Impact of vaccination and high-risk group awareness on the mpox epidemic in the United States, 2022–2023: a modelling study

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Summary

Background The unprecedented global outbreak of mpox in 2022 posed a public health challenge. In addition to the mpox vaccine campaign in the United States (US), community organisations and public health agencies initiated educational efforts to promote sexual risk reduction. This modelling study estimated the impact of the two-dose vaccination campaign and sexual behaviour changes coincident with high-risk group awareness on the mpox epidemic in the US.

Methods We fitted a deterministic, risk-structured SEIARV model to the epidemic curve of reported mpox cases in the US between May 22, 2022 and December 22, 2022. We evaluated the putative effects of the two preventive responses in the US – vaccination and sexual risk reduction – at the population-level, by calculating the prevention percentages of cumulative cases compared to the counterfactual scenario without interventions. We performed sensitivity analyses with four parameters: case reporting fidelity, vaccine effectiveness, proportion of asymptomatic cases, and assortative mixing.

Findings Model fitting revealed a basic reproduction number of 3.88 and 0.39 for the high-risk and low-risk populations, respectively, with 71.8% of mpox cases estimated from the high-risk population. A two-dose vaccination campaign, solely, could prevent 21.2% (10.2%–24.1%) of cases, while behaviour changes due to high-risk group awareness alone could prevent 15.4% (14.3%–20.6%). The combination of both measures were synergistic, with the model suggesting that 64.0% (43.8%–69.0%) of US cases were averted that would have otherwise occurred.

Interpretation Our models suggest that the 2022–2023 mpox epidemic in the US was controlled by a combination of two-dose mpox vaccination campaign and high-risk group awareness and sexual risk reduction.

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Keywords: Mpox; US outbreak; Vaccination; Sexual behaviour changes; Awareness; Mathematical modelling

Introduction

Mpox (monkeypox) is a viral zoonotic disease, causing smallpox-like symptoms, though less lethal, primarily rash, fever, and pain.[1] Mpox is transmitted through close contact with the blood, body fluid, skin lesions, or respiratory droplets of infected animals or humans.[1] It has been endemic in central and western African countries since the 1970s.[1] Since early May 2022, countries outside these endemic regions began reporting cases of mpox, quickly expanding into a global

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Research in context

Evidence before this study

We searched PubMed using the keywords ("mpox" OR "monkeypox" OR "MPXV" OR "monkey pox") AND ("vaccination" OR "vaccine" OR "awareness" OR "adapt" OR "change") AND ("effectiveness" OR "efficacy" OR "impact" OR "effect" OR "influence" OR "change") AND ("men who have sex with men" OR "MSM" OR "high-risk" OR "high risk" OR "at-risk" OR "at risk") up to 6 October 2023, without any restrictions. We excluded studies unrelated to mpox, case reports, reviews, protocols, survey studies exclusively on vaccine willingness, and diagnostic or virology studies. We identified 25 studies to guide model parameter estimations. Eleven focused on the individual level of protection provided by the mpox vaccine, five on the population-level observation of the behaviour of gay, bisexual, and other men who have sex with men (GBMSM) and their vaccination status during the global outbreak, and nine on the modelling of mpox outbreaks. Two modelling studies from the UK came to similar conclusions that the downturn of the mpox incidence in the UK should result primarily from the reductions in sexual risk behaviour of the GBMSM in combination with the population immunity following a number of infections and the reduction of the effective infectious period, rather than the one-dose or full-dose vaccination, as the relatively insufficient vaccination only averted a small percentage of infections in the UK. None of the studies estimated the combined effect of both the two-dose mpox vaccination campaign and population behavioural changes in the United States, where the vaccination campaign was initiated in late May, and supplies were expanded in early July.

Added value of this study

This is the first study, to our knowledge, to incorporate both the two-dose mpox vaccination campaign and the awareness of the high-risk population in a mathematical modelling study in the United States, and to demonstrate the synergistic effect with high effectiveness of the combination of both intervention measures in averting the numbers of US mpox cases during the 2022–2023 mpox epidemic. Our model results estimate that the two-dose mpox vaccination campaign may have prevented 21.2% (sensitivity analysis: 10.2%–24.1%) of mpox cases, awareness and behaviour change in the high-risk population may have prevented 15.4% (sensitivity analysis: 14.3%–20.6%), and the combination of both measures may have prevented 64.0% (sensitivity analysis: 43.8%–69.0%) of mpox cases, compared to the counterfactual scenario (absence of both measures).

Implications of all the available evidence

The mpox vaccine, highly effective among the at-risk population at the individual level (preventing against mpox infection and reducing severity of symptoms), is also highly effective at the population level (controlling mpox outbreaks) when combined with awareness of changes in risky sexual behaviour. Knowledge of this likely synergistic effect can help prepare future epidemic response planning.

outbreak. Over 8.8 million incident cases and 150 deaths from 110 countries had been reported by July 2023.[2] Prior to 2022, there had been more isolated cases of mpox documented in non-endemic regions. In 2003, there was an autochthonous mpox infection cluster in the United States (US) suspected to have been introduced by pet store imports of African rodents, and during 2018–2019, there were clusters in locations such as the United Kingdom (UK) and Singapore, attributed to index cases from Nigeria.[1] However, the 2022–2023 mpox outbreak marked the first time that chains of person-to-person transmission of mpox virus occurred on a global scale, with most of the transmission happening through sexual contact; an estimated 86% of the cases occurred among men who have sex with men (MSM), based on case reporting to the World Health Organization (WHO).[2,3]

