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RESEARCH ARTICLE

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Assessing transmission risks and control strategy for monkeypox as an emerging zoonosis in a metropolitan area

Pei Yuan[1,2] | Yi Tan[1,2] | Liu Yang[1,2,3] | Elena Aruffo[1,2] | Nicholas H. Ogden[2,4] | Jacques Bélair[2,5] | Jane Heffernan[2,6] | Julien Arino[2,7] | James Watmough[2,8] | Hélène Carabin[9,10,11,12] | Huaiping Zhu[1,2]

[1]Laboratory of Mathematical Parallel Systems (LAMPS), Department of Mathematics and Statistics, Centre for Diseases Modeling (CDM), York University, Toronto, Canada

[2]Centre for Diseases Modeling (CDM), York University, Toronto, Canada

[3]School of Mathematics and Statistics, Northeast Normal University, Changchun, Jilin, China

[4]Public Health Risk Sciences Division, National Microbiology Laboratory, Public Health Agency of Canada, Ottawa, Canada

[5]Département de Mathématiques et de Statistique, Université de Montréal, Montréal, Québec, Canada

[6]Department of Mathematics and Statistics, York University, Toronto, Canada

[7]Department of Mathematics, University of Manitoba, Winnipeg, Manitoba, Canada

[8]Department of Mathematics and Statistics, University of New Brunswick, Fredericton, New Brunswick, Canada

[9]Département de Pathologie et Microbiologie, Faculté de médecine vétérinaire, Université de Montréal, Saint-Hyacinthe, Québec, Canada

[10]Département de médecine sociale et préventive, École de santé publique de l'université de Montréal, Montréal, Québec, Canada

[11]Centre de Recherche en Santé Publique (CReSP), de l'université de Montréal et du CIUSS du Centre Sud de Montréal, Montréal, Québec, Canada

[12]Groupe de Recherche en Épidémiologie des Zoonoses et Santé Publique (GREZOSP), Université de Montréal, Saint-Hyacinthe, Québec, Canada

Correspondence
Huaiping Zhu, Laboratory of Mathematical Parallel Systems (LAMPS), Centre for Diseases Modeling (CDM), Department of Mathematics and Statistics, York University, 4700 Keele Street, Toronto, Ontario M3J1P3, Canada.
Email: huaiping@yorku.ca

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Abstract

To model the spread of monkeypox (MPX) in a metropolitan area for assessing the risk of possible outbreaks, and identifying essential public health measures to contain the virus spread. The animal reservoir is the key element in the modeling of zoonotic disease. Using a One Health approach, we model the spread of the MPX virus in humans considering potential animal hosts such as rodents (e.g., rats, mice, squirrels, chipmunks, etc.) and emphasize their role and transmission of the virus in a high-risk group, including gay and bisexual men-who-have-sex-with-men (gbMSM). From model and sensitivity analysis, we identify key public health factors and present scenarios under different transmission assumptions. We find that the MPX virus may spill over from gbMSM high-risk groups to broader populations if the efficiency of transmission increases in the higher-risk group. However, the risk of outbreak can be greatly reduced if at least 65% of symptomatic cases can be isolated and their contacts traced and quarantined. In addition, infections in an animal reservoir will exacerbate MPX transmission risk in the human population. Regions or communities with a higher proportion of gbMSM individuals need greater public health attention. Tracing and quarantine (or "effective quarantine" by postexposure

Pei Yuan, Yi Tan, and Liu Yang contributed equally to this work.

vaccination) of contacts with MPX cases in high-risk groups would have a significant effect on controlling the spreading. Also, monitoring for animal infections would be prudent.

KEYWORDS
compartment models, control, monkeypox, risk assessment, zoonosis disease

1 | INTRODUCTION

Monkeypox (MPX) is a viral zoonosis first identified in 1958 in a laboratory monkey. Recently, the disease has regained public concern due to the emergence of multiple cases in nonendemic areas and the prominence of sexual transmission routes.[1,2] At the time of writing, the current outbreak has lasted close to 2 months since MPX cases were reported in the United Kingdom on May 6, 2022. Since then, there have been an increasing number of nonendemic regions reporting MPX cases including Canada, Spain, Germany, Portugal, and the United States. As of June 27, 2022, there have been close to 3413 laboratory-confirmed cases from 50 countries/territories in five World Health Organization (WHO) regions, mainly in nonendemic regions,[3] while the majority of cases from previous outbreaks were found in Central and West Africa, notably the Central African Republic, the Democratic Republic of the Congo, Nigeria, and Republic of the Congo.[4,5] Given the current spreading of the virus, public health agencies of many countries monitor the situation and the WHO declared that declared MPX a Public Health Emergency of International Concern (PHEIC) on July 23, 2022.[6]

MPX symptoms, similar to those of smallpox, involve two stages from the initial prodromal to the rash substage. Initial symptoms are typically flu-like, including fever, chills, exhaustion, headache, and muscle weakness.[7] These symptoms are followed by a widespread rash on the face and body, including inside the mouth and on the palms of the hands and soles of the feet.[7] After the onset of symptoms, MPX infection can progress to a more severe stage or even death. In outbreaks in Africa, the case fatality rate varies from 1% to 10%.[8]

As an emerging zoonosis, humans can be infected with MPX through close contact with infected humans, animals, and contaminated objects or surfaces.[9] The virus can be transmitted by bodily fluids, such as saliva from coughing (health care workers without appropriate personal protective equipment may be vulnerable) and direct physical contact, including sexual contact.[9] Some studies indicated the possibility of transmission from mother to fetus (through close contact during and after birth), but with very limited evidence.[9] In addition, the risk of becoming infected with MPX does not depend only on the mode of transmission, but also on the level of exposure linked to where individuals live or work. For example, laboratory personnel and health care workers could have a higher risk,[10] given the high levels of exposure in the workplace. However, the vast majority of cases in the current outbreaks have been reported in the gay, bisexual, and other men-who-have-sex-with-men (gbMSM) communities, which was not seen in previous outbreaks.[11-13] This is quite possibly linked to a mutated virus that made its way into highly interconnected sexual networks within the gbMSM community, with much uncertainty of transmission efficiency based on limited and skewed data.[11] Moreover, the possibility of the virus spreading through airborne droplets among the human population is fraught in the global society.[9]

The current outbreaks of MPX are not the first documented outside endemic countries. The first occurred in the United States in 2003, resulting in more than 70 people being infected, some of the cases were infected by pets that were in contact with contaminated rodents imported from Ghana.[14] Animal-to-human infection may occur by a bite or scratch of animals, bush meat preparation, or direct contact with body fluids or lesion material of infected animals.[2,9] Eating inadequately cooked meat and other infected animal products are also risk factors for infection.[2] While the MPX virus can spread among humans, its transmission from animals to humans also causes concerns, especially if the virus establishes in animals outside Africa.[15] The increasing pattern of the current spreading raises concern for the formation of animal reservoirs in wildlife which may lead to repeated human outbreaks.[15]

Possible animal hosts of MPX include a range of rodents (e.g., rats, mice, hamsters, gerbils, squirrels, chipmunks, etc.) and nonhuman primates (e.g., monkeys).[9,14] Animal-to-animal transmission may be due to close contact with infected animals or animal tissue, and a range of animal species are thought to be able to infect humans.[16] Even though the first recorded cases in each country documenting MPX infections may not come from animals, the animal reservoir may be a key element to MPX control (or control of any other zoonotic disease) as there is also a probability that human transmission could cause the virus to spill back into animals.[17,18] Besides, due to warming and other environmental changes, populations of animal hosts like rodents may burst in favorable seasons, leading to an increased risk of transmission in both humans and animals.[19]

All the new risk factors cause concern about such an emerging threat. MPX requires urgent tackling, as suggested by WHO,[20] and the risk of infection in the naive population needs to be assessed to inform the public, even in the presence of uncertainty. Although infection risk in the general population is considered low,[11] the spillover effect from the gbMSM community or other high-risk groups (HRG) should not be ignored, given the possibility of increasing transmission efficiency due to the virus evolution.

