in vaccine or education campaigns.

Human infectious disease burden remains high in many countries where this century's outbreaks of emerging and re-emerging pathogens have been described as the "new era of infectious disease" [130]. Climate change is leading to changes in natural ecosystems across the globe, a consequence of which has been linked to the increased emergence of human infectious diseases [98]. More than half of infectious diseases affecting human populations have been aggravated by climate hazards by pathways such as bringing pathogens closer to people or implicitly causing favourable changes to viral fitness traits [131]. Mathematical models of infectious diseases such as Influenza virus [132], West Nile virus [133], SARS-CoV-2 [134], and Malaria [135] that consider climatic variables have demonstrated utility for policy-makers decisions for planning public health prevention and responses strategies [136]. The results of this review revealed that the practice of including climatic variables in the mathematical modelling of mpox is still scarce. The evidence available suggests climate variables can significantly impact mpox transmission and pathogenesis by affecting the reservoir-human contact environment [104–106]. Thus, it is essential to consider climatic variables at local, regional, and global scales in future mpox mathematical modelling studies to further understand its complex dynamics with potential reservoirs and potential impacts on human populations.

The 2022 emergence of mpox as a global threat has led to over 80,000 cases in non-endemic countries as of November 17th of 2022. As mpox has gained global attention, higher resolution studies reporting regular case counts, as well as longitudinal serological measures (such as IgGs, and CD4/CD8 responses) can be increasingly utilized in mathematical modelling approaches to gain deeper insight into viral dynamics and predictive power. Moving forward, an interdisciplinary approach between clinicians and mathematicians can work to better inform timescales of clinical data acquisition to gain the optimal information on disease dynamics from limited data sets [15]. To date, no within-host modelling studies of mpox have been carried out to our knowledge.

There have been historical efforts to quantify an immunological correlate of protection in humans against mpox [47], however, a robust correlate of protection against the 2022 strain is currently not known [38]. Serological studies can be leveraged by mathematical approaches to correlate humoral and cellular longitudinal responses with case severity, or vaccine efficacy, such as that done for SARS-CoV-2 [16]. It is also important to understand differences

in within-host dynamics amongst cohorts containing various comorbidities, notably high-risk individuals coinfected with syphilis or HIV [137]. Longitudinal studies working to understand the risks of vaccination in these vulnerable populations are also lacking. As has become evident throughout the SARS-CoV-2 pandemic, there are many long-term consequences of SARS-CoV-2 that can present as neurological or psychiatric [138], cardiovascular [139], and various immunological dysfunctions [140]. As long-term studies for mpox emerge, mathematical modelling can be a useful tool used to predict the proportion of those expected to suffer long-term consequences from mpox infection.

1.Ethics Approval and consent to participate 2.Consent for publication 3.Availability of data and materials 4.Competing interests 5.Funding 6.Authors' contributions 7.Acknowledgements 8.Authors' information (optional).

6 Declarations

6.1 Ethics Approval and consent to participate

Not applicable.

6.2 Consent for publication

Not applicable.

6.3 Availability of data and materials

Sources for all plotted data have been referenced within the figure captions. Data is available from Chapin S. Korosec, email: chapinSkorosec@gamil.com.

6.4 Competing interests

The authors declare that they have no competing interests.

6.5 Funding

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6.6 Authors' contributions

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