The first mpox case in the US was confirmed on 17 May, 2022 in Massachusetts; more than 30,000 incident cases and 32 deaths were reported in the US by January 2023.[4] Some jurisdictions initiated JYNNEOS® vaccine (Bavarian Nordic A/S, Hellerup, Denmark) campaigns at the beginning of the outbreak,[5] and the US Food and Drug Administration issued an emergency use authorisation (EUA) for the intradermal injection of JYYNEOS® vaccine on 9 August, 2022 to increase access to the vaccine.[4] JYNNEOS® vaccine, approved in 2019 for the prevention of smallpox and mpox infection in adults 18 years or older, has an effectiveness of 35.8–75.2% for 1-dose and 66.0–85.9% for 2-doses.[6] By January 2023, vaccination coverage among persons at risk in the US reached an estimated 37% for the first dose and 23% for the second dose.[4] In surveys, 40–60% of MSM reported reducing their number of sexual partners, one-time sexual encounters, and/or other high-risk sexual behaviours after learning about the outbreak.[7] The mpox epidemic in the US peaked on 1 August, 2022,[8] and then declined markedly.

It is not known the extent to which limited vaccine coverage and effectiveness and/or behaviour changes translated into a reduction in the number of mpox cases. The extent to which these two interventions may have been synergistic is also unknown. Estimating these effects in the 2022 US outbreak can guide priorities to prepare for subsequent mpox spread and may be relevant for other emerging or re-emerging infectious diseases. We used dynamic models to estimate the impact of the two-dose JYNNEOS® vaccination campaign and

the behaviour change consequent to high-risk group awareness on the 2022 mpox epidemic in the US, based on careful parameter estimations using surveys, national-wide statistics on mpox cases, and data on vaccine administration.

Methods

Study design

This is a dynamic modelling study on the impact of mpox vaccination and high-risk group awareness on the mpox epidemic in the United States. We first constructed a mathematical model based on natural history and transmissibility of mpox infection as well as JYNNEOS® vaccine effectiveness, then fitted the model to actual daily reported mpox cases published by the US Centers for Disease Control and Prevention (CDC, Atlanta, GA, USA).

Ethics

The study was approved by the Research Ethic Committee of National Taiwan University Hospital (Taipei, Taiwan) with a review exemption (#202306075W). Informed consent of participants was waived for this study as an infectious disease mathematical modelling study, which did not involve the use of information of individual human subjects or potential for personal identification.

Structure of mpox mathematical model

We constructed a deterministic, risk-structured "susceptible-exposed-infectious-asymptomatic-recovered-vaccinated" (SEIARV) compartmental model that considered high-risk and low-risk sub-populations, building upon an appropriate SEIARV model of hepatitis A disease by Lin KY et al.[9] We separated populations in each risk group into 11 compartments by stage of natural history and vaccination status (Fig. 1). The high-risk group consists of MSM 13 years or older and at risk of acquiring mpox through risky sexual behaviours. For model construction, we considered pre-symptomatic transmission to occur up to 4 days before symptom onset,[10] and decreased transmission after patients become ill. We also assumed substantially higher infectiousness of symptomatic patients compared with those who remained asymptomatic throughout the course of infection,[11–14] as well as the 14-day induction period after the first and second doses of vaccination. The Supplemental material provides the differential equations applied to each compartment.

Model parameterisation

We estimated real-world effectiveness of JYNNEOS® vaccine from large case control studies.[15,16] We estimated model parameters for the natural history of mpox infection from published empirical studies (Table 1). Daily reported mpox cases came from US CDC reports.[8] We estimate the total at-risk population, N, based on the number of persons aged 13 years or older who have HIV or HIV pre-exposure prophylaxis (PrEP) prescription, adjusted for unknown persons and those who are at high risk but do not take PrEP by two folds.[21] We estimated the effective population size of the high-risk group, the transmission coefficients, and the initial numbers in the compartments that are or will be infectious for mpox (Tables 1 and 2), by fitting the model to actual US mpox epidemic curve during the period between May 22, 2022 and December 22, 2022, using the least square method. We considered 10 May, 2022 as the first day of our model simulation, the date of illness onset for the first case of mpox in the US.[8]

Statistical analysis

To stabilise the variance and mitigate the impact of the large values data on the fitting results, we first took the square root of the daily mpox reported cases and model simulated cases before applying the least square method. We used mean square error (MSE) as the goodness-of fit statistics to determine the performance of model fitting and selection of best-fit model with the smallest MSE under the base scenario as well as under the sensitivity analyses:

$\mathrm{MSE} = \frac{1}{n}\sum_{i=1}^{n}(\sqrt{Y_i}-\sqrt{\widehat{Y}_i})^2$, where n is the number of days observed that was used in model fitting; Y_i is the number of real-world US mpox reported cases for the i th day; $\widehat{Y}_i$ is the number of model simulated US mpox reported cases for the i th day.

Vaccination

We calculated the rate of vaccination for first and second doses of JYNNEOS® in the model based on daily JYNNEOS® doses administered and reported to the CDC.[5] Currently, the US CDC provides daily statistics on the number of vaccine doses administered. However, the precise proportion of high-risk MSM (with multiple sexual partners) among the vaccine recipients is not readily available. In our modelling approach, we have addressed this data gap by distributing the daily dose of vaccine administration in a 2:1 ratio between the high-risk and low-risk groups. This is equivalent to a 48-fold $(\frac{\frac{2}{3}\ /\ 4\%}{\frac{1}{3}\ /\ 96\%})$ higher vaccination rate for the high-risk group because the high-risk group constitutes approximately 4% of the total at-risk population, as indicated by our fitting results. We assumed that all vaccines administered in the model were for pre-exposure prophylaxis, not for experimental therapeutic purposes (Supplemental Fig. S1).