Available studies have shown that the infectiousness of smallpox patients is much greater after the rash has developed, suggesting that rash-motivated isolation supplies a window for effective control of smallpox.[21] Contact tracing was also proven to be effective in the control of smallpox,[22] and is, therefore, expected to be effective in preventing and controlling MPX too. The mass vaccination campaign with highly efficacious vaccine was crucial and successful in eradicating smallpox globally.[23] Since the basic reproduction number of MPX is considered less than that of smallpox, and also the MPX virus mainly spreads among individuals with high-risk exposure, therefore, contact tracing and ring vaccination naturally become two possible tools for containment of the current outbreak.[24] However, what public health measures are needed to protect the general population from the current outbreaks remains uncertain.

The increasing spread of MPX in nonendemic communities requires an urgent response, in particular in susceptible metropolitan areas. In this study, we will build dynamical models to mimic the spread of MPX as an emerging zoonosis in some hypothetical metropolitan area, including high- and low-risk human-to-human transmission, and transmission from animals to humans. These considerations allow for an in-depth study of the transmission mechanisms among and between the animal reservoir and humans, leading to the estimation of the risk of outbreaks under assumptions on different transmission routes and possibility, the identification of model parameters that are particularly influential, and public health measures that may be effective in containing virus spread.

2 | METHODS

2.1 | Modeling overview

We constructed a dynamic model for MPX transmission within and between human and animal populations. Based on risk assessments in different population categories exposed to MPX virus,[10] the human population was divided into two groups: the low-risk group (LRG, i.e., broader population [subscript 1]) and the HRG (members of the gbMSM community with multiple sexual partners [subscript 2]). The natural reservoir of MPX remains unknown, however, African rodents and nonhuman primates may harbor the virus and infect people.[25] Wild rodents as an example of animal reservoirs were included, but our model can comprise any of the mentioned potential reservoir species, as well as new reservoirs if were to emerge. The model followed the susceptible-exposed-infected-recovered framework extended to include Infectious P (prodromal phase)—infectious I (rash phase)—isolated Q_h (infectious)—isolated Q_S (susceptible) subpopulations (Figure 1). The seasonality of rodent populations was included based on the White Footed Mouse *Peromyscus leucopus*.[26] The description of the model assumptions, variables, and parameters are summarised in Tables 1–4 and details of modeling are in Supporting Information: Appendix A.

2.2 | Transmission

Transmission in the human population was modeled using a transmission risk parameter and a contact matrix that describes contacts between and within-population subgroups. The reproduction number of MPX transmission within the HRG was assumed to be 1.2–1.5 for the baseline scenario.[5,39,40] The reproduction numbers within the HRG and within the animal reservoir were assumed to be the same. The probabilities of transmission per contact among HRG and LRG were assumed to be 9.1%–11.4%, and 0.46%–0.57%, respectively. These transmission probabilities were calculated from the basic reproduction number R_0 derived from our simplified model without public health control measures (see Supporting Information: Appendix B for details) by fixing other parameters (Table 3). We also

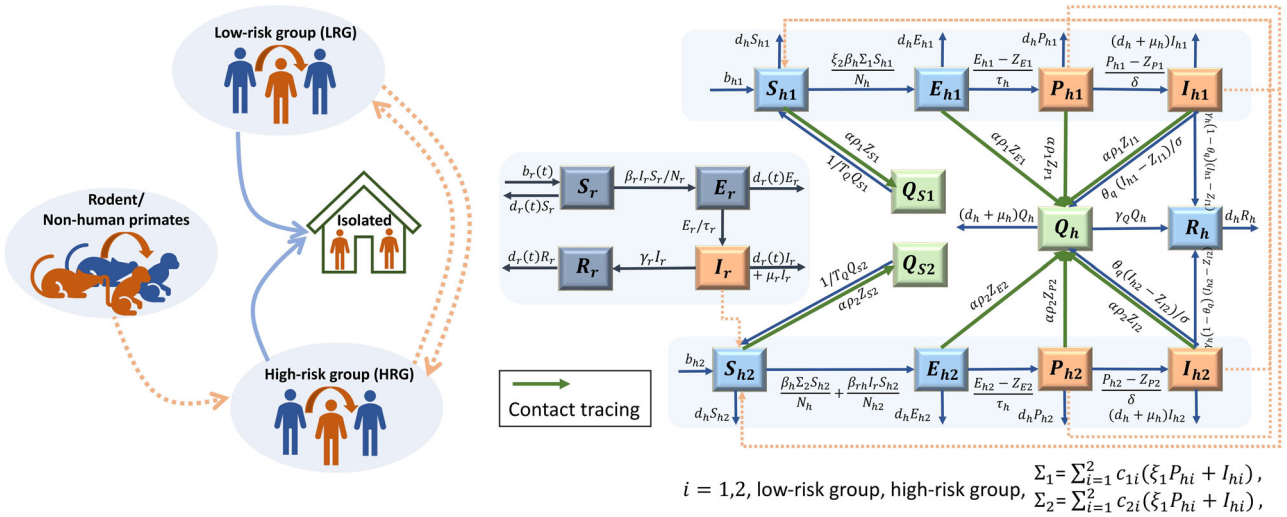

FIGURE 1 Schematic diagram (left panel) and flow chart (right panel) of the monkeypox transmission model in both human and rodent populations. The human population is divided into two groups: low-risk group (LRG, $i = 1$) and high-risk group (HRG, $i = 2$).

TABLE 1 Model assumptions

Model assumptions	
Population classification	• The human population is divided into two groups: low-risk group (LRG, $i = 1$) and high-risk group (HRG, $i = 2$).
Demographic	• The birth and death rate of LRG human population and rodent populations are considered.
Monkeypox transmission	• Infectious individuals in both the prodromal phase (with lower infectiousness ξ_1, assumed to be 75% of that during the rash stage) and acute phase can transmit the virus. • The traced and isolated individuals are not involved in the transmission. • The transmission risk of LRG individuals is lower than that of HRG individuals, with a scaling factor ξ_2 (assumed to be 0.05). • LRG individuals are assumed to have no contact with the rodent population and can only be infected by infectious LRG and HRG individuals. • The HRG individuals can be infected by the infectious LRG and HRG individuals and infectious rodents (by definition, the HRG includes individuals who come into contact with rodents because of their work). While the HRG and LRG would equally be exposed to rodents, for simplicity infections in rodents are transmitted to the HRG. • The contacts among LRG individuals mainly come from the LRG individuals, with the proportion k_1 (assumed to be 0.6) of the contact rate baseline in the human population. • The contact rate in the HRG is higher than that in the LRG, by a factor k_2 of the contact rate baseline (assumed to be 1.3). • The contact between HRG individuals and LRG individuals is low, accounting for $(1 - k_1)$ of the contact rate baseline. • The human to rodent transmission is ignored and rodents can only be infected by the infectious rodent. • The vertical transmission is ignored.
Control measures (if with confirmed case)	• Part of infected individuals with rash symptoms will go to hospital seeking medical help and then be confirmed and isolated. • Part of close contact of confirmed symptomatic cases will be traced and quarantined. • The traced susceptible people will back to susceptible group after the required quarantined period. • Part of the traced individuals will comply with the isolation strategy. • The confirmation and isolation of symptomatic case and the tracing and isolation of close contacts requires some time.

investigated scenarios with increased reproduction numbers ranging from 1.8 to 2.25. Moreover, we calculated the control reproduction number R_c for the original and simplified model with contact tracing and isolation control measures, using the next-generation matrix method (Supporting Information: Appendix B).[41]

2.3 | Seasonality of the host rodent population

The seasonality of the host population is thought to be an essential factor affecting MPX transmission.[42] In the reservoir host's breeding season with high activities, the transmission risk of MPX may increase significantly. Here, following the studies of Ogden et al.,[26] we assumed that the rodents have a higher birth rate in the spring and summer seasons from April to August, and a higher death rate in the winter period from December to March. Hence, the time-dependent birth rate and death rate of the rodent population were modeled as

$$b_r(t) = (3.5 - 300(1 - K))(1 - (0.09log(1.01 + 120))) \times 0.5 \times 0.0275 \times Nr,$$

$$d_r(t) = \begin{cases} 0.012, & \text{from April 1 to Novermber 30,} \\ 0.016, & \text{from December 1 to March 30,} \end{cases}$$

where Nr is the total number of rodents, and

$$K = \begin{cases} 1, & \text{from April 1 to Sep 1,} \\ 0.992, & \text{in other times.} \end{cases}$$

Here, we considered a normal season for rodent population reproduction, and the situation of more favorable conditions for rodent reproduction due to climate change is not considered. The seasonality of the population dynamics of rodents was also presented in Supporting Information: Appendix Figure 1.

TABLE 2 Variables used in the modeling of monkeypox transmission and their assumed initial values

Variables	Description	Initial value (assumed)	
$S_{hi}(t)$	Number of susceptible individuals in group i at Day t	$i = 1$ $(1 - p_{HRG})N_h$	$i = 2$ $p_{HRG}N_h - 1$ $(p_{HRG}N_h)$
$E_{hi}(t)$	Number of exposed individuals in group i at Day t	0	
$P_{hi}(t)$	Number of infectious individuals in the prodromal phase in group i at Day t	$i = 1$ 0	$i = 2$ 1 (0)
$I_{hi}(t)$	Number of confirmed infectious individuals with rash symptoms in the acute phase in group i at Day t	0	
$Q_h(t)$	Number of traced and isolated individuals who are exposed and infectious at Day t	0	
$Q_{Si}(t)$	Number of traced and isolated individuals who are susceptible in group i at Day t	$i = 1$ 0	$i = 2$ 0
$R_h(t)$	Number of recovered individuals at Day t	0	
$S_r(t)$	Number of susceptible rodents at Day t	N_r $(N_r - 1)$	
$E_r(t)$	Number of exposed rodents at Day t	0	
$I_r(t)$	Number of infectious rodents at Day t	0 (1)	
$R_r(t)$	Number of recovered rodents at Day t	0	

Note: The vaule in the bracket indicate that the initial infection case originating from the rodent population.

2.4 | Scenario analysis

We performed numerical simulations of our model with the setting of a hypothetical metropolitan city with initial human and rodent population sizes of 5 000 000 and 8 000 000, respectively. The starting time of the simulation was set as May 1, 2022; the model is then run for 1000 days. Tables 2–4 give the initial values, parameters with fixed values, and prior distribution of some parameters used for simulations, respectively. Table 5 lists and describes all the scenarios projecting the daily new infections in the LRG, HRG, and rodent populations (per 100 k) presented. In scenarios A, B, and C, the mean, and confidence interval (95%) of the number of infection cases are obtained from 5000 parameter sets sampling from the prior distribution (uniform) of parameters, by the Latin hypercube sampling (LHS) method.[43,44] In scenarios D and E, we only presented the mean of all the simulations. We conducted analyses using MATLAB (R2020a).[45]

2.5 | Sensitivity analysis and key factors

We conducted a sensitivity analysis to address the uncertainty of some key parameters, by employing the LHS and partial rank correlation coefficient (PRCC) method.[43] We generated 2000 samples of these investigated parameters, including the probability of transmission per contact among HRG, the isolation proportion of symptomatic cases, the proportion of contact tracing in the LRG and HRG, and the number of rodents in the initial state. The ranges of parameters used in the LHS are reported in Supporting Information: Appendix Table A1. We then explored the relationship between the parameters and the cumulative cases by calculating the values of PRCC; parameters with a PRCC magnitude above 0.5 are considered to be significant in the model outcomes.[46] In addition, we conducted the sensitivity analysis regarding the control reproduction number R_c for the original model without simplification using the parameters associated with the control measures and compared the effect of different control measures by normalizing the correlation coefficient.

3 | RESULTS

3.1 | Isolation of infectious cases to control MPX spread

An outbreak of MPX transmission is possible if public health measures are not in place, even when only human-to-human transmission is involved (Figure 2A). The average peak of daily new infections of MPX in HRG may reach 100 per 100 000 for the metropolitan area with HRG individuals accounting for 3.5% if no public health control measures are implemented. However, this risk can be greatly reduced if an isolation strategy is implemented. If 65% of the infectious cases are isolated, MPX transmission can be controlled or maintained at a very low level of endemicity (Figure 2B). For a metropolitan area with 5 000 000 residents, the average number of daily new infections in the HRG is

TABLE 3 Parameters with the fixed values used in the modeling of monkeypox transmission

	Parameter	Definition	Value	Refs.
Demographic related	p_{HRG}	Proportion of the population that is in the HRG	0.035	Assumed
	b_h	Average daily birth in the human population	129	[27]
	b_{h1}	Average daily birth of LRG in the human population	$129 \times p_{HRG}$	[27]
	b_{h2}	Average daily birth of HRG in the human population	$129 \times (1\text{-}p_{HRG})$	[27]
	d_h	Average daily death rate of the human population	0.00002219	[27, 28]
	$b_r(t)$	Average daily birth rate of the rodent population	-	[26]
	$d_r(t)$	Average daily death rate of the rodent population	-	[26]
	N_h	Total size of the human population	5 000 000	Assumed
	N_r	Total number of rodents population	8 000 000	Assumed
Transmission related	τ_h	Average incubation period of MPX in the human population	13	[29]
	μ_h	Daily disease induced death rate in the human populations	3.6%/21	[3]
	μ_r	Daily disease induced death rate in the rodent populations	0.35/21	[30-32]
	τ_r	Average incubation period of MPX in the rodent population	7	[33]
	T_Q	Duration of the isolation period for contact-traced individuals	21	[34]
	T_1	Time from first infectious case imported to the region to the first confirmed human case with rash symptoms	20, human initial (-, rodent initial)	Assumed
	$1/\gamma_h$	Average number of days of recovery needed for infectious individuals with rash symptoms	21	[29]
	$1/\gamma_r$	Average number of days of recovery needed for infectious rodent	21	[35]
	ξ_1	Scaling factor of infectiousness of infected in the prodromal phase compared to infections with rash symptoms	0.75	Assumed
	ξ_2	Scaling factor of transmission efficiency of LRG individuals compared to HRG individuals	0.05	Assumed
	c_0	Baseline contact rate among the overall population	10.8	[36]
	k_1	Proportion of contacts within the LRG in overall contacts	0.6	Assumed
	k_2	Scaling factor of contact rate among HRG compared to baseline contact	1.3	Assumed
	c_{ij}	Matrix of contacts among the groups	$c_{11} = c_0k_1, c_{12} = c_0(1 - k_1)$ $c_{21} = c_{12}, c_{22} = c_0k_2$	

Abbreviations: HRG, high-risk group; LRG, low-risk group.

below 1 under the assumption of R_0 between 1.2 and 1.5, if the isolation strategy is respected efficiently.