Behaviour change in response to mpox epidemic

An estimated 50% of MSM in the US reported taking actions to reduce their risk of acquiring mpox by reducing engagement in risky sexual behaviours since

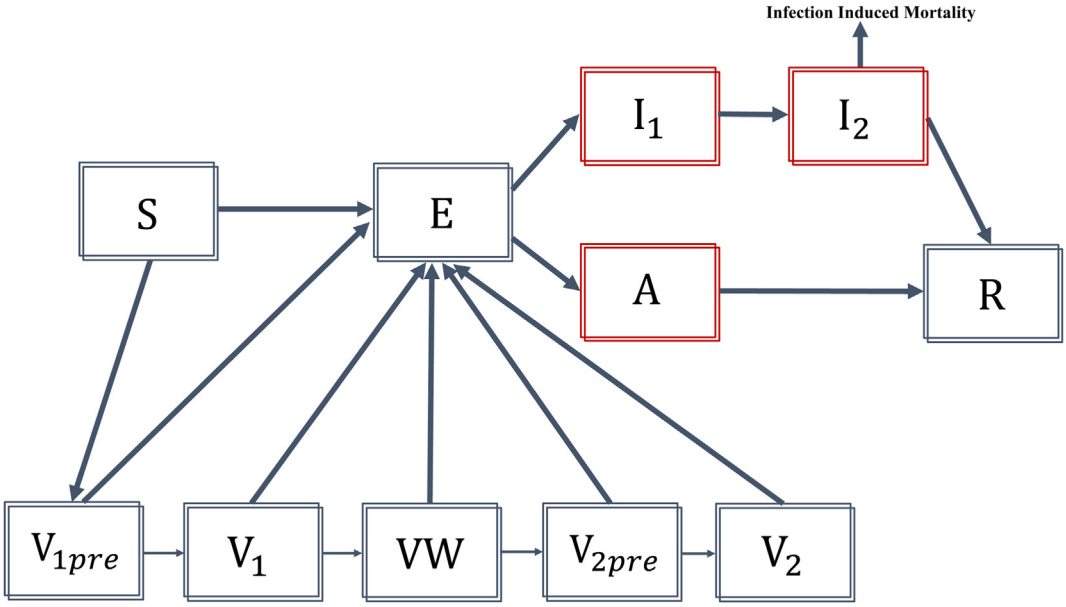

Fig. 1: **Schematic diagram of SEIARV compartmental model.** The model population is classified into low-risk and high-risk group, illustrated by stacked compartments. The compartments are: S (susceptible), E (exposed), I_1 (pre-symptomatic), I_2 (symptomatic), A (asymptomatic), R (recovered), V_{1pre} (less than 14 days since first dose vaccination, without complete first-dose effectiveness), V_1 (first dose vaccinated with complete first-dose effectiveness), VW (more than 28 days since first dose vaccination, eligible for the second dose), V_{2pre} (less than 14 days since second dose vaccination, without complete second-dose effectiveness), V_2 (second dose vaccinated with full effectiveness). The compartments that are infectious are indicated with red frame.

they learned of the mpox outbreak, according to a CDC survey.[7] We therefore assumed that 50% of the high-risk group in our model reduced by 50% their previous risky sexual behaviours since they started to develop awareness on 22 May, 2022, when the first week of mpox vaccine administration was recorded by US CDC. This would yield an alteration of mpox transmission coefficient in the model from β_{HH}, β_{HL}, β_{LH}, to 0.75 β_{HH}, 0.75 β_{HL}, 0.75 β_{LH} since 22 May, 2022.

Main outcome

We evaluated the preventive effect of current preventive responses in the US (vaccination and high-risk group awareness) at the population-level by calculating the prevention percentage of cumulative reported cases and cumulative infections (symptomatic and asymptomatic) compare to the numbers of cases or infections under the counterfactual scenario without any interventions between May 22, 2022 and December 22, 2022. The formula for calculating the prevention percentage is as follows:

$$\frac{\text{number of mpox cases averted through preventive response}}{\text{number of mpox cases under the scenario without any preventive response}}$$

Sensitivity analysis

We performed a one-way sensitivity analysis by varying parameters with values of uncertainty, including the proportion of mpox cases reported in the US (*rp*), the proportion of asymptomatic cases (τ), JYNNEOS® vaccine effectiveness (p_1 and p_2), and assortative mixing (β_{LL} vs. β_{HL}, β_{LH}); as well as a three-way sensitivity analysis on the combination of the first three aforementioned parameters, to assess their impact on the prevention percentages of cumulative reported cases and cumulative infections compare to those estimated under the counterfactual scenario without any interventions.

We conducted all analyses using STELLA® software version 3.3.0 (ISEE Systems, Lebanon, NH 03766, USA).