3.2 | Impact and concerns about possible increased transmission efficiency

There is evidence of increased transmission efficiency among gbMSM.[47] Hence, we investigate the scenario that the transmission risk increases by 50%, making the HRG R_0 range between 1.8 and 2.25. Under this hypothesis, the average number of daily new MPX cases reaches 200 per 100 000 in HRG and 100 per 100 000 in LRG despite 65% of infections with rash being isolated (Figure 3A). However, the cases drop significantly in both HRG and LRG of people if 60% of the close contact of infection can be traced along with 65% rash-motivated isolation, with a peak occurring much later. This indicates that tracing close contacts of infection with rash in HRG will be an efficient way to reduce the infection size among the human population facing a possible increased transmission efficiency of the virus (Figures 3B and 5). Besides, we conducted the sensitivity analysis of the transmission risk among the human population to justify the parameter uncertainty (Figure 7).

3.3 | The role of animals in MPX transmission

Humans are at greater risk of outbreaks if animal hosts contribute to the transmission (Figure 4). We also observe that rash-motivated isolation may not be sufficient to protect the susceptible HRG individuals due to the reinforcement of animal-to-human transmission, although the total number of cases decreases (Figure 4B).

TABLE 4 Prior distributions of some key parameters used in the modeling of monkeypox transmission

Parameter	Definition	Interval	Source of values
δ	Average number of days from prodromal phase to acute phase	1–5	[29]
$1/\rho_1$	Average number of days of the close contact in the LRG needed to be traced	1–5	[2, 37]
$1/\rho_2$	Average number of days of the close contacts in the HRG needed to be traced	1–5	[2, 37]
σ	Average number of days for infectious individuals to go from showing rash symptoms to seeking medical help, be confirmed and isolated	1–13	[38]
$1/\gamma_Q$	Average number of days of recovery needed for isolated individuals	21–36	Assumed
p_{c1}	Percentage of contact tracing in the LRG	0.1–0.4	Assumed
p_{c2}	Percentage of contact tracing in the HRG	0.1–0.6	Assumed
θ_q	Proportion of infectious individuals with rash symptoms who seek medical help, be confirmed and isolated	0.5–0.8	Assumed
α	Proportion of individuals who comply with the isolation strategy	0.3–0.5	Assumed
β_h	Probability of transmission per contact among HRG	0.091, 0.114	Assumed
β_r	Product of contact rate among rodents and probability of transmission per contact among the rodent population	0.001, 0.00125	Assumed
β_{rh}	Product of contact rate between rodents and humans and probability of transmission per contact from the rodent to the human population	0.1, 0.125	Assumed

Abbreviations: HRG, high-risk group; LRG, low-risk group.

TABLE 5 List of scenarios' settings used to project cases of monkeypox

Scenarios	Settings
A	A human infectious case is imported into the region. The proportion of individuals in the HRG among the total population is 3.5%. • No public health control measures are conducted (*baseline*). • No contact tracing, 65% of infections with rash symptoms are isolated after confirmation.
B	A human infectious case is imported into the region. The transmission efficiency among human population increases by 50%. The proportion of individuals in the HRG among the total population is 3.5%. • No contact tracing, 65% of infections with rash symptoms are isolated after confirmation. • 65% of infections with rash symptoms are isolated after confirmation, and contact tracing concerns 60% of close contacts of infections in the HRG.
C	A rodent infectious case is imported into the region. • No public health control measures are conducted. • No contact tracing, 65% of infections with rash symptoms are isolated after confirmation. • The overall transmission efficiency increases by 50%. 65% of infections with rash symptoms are isolated after confirmation and contact tracing concerns 60% of close contacts of infections in the HRG.
D	A human infectious case is imported into the region. The transmission efficiency among human population increases by 50%. 65% infections with rash symptoms are isolated after confirmation. The proportion of individuals in the HRG among the total population is 3.5%. • Contact tracing 30%/50%/70% of close contact of infections in the HRG. • Contact tracing 30%/50%/70% of close contact of infections in the LRG.
F	A human infectious case is imported into the region. No contact tracing. 65% of infections with rash symptoms are isolated after confirmation. • The proportion of individuals in the HRG among the total population is 2%/4%/6%.

Abbreviations: HRG, high-risk group; LRG, low-risk group.