Role of the funding source

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Parameter	Description	Value (unit)	Source
B	Transmission coefficient of mpox	β_{HH}: determined by fitting data $\beta_{LL} = \beta_{HL} = \beta_{LH}$: set at the level of a fraction of β_{HH} to keep $R0_H = 10\ R0_L$[a] (sensitivity analysis: $2\beta_{LL} = \beta_{HL} = \beta_{LH}$: set at the level of a fraction of β_{HH} to keep $R0_H = 10\ R0_L$)	Fitting real world epidemic curve. Assume that the value of R0 of the high-risk group is 10-fold higher than that of the low-risk group
Θ	Proportion of symptomatic patients who still engage in activity associated with transmission risk	0.3	Lee YL et al.[17]
δ	Relative risk of transmission of asymptomatic mpox patients, compared with that of symptomatic patients	0.1	Assumption
τ	Proportion of patients remained asymptomatic throughout the course of infection	0.06 (sensitivity analysis: 0.2)	Reda A et al.[18] (sensitivity analysis: assumption)
σ	Rate of progression from *E* to I_1 or A (reciprocal of incubation period minus pre-symptomatic period)	1/(8.23–4) (day^{-1})	Wei F et al.[19]
γ_{sym}	Rate of progression from I_1 to I_2 (reciprocal of pre-symptomatic period)	1/4 (day^{-1})	Miura F et al.[10]
γ_1	Rate of progression from I_2 to *R* (reciprocal of infectious period for symptomatic patients)	1/21 (day^{-1})	WHO[1]
γ_2	Rate of progression from *A* to *R* (reciprocal of infectious period for asymptomatic patients)	1/(21 + 4) (day^{-1})	Miura F et al.,[10] WHO[1]
m	Infection-related mortality rate for symptomatic mpox	0.0000611 (day^{-1})[b]	WHO[2]
p_1	Vaccine effectiveness of first dose JYNNEOS® vaccination against mpox	75.2% (sensitivity analysis: 35.8%)	Dalton AF et al.[15] (sensitivity analysis: Deputy NP et al.[16])
p_2	Vaccine effectiveness of full dose (two dose) JYNNEOS® vaccination against mpox	85.9% (sensitivity analysis: 66.0%)	Dalton AF et al.[15] (sensitivity analysis: Deputy NP et al.[16])
μ	Rate of entry into (by arriving 13 years) and exit from (through natural death) the model	1/365*64.5 (day^{-1})	Life expectancy at 13 years in the US: 64.5[20]
rp	Proportion of mpox cases reported in the US	50% (sensitivity analysis: 25%–75%)	Assumption (sensitivity analysis: assumption)
N	Total model population: high-risk and low-risk group in US	1,436,642*2 = 2,873,284	CDC AtlasPlus,[21] adjusted for unknown HIV patients and high-risk people who did not take PrEP by multiplying the total number of HIV patients and people on PrEP prescription by two-fold.
n_H	Proportion of the model population in the high-risk group	Determined by fitting data	Fitting real world epidemic curve
n_L	Proportion of the model population in the low-risk group	Determined by fitting data	Fitting real world epidemic curve

[a]β_{HH}: transmission coefficient for mpox transmission from high-risk individuals to high-risk individuals. β_{HL}: transmission coefficient for mpox transmission from low-risk individuals to high-risk individuals. β_{LH}: transmission coefficient for mpox transmission from high-risk individuals to low-risk individuals. β_{LL}: transmission coefficient for mpox transmission from low-risk individuals to low-risk individuals. We assumed the basic reproductive number for the high-risk group ($R0_H$) to be 10 times that of the low-risk group ($R0_L$) due to evidence on higher proportion of mpox transmission occuring through sexual contacts compare to non-sexual contacts during the current 2022–2023 outbreak according to WHO.[2] [b]Case fatality ratio ρ = 0.00128 (111/86,516),[2] m = ρ (μ + γ_1)/(1-ρ) = 0.0000611.

Table 1: **Model parameters, values and data references.**

and Technology Council (grant number MOST-109-2314-B-002-147-MY3 and NSC-112-2314-B-002-216-MY3), and by US National Institutes of Health (grant number P30MH062294). Funding sources had no role in study design, data collection/analyses/interpretation, manuscript preparation, or submission. The corresponding author had full access to all of the study data and took final responsibility for the decision to submit for publication.

Results

Model simulation of mpox epidemic curve fitted to the real-world US outbreak data is illustrated in Fig. 2. The effective proportion of the population in the high-risk and low-risk groups, estimated by the best model simulation, was 4% (114,931) and 96% (2,758,352) of the total population at risk (N), respectively. The fitted initial population were 20 each for the I_{1H}, E_H, A_H compartment and 2 each for the I_{1L}, E_L, A_L compartment. β_{HH} was estimated at 8.93 day^{-1}, while β_{HL}, β_{LH}, β_{LL} were each estimated at 0.04 day^{-1} under the best-fitted model, yielding the basic reproduction number for the high-risk and low-risk population to be 3.88 and 0.39, respectively. Details for calculation of the basic reproduction numbers are provided in the Supplemental material. The MSE of the best-fit model in the base scenario was 2.088. This low MSE (1.5% of 139, the mean number of daily reported mpox cases in the US between 22 May and 22 December, 2022) suggested that the model performed quite well against the variance-stabilised data, indicating a high level of accuracy in fittings.

In the context of the two-dose vaccine administration campaign and high-risk group awareness, daily reported mpox cases generated by the best-fitted model (Fig. 2) peaked on 6 August, 2022 with 505 cases reported that day, and declined to a very low level by the end of 2022.