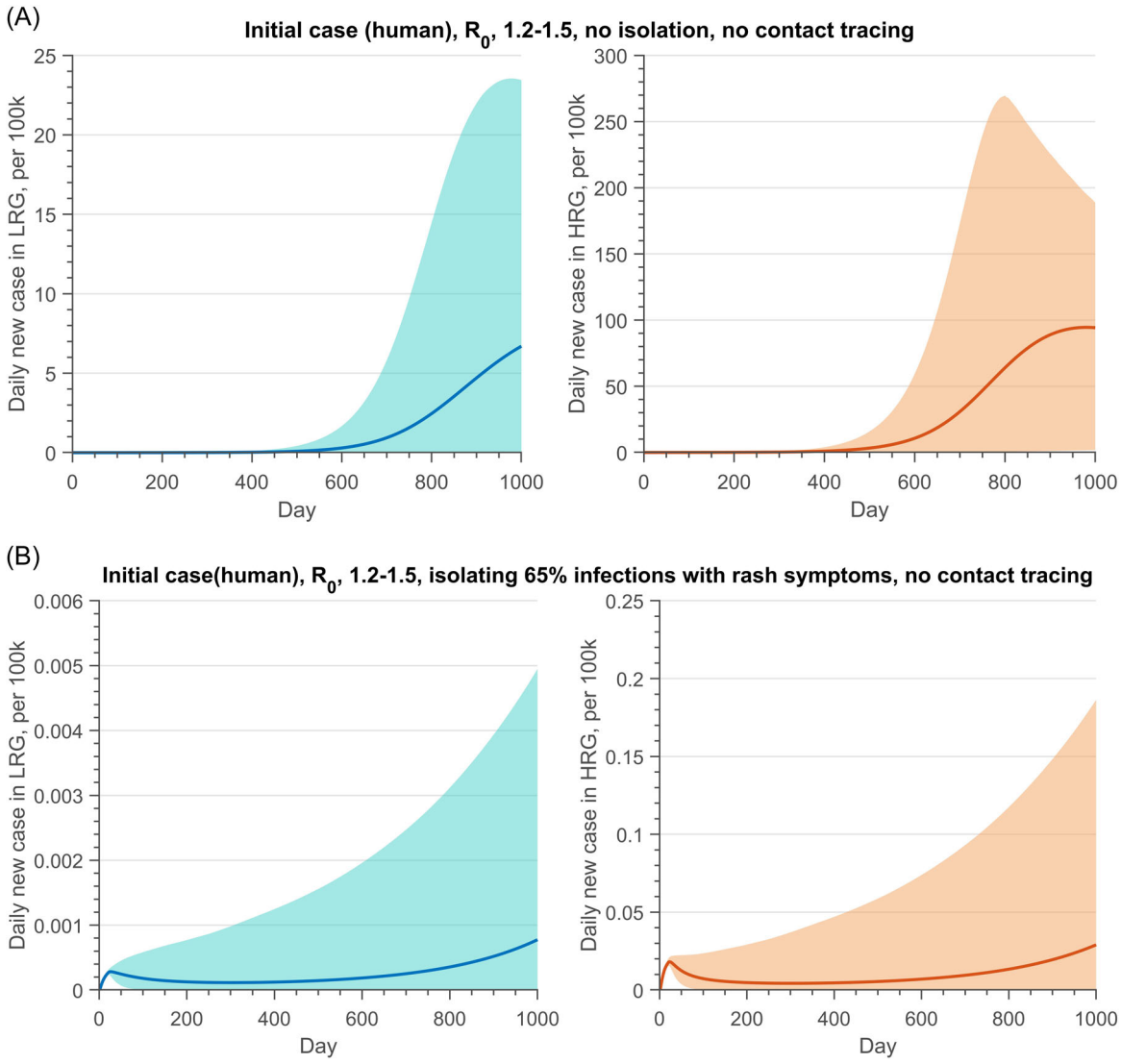

FIGURE 2 Projections of daily new infections (per 100 k) in the LRG and HRG if the initial case is a human infection, under the different public health control measures. (A) No isolation, and no contact tracing; (B) no contact tracing but isolation of 65% of infections with rash symptoms. The shaded areas show the 95% confidence interval of the infections. HRG, high-risk group; LRG, low-risk group.

Moreover, the situation can become even more worrisome under the possibility of increased transmission efficiency due to the evolution of the virus, the prevalence of host and changing environment. We may observe much earlier peaks and multiple waves driven by animal transmission (Figure 4C). The isolation strategy is beneficial for outbreaks mitigation (Figure 7), nevertheless, it may not be sufficient if the virus spreads in the animal populations. Other public health measures such as contact tracing, monitoring, and controlling infections in the animal population, may also be needed.

3.4 | Contact tracing in HRG helps to control MPX spread

Figure 5 presents the comparison of mitigation effects on MPX transmission among contact tracing in HRG and LRG, under the assumption of R_0 between 1.8 and 2.25 and 65% rash-motivated isolation. Contact tracing in HRG shows a better effect on the containment of transmission as expected, compared to tracing in LRG. In addition, it shows the possibility of keeping the MPX prevalence at a low level by employing control measures in combination with rash-motivated isolation and contacting tracing in HRG, even facing the 50% increased transmission efficiency.

3.5 | Regions with larger number of gbMSM communities need more attention

Moreover, the smaller the initial proportion of individuals in the HRG, the fewer infections in the human population (Figure 6), which is also confirmed by the sensitivity analysis (Figure 7). This result suggests that in a community with the proportion of HRG being 2% or 4%, it

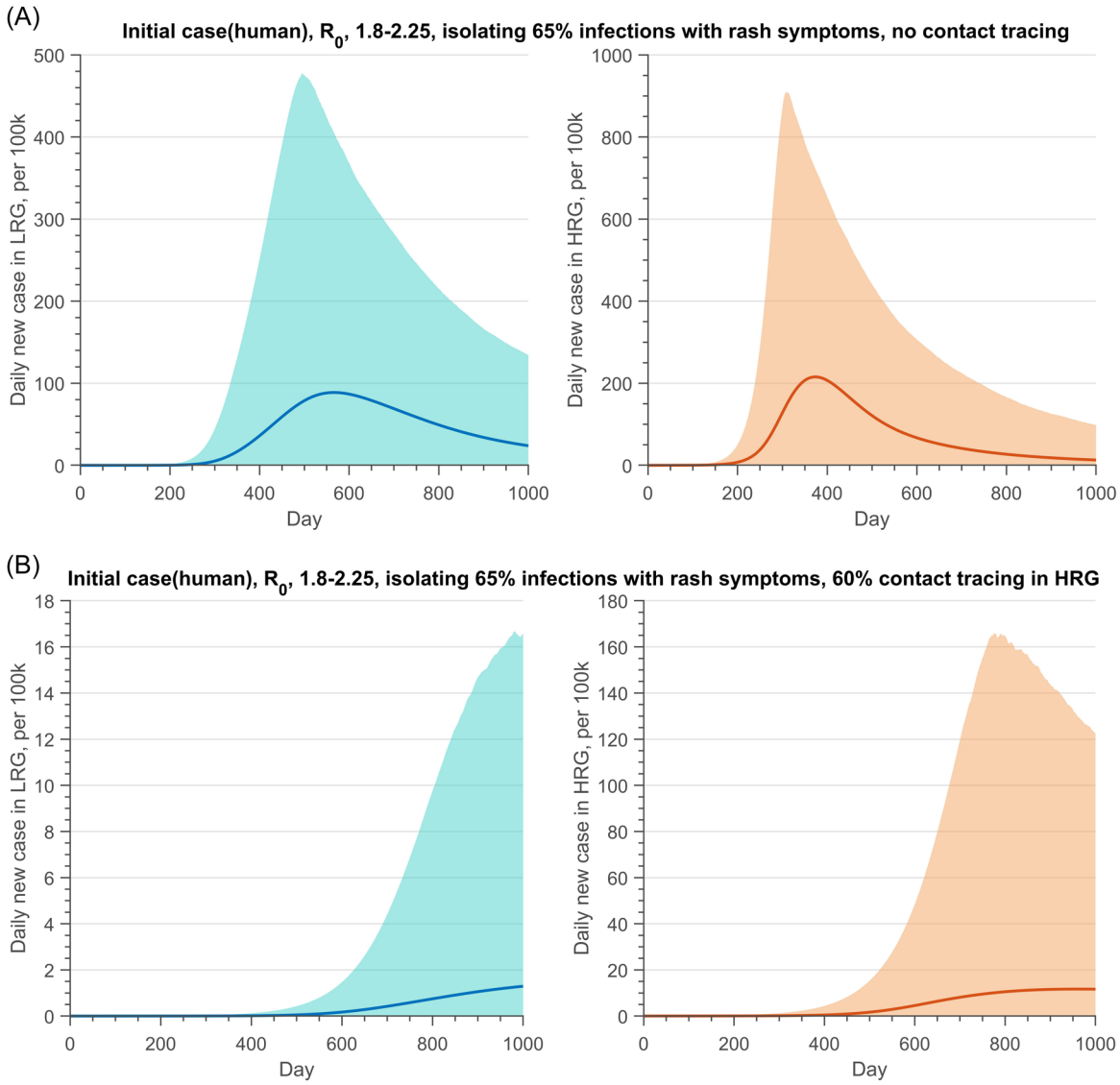

FIGURE 3 Projections of daily new infections (per 100 k) in the LRG and HRG if the initial case is a human infection and the transmission efficiency increases by 50%, under the different public health control measures. (A) No contact tracing and isolation of 65% of infections with rash symptoms; (B) isolating 65% of infections with rash symptoms and tracing 60% of close contacts of the infections with rash symptoms in the HRG. The shaded areas show the 95% confidence interval of the infections. HRG, high-risk group; LRG, low-risk group.

takes a longer time before cases start increasing, whereas a 6% increase of the size of the group leads to a much earlier peak. This result indicates the importance of educating the public about MPX transmission, since a city with a higher population of gbMSM has a much higher possibility of an MPX outbreak.