Status	Description	Initial Value
S	Population susceptible to mpox (S_H and S_L)	S_H: $N \times n_H$; S_L: $N \times n_L$
E	Population exposed to mpox but not yet infectious (E_H and E_L)	E_H : determined by fitting data; E_L: 0.1 E_H[a]
I_1	Population acquiring symptomatic mpox in their pre-symptomatic phase, infectious (I_{1H} and I_{1L})	$I_{1H} = E_H$; $I_{1L} = E_L$
I_2	Population acquiring symptomatic mpox in their symptomatic phase, infectious (I_{2H} and I_{2L})	I_{2H}: 1[b]; I_{2L} : 0
A	Population with asymptomatic mpox, infectious (A_H and A_L)	$A_H = E_H$; $A_L = E_L$
R	Population recovered and immune to mpox (R_H and R_L)	$R_H = R_L = 0$
V_{1pre}	Population with less than 14 days since first dose vaccination, without complete first-dose effectiveness (V_{1preH} and V_{1preL})	$V_{1preH} = V_{1preL} = 0$
V_1	Population with more than 14 days but less than 28 days since first dose vaccination, with complete first-dose effectiveness (V_{1H} and V_{1L})	$V_{1H} = V_{1L} = 0$
VW	Population with more than 28 days since first dose vaccination, eligible for the second dose (VW_H and VW_L)	$VW_H = VW_L = 0$
V_{2pre}	Population with less than 14 days since second dose vaccination, without complete second-dose effectiveness (V_{2preH} and V_{2preL})	$V_{2preH} = V_{2preL} = 0$
V_2	Population with more than 14 days since second dose vaccination, with full vaccine effectiveness (V_{2H} and V_{2L})	$V_{2H} = V_{2L} = 0$

[a]We assumed the initial high-risk population in the status that are or will be infectious except for I_2 (E_H, I_{1H}, and A_H) status to be 10 times that of the low-risk population (E_L, I_{1L}, A_L) due to evidence on higher proportion of mpox transmission occuring through sexual contacts compare to non-sexual contacts during the current 2022–2023 outbreak according to WHO.[2] [b]One case of mpox was reported to the US CDC on 10 May, 2022.[8]

Table 2: **Model compartments and their initial values. Compartments of the high-risk and low-risk group are indicated with subscript H for the high-risk group and subscript L for the low-risk group.**

Number of cumulative cases estimated by the model during 22 May through 22 December, 2022 was 29,559 (±5%: (28,081, 31,036)), which is similar to the actual reported number of 29,918 cases.[8] Among the 29,559 model-simulated cases, 71.8% (21,227) were from the high-risk group. This is also comparable to the actual proportion of mpox cases in the US from males aged 16–45 years (78.6%),[22] an age group that is most actively involved in sexual activities (taking into account that the actual reported cases of males also include a portion that did not engage in risky sexual behaviours).

Fig. 3 presents the daily reported mpox cases simulated under some counterfactual scenarios without either campaign of vaccine administration or high-risk group awareness. The simulated epidemic curve in the absence of any preventive measures reach an extremely large peak on 31 July, 2022 with 1528 cases reported that day, and also yields a prolonged epidemic, producing 82,160 cumulative reported cases between 22 May and 22 December, 2022. By incorporating only the vaccine administration, the simulated epidemic curve would peak at a slightly lower level compared to the scenario

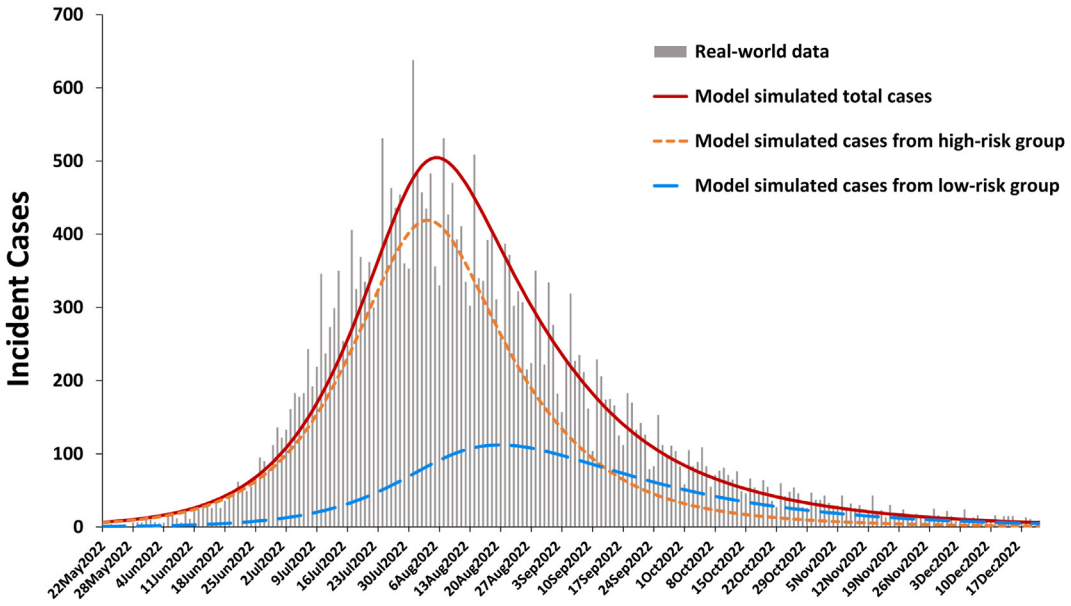

Fig. 2: **Real-world daily reported cases and model predicted daily reported cases of mpox in the US from 22 May to 22 December, 2022.** Real-world data are presented in bar chart; model simulations are presented in line graphs.