3.6 | Sensitivity analysis and key factors

We observe that HRG individuals have a significant effect on the cumulative number of cases. Our results also show that rash-motivated case isolation presents a negative correlation with cumulative cases (Figure 7A). Meanwhile, compliance with the isolation strategy and implementation of contact tracing in HRG is negatively correlated to cumulative cases, indicating the importance of those control measures in mitigating the MPX outbreak (Figure 7A). On the other hand, if the animal populations are involved in the MPX transmission, the cumulative number of human cases is distinctly influenced by the size of the rodent population, the transmission risk among the rodent population, and, therefore, risk between rodents and humans (Figure 7B). The sensitivity analysis suggests that control of MPX requires not only rash-motivated isolation, but also efficient contact tracing, and population adherence to the strategy. Furthermore, the monitoring

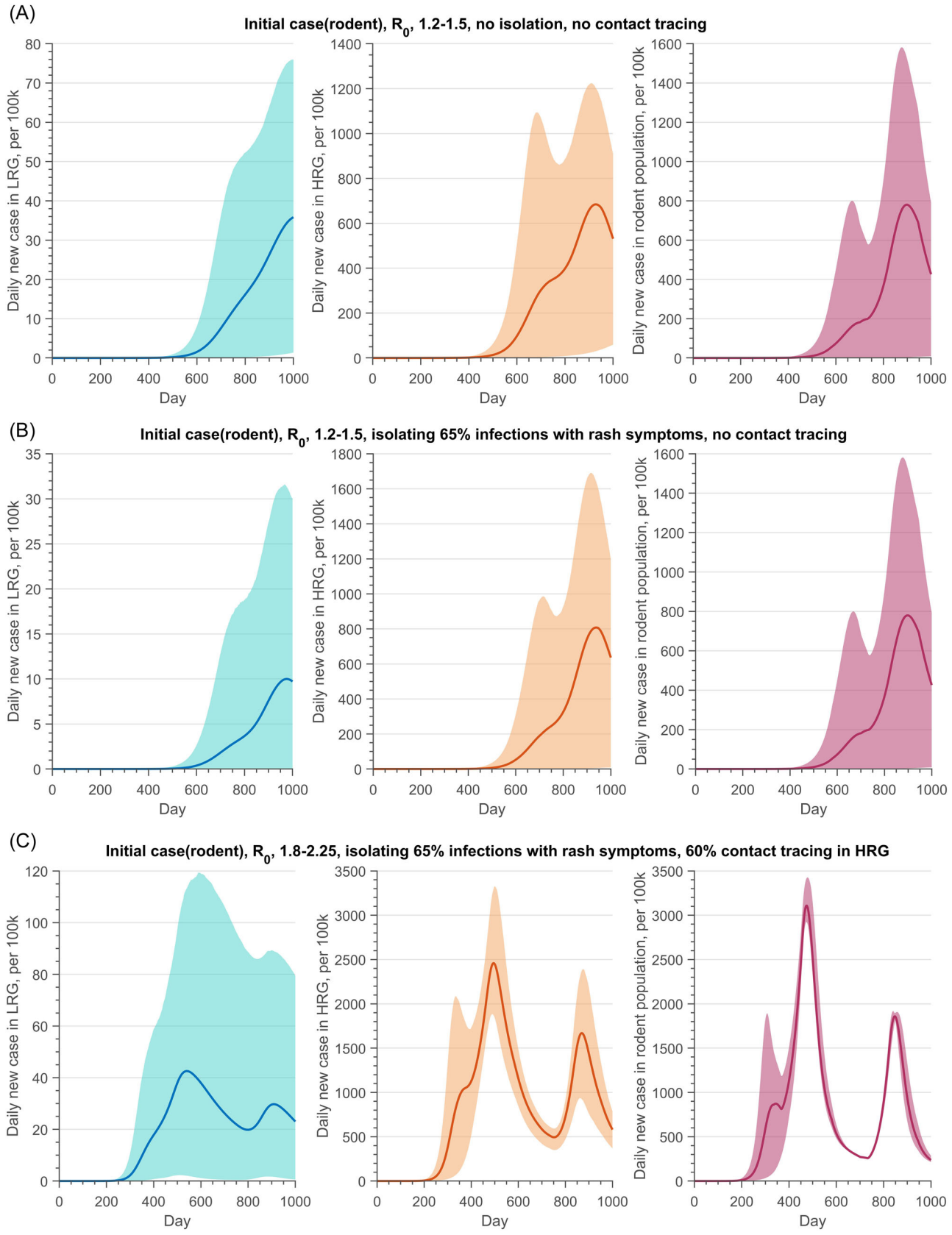

FIGURE 4 Projections of daily new infections (per 100 k) in the LRG, HRG, and rodent population if rodents are involved in the transmission under different scenarios. (A) No isolation, and no contact tracing; (B) isolating 65% of infections with rash symptoms and no contact tracing; (C) isolating 65% of infections with rash symptoms and tracing 60% of close contacts of the infections with rash symptoms in the HRG and increased 50% of overall transmission efficiency. The shaded areas show the 95% confidence interval of the infections.HRG, high-risk group; LRG, low-risk group.

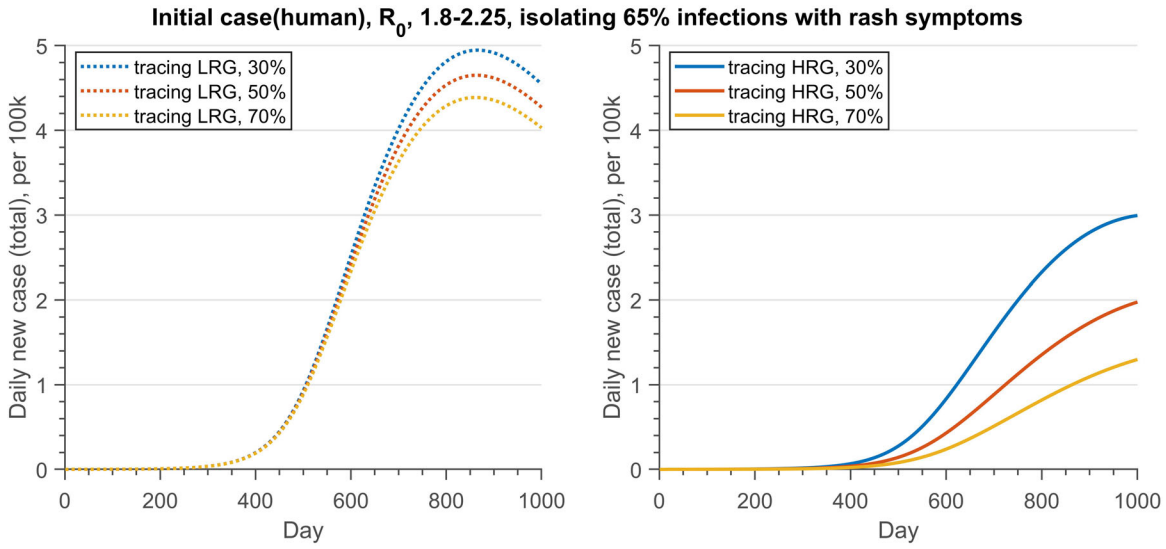

FIGURE 5 Projections of daily new infections (per 100 k, total) if the transmission efficiency increases by 50% and 65% of infections with rash symptoms are isolated, under the different contact tracing proportions in the HRG (solid line) and LRG (dash line), 30% (light blue), 50% (orange), and 70% (yellow). Note that when the contact tracing in HRG is included, there is no contact tracing in LRG, and vice versa. HRG, high-risk group; LRG, low-risk group.