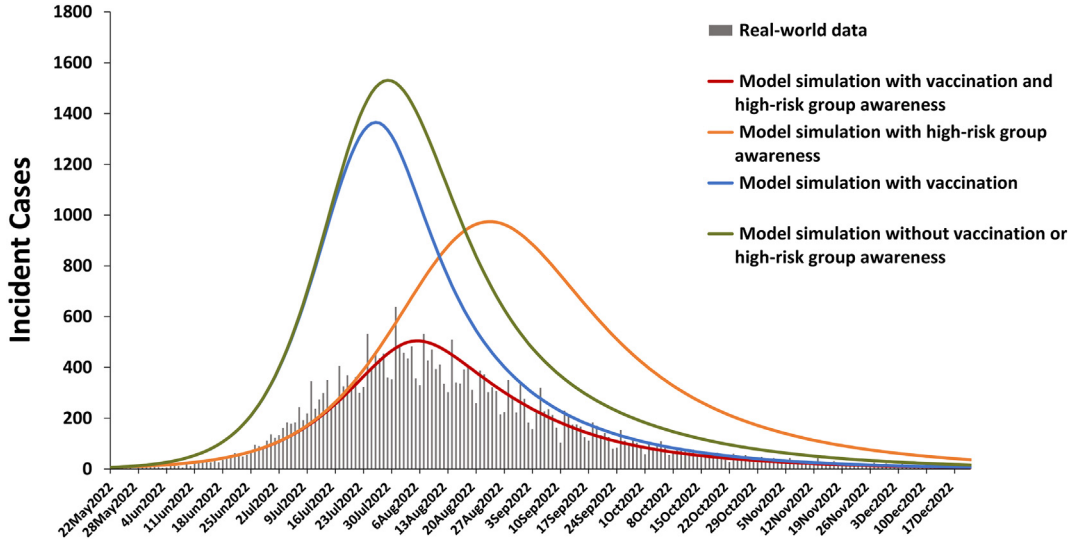

Fig. 3: **Modelling results of daily reported mpox cases for different scenarios.**

without any preventive measures, with 1365 cases reported on 27 July, 2022. On the other hand, with only the high-risk group awareness starting from 22 May, 2022, the simulated epidemic curve would peak at an apparently lower level, with 974 cases reported on 24 August, 2022. However, this high-risk group awareness alone scenario would endure a much longer period of epidemic compared to the three other scenarios (vaccination ± awareness or no intervention).

By summing the simulated daily reported cases and daily infections under each scenario, we estimated that 2-dose vaccination administration, solely, could prevent 21.2% of reported cases or 21.2% of infections (symptomatic and asymptomatic) by the end of 2022, while high-risk group awareness could prevent 15.4% of reported cases or 15.3% of infections, compared to the scenario without any preventive measures (Table 3, Table 4). With both the vaccine administration and high-risk group awareness, our model suggested how the mpox epidemic in the US was successfully controlled, preventing 64.0% of reported cases and 64.0% of infections.

We further investigated the influence of varying parameters on the prevention percentage (Tables 3 and 4). In the one-way sensitivity analysis (Table 3), the proportion of mpox cases reported in the US and the proportion of asymptomatic cases had some effect on the estimates of prevention percentage for the preventive measures individually (12.9%-24.1% for vaccination, and 14.3–15.4% for high-risk group awareness), and for the combination of vaccination and awareness/risk reduction (47.4%–69.0%). Relaxing the relation between β_{LL} and β_{HL}, β_{LH} to two-fold ($2\beta_{LL} = \beta_{HL} = \beta_{LH}$) has more effects on the estimates of prevention percentage for high-risk group awareness (20.6%) than that of vaccination (22.7%). With a one-way sensitivity analysis with lower vaccine effectiveness, the vaccination campaign alone would only avert 10.2% of reported cases or 10.2% of infections. The preventive proportion for the combination of both preventive measures also dropped to 43.8% and 43.8% for reported cases and infections, respectively. The apparently lower estimates of prevention percentage under the lower vaccine effectiveness scenario are consistent in the three-way sensitivity analysis with the combination of different proportion of mpox cases reported and the proportion of asymptomatic cases. In all scenarios, the vaccination campaign and high-risk group awareness demonstrated synergistic effects (the joint effect, in terms of the percentages of prevented cases or infections, is larger than the sum of each individual effect) rather than merely addictive effects (the joint effect is only the same as the sum of each individual effect). The prevention percentage of cumulative infections had similar results to that of cumulative reported cases (Tables 3 and 4).

Discussion

Our modelling study sought to parse the relative likely contributions of both the 2-dose mpox vaccination campaign and the awareness of the high-risk population for risk reduction. Using real-world data for parameter estimations, we found a synergistic effect with high effectiveness of the combination of both intervention measures in averting the number of mpox cases during the 2022–2023 mpox epidemic in the US. Our results indicate that the two-dose mpox vaccination campaign prevented 21.2% (sensitivity analysis: 10.2%–24.1%) of mpox cases, the high-risk group awareness prevented 15.4% (sensitivity analysis: 14.3%–20.6%) of mpox cases, and the combination of both measures prevented

	Vaccination percentage of prevented cases (percentage of prevented infections)	High-risk group awareness percentage of prevented cases (percentage of prevented infections)	Vaccination and high-risk group awareness percentage of prevented cases (percentage of prevented infections)
The base scenario	21.2% (21.2%)	15.4% (15.3%)	64.0% (64.0%)
Reporting rate = 25%	12.9% (12.9%)	14.3% (14.2%)	47.4% (47.4%)
Reporting rate = 75%	24.1% (24.1%)	15.4% (15.3%)	69.0% (69.0%)
Asymptomatic rate = 20%	18.4% (18.4%)	15.0% (14.9%)	58.7% (58.8%)
First dose VE = 35.8%, Second dose VE = 66.0%	10.2% (10.2%)	17.3% (17.2%)	43.8% (43.8%)
$2\beta_{LL} = \beta_{HL} = \beta_{LH}$	22.7% (22.7%)	20.6% (20.5%)	65.4% (65.4%)

VE, vaccine effectiveness.