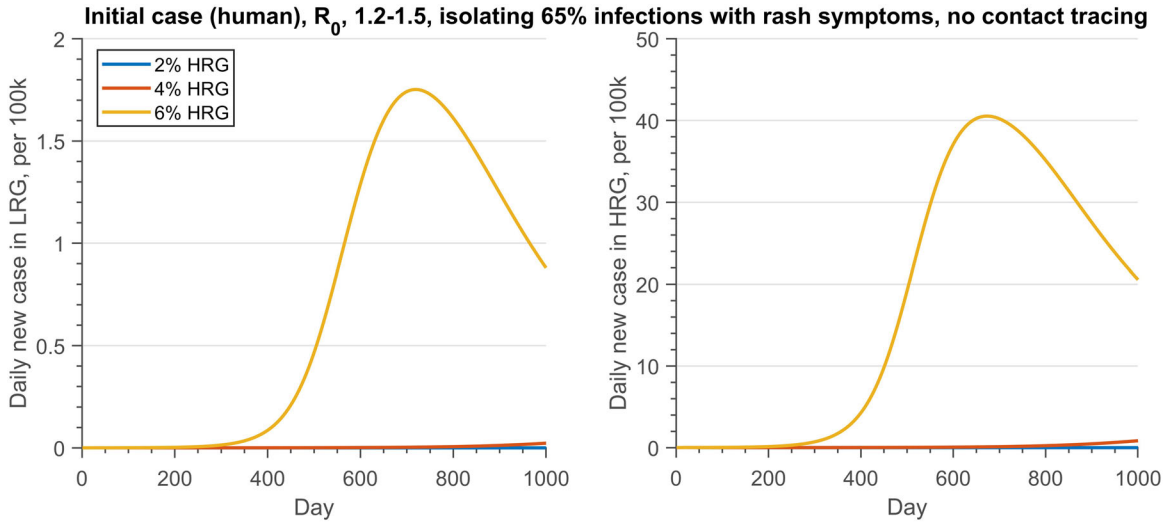

FIGURE 6 Projections of daily new infections (per 100 k) in the LRG and HRG if isolating 65% of infections with rash symptoms, under the different initial proportions of HRG individuals, 2% (light blue), 4% (orange), and 6% (yellow). HRG, high-risk group; LRG, low-risk group.

and control of the infection among the animal populations is also crucial to protect the broader human population.

Figure 8 shows that the most significant measure is the rash-motivated isolation strategy. Meanwhile, the average number of days for infectious individuals from showing rash symptoms to seeking medical help then to be confirmed and isolated also play a key role in the prevention and control of the infection. Moreover, contact tracing in HRG is more important than that in LRG, which is also illustrated by the sensitivity analysis of cumulative cases.

4 | DISCUSSIONS

Cases of MPX have been rising worldwide in the last 2 months, raising widespread concern. Since MPX is a zoonosis, we have used a One Health approach to model its transmission and assess the risk of an outbreak in a hypothetical metropolitan area inhabited by humans of different risk groups, and animal hosts as well. We have also conducted a sensitivity analysis to identify the key parameters needed to establish confidence in our model, notwithstanding the uncertainties in current MPX transmission.

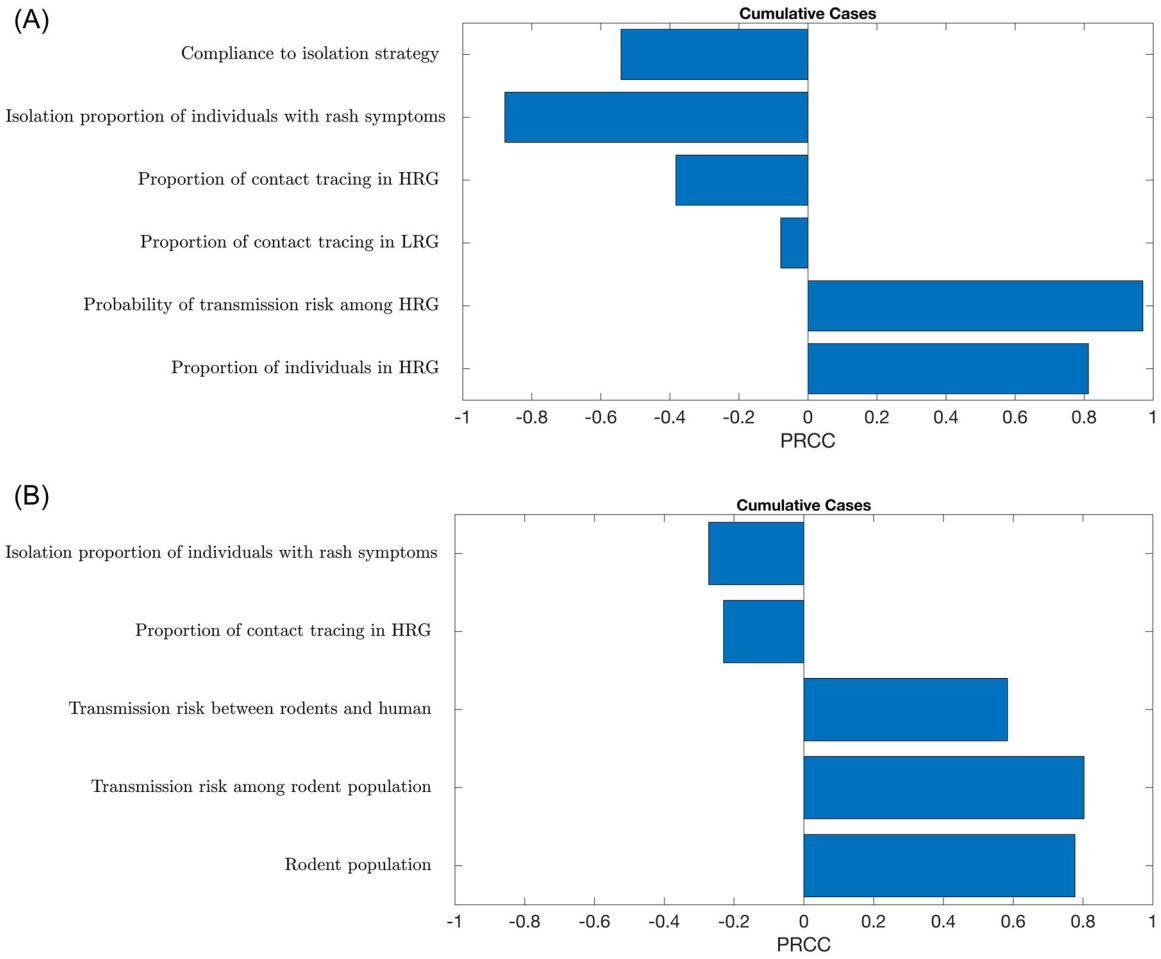

FIGURE 7 The sensitivity analysis on cumulative cases if the initial case is a human infection (A) or rodent infection (B).