Table 3: **One-way sensitivity analysis of parameters with uncertainty on the impact of the prevention percentages of mpox reported cases and mpox infections for vaccination and high-risk group awareness.**

64.0% (sensitivity analysis: 43.8%–69.0%) of mpox cases, compared to the counterfactual scenario in the absence of both measures.

The 2022–2023 global mpox outbreak, as well as the epidemic in the US, has the majority of infections observed to transmit among men through male-to-male sexual contact, with far fewer heterosexual sexual transmission, and skin-to-skin non-sexual transmission to children.[2] Our risk-structured mpox mathematical model successfully captured these distribution characteristics of cases among high- and low-risk populations. In the simulated results of our model, 71.8% of cases were from the high-risk group, a value comparable to the actual distribution of mpox cases in the US among males aged 16–45 years (78.6%).[22] The epidemic curve for the low-risk group in our model exhibited a later onset and also peaked later compared to that of the high-risk group. This is also consistent with the real-world situation, where the proportion of cases in the US that reported other than male-to-male sexual contact (including women, and men with no known male-to-male sexual contact) accounted for nearly 0% of the total reported contacts in May 2022, gradually rose to about 10–15% in June and July, and comprised over 30% of the total reported contacts in late August 2022.[23]

Our model suggests that the US mpox epidemic may have been controlled due to the combination of 2-dose vaccination campaign and high-risk group awareness with risk reduction. The alarm raised by the 2022–2023 mpox outbreak motivated MSM to take action to reduce the risk of infection in the US. Results globally seem to support the impact of community messaging and risk reduction. A study from Australia found that participants recruited from a sexual health clinic and MSM communities reported reduced sexual activities during the outbreak.[24] This reduction included reduced sex with casual partners (53.9%), cessation of drug use proximate to sexual activity ("chemsex"; 49.8%), abstaining from group sex (45.3%), and an increase in condom use for anal sex (26.2%).[24] Additionally, most participants possessed correct knowledge of the mpox transmission route (94.7%), showed willingness toward vaccination (68.3%), and were concerned about the mpox epidemic.[24]

Either vaccination campaign or high-risk group awareness alone demonstrate limited prevention

	Vaccination percentage of prevented cases (percentage of prevented infections)	High-risk group awareness percentage of prevented cases (percentage of prevented infections)	Vaccination and high-risk group awareness percentage of prevented cases (percentage of prevented infections)
The base scenario: Reporting rate: 50%,Asymptomatic rate = 6%, First dose VE = 75.2%, Second dose VE = 85.9%	21.2% (21.2%)	15.4% (15.3%)	64.0% (64.0%)
First dose VE = 75.2%, Second dose VE = 85.9%			
Reporting rate: 25%–75%, Asymptomatic rate = 6%	12.9%–24.1% (12.9%–24.1%)	14.3%–15.4% (14.2%–15.3%)	47.4%–69.0% (47.4%–69.0%)
Reporting rate: 25%–75%, Asymptomatic rate = 20%	12.8%–21.3% (12.8%–21.3%)	14.2%–15.1% (14.2%–15.0%)	46.8%–64.4% (46.8%–64.4%)
First dose VE = 35.8%, Second dose VE = 66.0%			
Reporting rate: 25%–75%, Asymptomatic rate = 6%	5.6%–10.8% (5.6%–10.9%)	14.7%–17.3% (14.6%–17.2%)	30.1%–45.1% (30.1%–45.1%)
Reporting rate: 25%–75%, Asymptomatic rate = 20%	4.6%–8.8% (4.6%–8.8%)	14.3%–15.9% (14.2%–15.9%)	26.1%–39.5% (26.1%–39.5%)

VE, vaccine effectiveness.

Table 4: **Three-way sensitivity analysis of parameters with uncertainty on the impact of the prevention percentages of mpox reported cases and mpox infections for vaccination and high-risk group awareness.**

percentages (21.2% and 15.4%, respectively) in our study, given that the vaccine coverage for the at-risk population in the US only reached 37% for the first dose and 23% for the second dose by January 2023,[4] and the modest decrease in risky sexual behaviours associated with high-risk group awareness. That their combination exhibited such a synergistic effect (64.0%), nearly twice the sum of the effect of each intervention, sends a compelling public health message. From the modelling perspective, the high-risk group awareness rapidly reduced the transmission coefficients (β_{HH}, β_{HL}, β_{LH}) at the population level, while 2-dose vaccination campaign immunised the at-risk individuals and removed them from the susceptible pool, albeit with varying degrees of imperfect protection. The results of synergistic effects arise from the simultaneous implementation of population-level and individual-level control measures, which would likely be applied to other infectious disease risks when transmissibility is vaccine-preventable and behaviourally mediated. From the prevention policy perspective, awareness and vaccination campaign also act synergistically. When the high-risk MSM became aware of the mpox epidemic and changed their previous risky sexual behaviours, it was likely that they not only reduced the risk of contracting mpox, but also sought to obtain immunity against mpox through getting mpox vaccinations. On the other hand, the implementation of vaccination campaigns may raise public attention regarding mpox. These campaigns are often accompanied by public health education initiatives, encompassing information about the symptoms and transmission routes of mpox, as well as preventive measures. Such public health communications can enhance the understanding and knowledge of mpox for the public, thereby elevating the awareness and lead to behaviour changes.

Owing to the shortages of vaccine supply at the early stage of this unprecedented global mpox outbreak, multiple countries opted to prioritise administering as many first doses as possible to the high-risk population until the supply were sufficient for full-dose administration.[25] Prior published modelling studies focused on exploring strategies to enhance the effect of vaccination campaign in situations of vaccine shortages, including dose-sparing strategies and prioritising the vaccine for geographic networks with more initial infections and larger basic reproduction numbers.[26,27] A modelling study of the 2022 mpox outbreak suggested that the decline in mpox incidence in the UK was mainly attributed to immunity at the population level following infections and reduced exposure due to behaviour changes, rather than to the single-dose vaccination.[28] Another modelling study in the UK that published later also came to corresponding conclusions that the downturn of the mpox outbreak in the UK possibly resulted from moderate reductions in sexual risk behaviour of MSM in combination with the reduction of the effective infectious period. While the delayed initiation of vaccination only averted a small percentage of infections (9.8%), it helped to prevent the potential mpox resurgence.[29] However, the effectiveness of the first dose of the JYNNEOS® vaccine is substantially lower than that of full dose. Even with a 2-dose vaccination, titers of orthopoxvirus-neutralising antibody were observed to wane by the 2-year mark.[30] A single dose immunisation wanes even faster, indicating the need for boosters in the face of ongoing transmission and risk taking. As the subsequent vaccine supply gradually replenished, and an emergency use authorisation (EUA) for the intradermal injection of JYNNEOS® vaccine was issued,[4] 5-fold increases were seen in the availability of the vaccine; incorporating full 2-dose vaccination into modelling will illuminate the potential of vaccination at the population level.

Strengths of our study include our inclusion of up-to-date data on the US vaccination campaign, timely initiated in late May with expanded supplies after early July,[31] as well as high-risk group behaviour changes in our risk-structured modelling. We suggest that both vaccination and awareness among MSM played roles in controlling the mpox epidemic in the US, with significant synergistic effects. These novel findings are highly relevant to countries facing the mpox epidemics and may apply to other vaccine-preventable and behaviourally mediated infectious diseases. Our study also has limitations. First, we postulated that the reduction in risky sexual activity within the high-risk population would be maintained at least until the end of 2022. There were possibilities that a reversion to risky sexual behaviours and a decrease in awareness to a lower level could occur, as the high-risk population might become fatigued with preventive measures. The lack of detailed sexual risk survey data throughout the study period makes it challenging to quantify fluctuations in these behaviours with time. The potential transience of protective effectiveness of behaviour change highlights the synergism of the vaccination campaign with more durable protection. Second, we assumed a 10-fold difference in transmission potential between the high-risk and low-risk groups, based on currently obtainable informations.[2] The proportions of cases from the high-risk population simulated by our model align with the actual reports to the US CDC, supporting that the aforementioned assumptions should be reasonable, though we cannot be sure. Third, high-risk group awareness for mpox may theoretically increase the vaccination rate, and decrease the proportion of symptomatic patients who still engage in activity associated with transmission risk. However, our model did not incorporate these two theoretical component of awareness effects because vaccination rate was constrained by vaccine supplies, and there were no empirical studies that reported the actual decrease of the proportion of symptomatic patients who still engage in activity associated with

transmission risk after the awareness initiation. Finally, our sensitivity analyses show that estimates of prevention percentages for the vaccination campaign are sensitive to uncertain estimates of vaccine effectiveness and the proportion of mpox cases reported in the US. Still, in all scenarios, the vaccination campaign and high-risk group awareness demonstrated synergistic effects.

We conclude that our modelling evidence suggests that the JYNNEOS® mpox vaccine, highly effective among the at-risk population at the individual level (preventing against mpox infection and reducing severity of symptoms), is also highly effective at the population level (controlling mpox outbreaks), particularly when combined with high-risk group awareness and consequent changes in risky sexual behaviour. The combination of these measures has a synergistic effect. Our findings on the effect of vaccination, behaviour changes, and other control measures are highly relevant for countries facing the ongoing or reemerging threat of mpox. The model may also guide strategic preparedness for analogous epidemics of emerging or re-emerging infectious diseases.

Contributors

CTF and YCL designed the study. YCL, CTF, and THW performed the modelling analysis. YCL collected the mpox and vaccination data published by US CDC. CTF and YCL verified the underlying data of modelling analysis. YCL, CTF, and SHV interpreted the results and drafted the manuscript. WLS critically reviewed the manuscript. All authors reviewed and approved the final version of the manuscript. The corresponding author had full access to all of the study data and took final responsibility for the decision to submit for publication.

Data sharing statement

All the parameters and fitting data used in this paper are derived from publicly accessible sources. The STELLA code for the model of this study will be provided upon reasonable request to the corresponding author, given valid justifications.

Declaration of interests

All authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102407.

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