Our simulations suggest that the risk of an MPX outbreak remains high, especially in HRGs in the absence of intervention. In particular, the general population may be at risk if transmission efficiency increases among gbMSM or other HRGs. Such an occurrence due to virus evolution could render isolation of symptomatic cases insufficient to stop the spreading, and case detection and contact tracing in HRG would become an essential strategy to prevent bridging from HRG to LRG. Furthermore, regions with a higher proportion of gbMSM may face higher risks and require more stringent public health measures, including isolation and contact tracing. Moreover, the spread of the virus being closely associated with seasonal variations in animal host abundance and activity level, it is vital to monitor the incidence of MPX in animals to serve as an indicator for assessing the risk of MPX epidemics.

Although contact tracing in the gbMSM community is fraught with a number of ethical considerations concerning privacy, such as sexual behavior, education campaigns, and frank communication are important to detect higher risks of infection.[11] In this context, the risk of stigmatizing gbMSM cannot be underestimated if the control measures (like vaccines) focus on the gbMSM, and the consequences in delaying the seeking of medical care in these communities. On the other hand, raising awareness of the risk of MPX transmission, and ways to reduce contacts and risks of exposure to infection is also crucial.

Our modeling studies support the latest assessment of the WHO that the current spreading of MPX constitutes a global public health emergency.[6] Our take-home message is that the public health administration should be on high alert and take a more aggressive public health response when local emerging cases start, just like what the US CDC is doing to activate emergency operation centers for MPX response.[48]

Our modeling scenario simulations use parameters from available literature for previous outbreaks in Africa and can thus be improved with the accumulation of data in newly emerging areas, allowing more refined estimations of key model parameters to inform public health decision making. In the meantime, we will be able to determine the minimum required proportion of contact tracing to prevent MPX outbreaks. In our model, we did not consider the increasing concern of human-to-animal transmission routes since no such cases have been documented, and the risk is estimated to be low. The vaccination strategy may be applied to the HRGs, and thus need to be considered in our future work too.

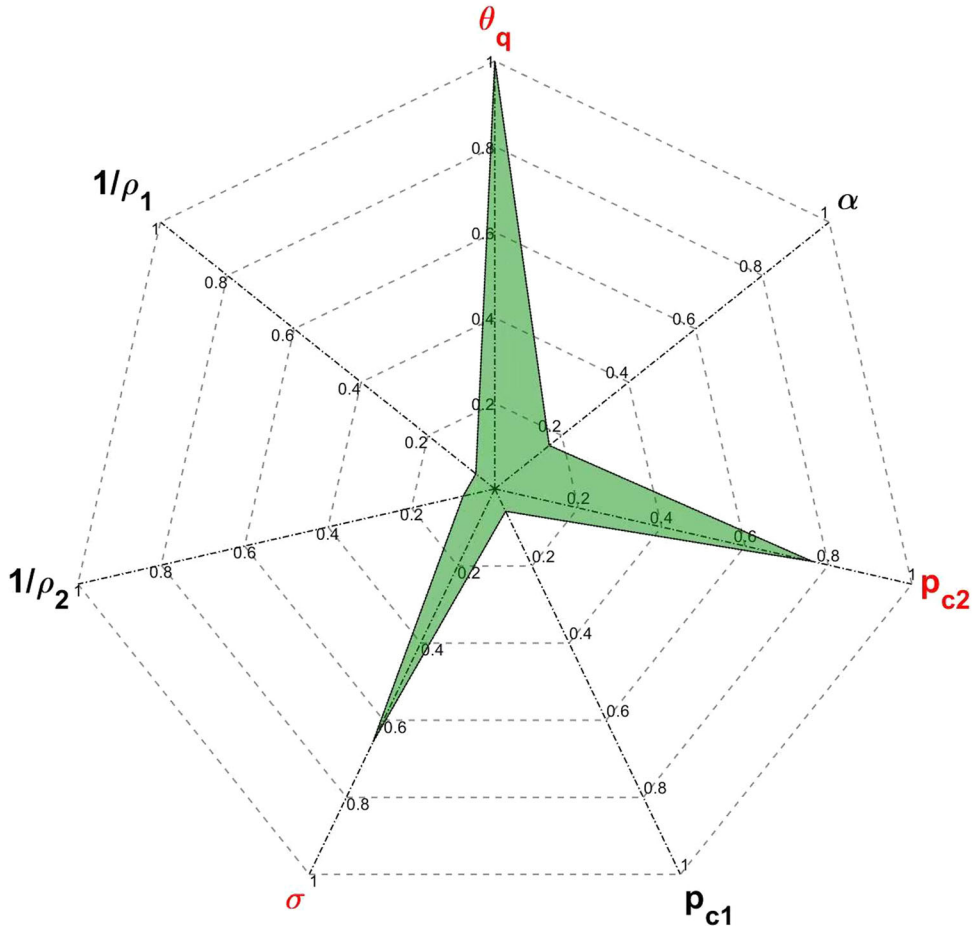

FIGURE 8 The radar diagram of sensitivity analysis regarding control reproduction number R_c without simplification with the control measures. θ_q is the proportion of infectious individuals with rash symptoms who seek medical help and then be confirmed and isolated; σ represents the average number of days for infectious individuals from showing rash symptoms to seek medical help (then be confirmed and isolated); p_{c1} (p_{c2}) is the percentage of contact tracing in the LRG (HRG); $1/\rho_1$ ($1/\rho_2$) is the average number of days of the close contact in the LRG (HRG) needed to be traced and isolated; α is the proportion of individuals who comply with the isolation strategy. The notations in red color indicate that the p value of the parameter is significant. HRG, high-risk group; LRG, low-risk group.

AUTHOR CONTRIBUTIONS

Conceptualization: Huaiping Zhu, Pei Yuan, Yi Tan, Liu Yang, and Nicholas H. Ogden. *Data curation*: Yi Tan, Liu Yang, and Pei Yuan. *Formal analysis*, Liu Yang, Pei Yuan, Yi Tan, and Huaiping Zhu; *Methodology*: Pei Yuan, Yi Tan, Liu Yang, and Huaiping Zhu. *Software*: Pei Yuan, Yi Tan, and Liu Yang. *Validation*: Pei Yuan, Yi Tan, and Liu Yang. *Visualization*: Pei Yuan, Yi Tan, and Liu Yang. *Writing - original draft*: Pei Yuan, Yi Tan, Liu Yang, Elena Aruffo, and Huaiping Zhu. *Writing - review and editing*: Julien Arino, Jacques Bélair, Jane Heffernan, James Watmough, Nicholas H. Ogden, Hélène Carabin, Elena Aruffo, Pei Yuan, Yi Tan, Liu Yang, and Huaiping Zhu. *Funding acquisition*: Huaiping Zhu, Julien Arino, Jacques Bélair, Jane Heffernan, James Watmough, and Hélène Carabin. *Supervision*: Huaiping Zhu.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data used in this study are presented in the manuscript and the Supporting Information: Appendix.

ETHICS STATEMENT

The study used data from the literature and publicly data, hence ethical approvals were not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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