Journal of Travel Medicine

International Society of Travel Medicine
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*Journal of Travel Medicine*, 2022, 1–3
https://doi.org/10.1093/jtm/taac101
Rapid Communication

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# Projecting the impact of testing and vaccination on the transmission dynamics of the 2022 monkeypox outbreak in the USA

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Submitted 10 August 2022; Revised 24 August 2022; Accepted 29 August 2022

The USA is emerging as the second epicentre of the 2022 monkeypox outbreak,[1,2] in addition to Europe. Delay in diagnosis and reporting is impeding the effective control of this outbreak.[3] In addition to scaling up and speeding up diagnostic testing, ring vaccination of contacts exposed to confirmed monkeypox cases is being implemented to limit the spread of monkeypox virus (MPXV) in the USA.[4] This study establishes a mathematical model to specifically recapitulate the transmission dynamics of the current monkeypox outbreak in the USA, and to project the impact of the most urgent interventions focusing on diagnostic testing and ring vaccination.

We constructed an epidemic dynamical model, which partitioned the total US population into seven epidemiological compartments based on the different status of disease diagnosis (Supplementary Figure S1 and Supplementary methods, supplementary data are available at *JTM* online). This model considers heterogeneous (both close/sexual and general) contacts,[2,5] associated with different secondary attack rates and different number of contacts exposed to an infected individual. The efficacy of currently available smallpox vaccines against monkeypox was estimated as 85% for both routine vaccination and ring vaccination.[6] The incorporated parameters and datasets were taken from authentic sources (Supplementary Table S1, supplementary data are available at *JTM* online).

We retrospectively (prior to 15th July) simulated the MPXV epidemic dynamics across the most heavily affected states in the USA. Notable gaps were observed between estimated and confirmed numbers of cases in six representative states. The total number of infected cases is estimated as 1.8 (95% CI 1.3–3.4) times of the reported number (Figure 1A). This suggests that a substantial proportion of infected cases were not diagnosed or reported during this period of the outbreak.

At the early stage of the outbreak, the average time from disease onset to diagnostic confirmation and reporting required 9 days.[7] Infected but unconfirmed cases exacerbated the spread of MPXV. If this reporting delay could be shortened to 5 or 3 days, the number of cumulative infections would be reduced by 96.9 and 99.4%, respectively, by the end of 2022 (Figure 1B and Supplementary Figure S2, supplementary data are available at *JTM* online). Notably, 16.2 thousand infections could be prevented for the state of New York alone, by shortening the diagnosis delay from 5 to 3 days.

The implementation of ring vaccination has a clear coverage-dependent effect on curbing the spread of MPXV (Figure 1C). If the median delay from disease onset to confirmation were shortened to 5 days, but without ring vaccination, there would be 74 169 cumulative infections in 2022 in the USA. Vaccinating 20% of exposed contacts would reduce cumulative cases by

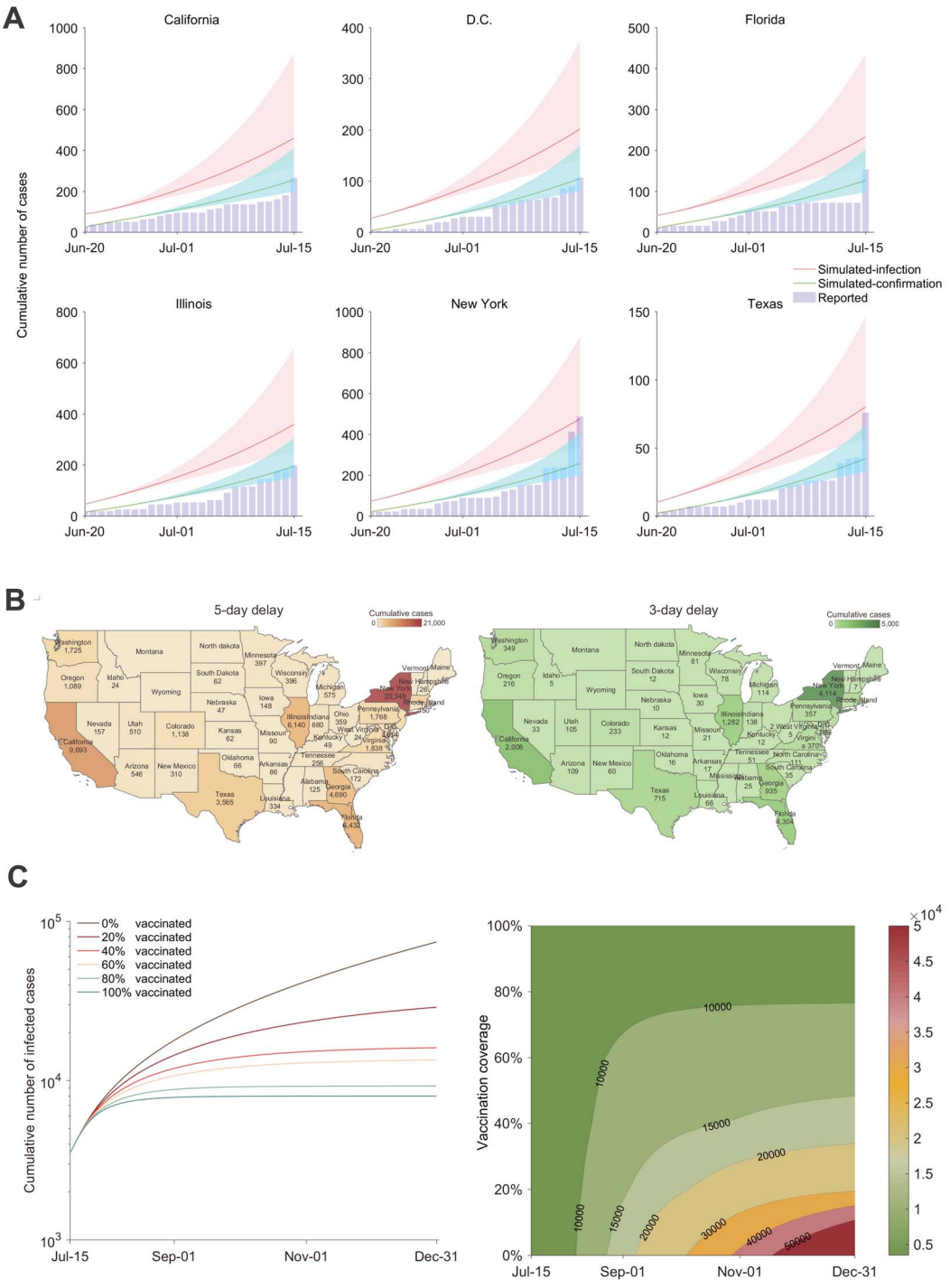


**Figure 1.** Retrospective simulation of the monkeypox outbreak in the USA, and assessing the impact of rapid diagnosis and ring vaccination on curbing monkeypox spread. (A) Model simulation to fit the spread of MPXV in some representative states of the USA from 20th June to 15th July. The model considers an average delay of 9 days from disease onset to laboratory confirmation in the early outbreak phase. Reported case numbers were obtained from an open-access epidemiological database (https://github.com/globaldothealth/monkeypox). The shaded areas represent the 95% confidence interval related to parameters. (B) We quantified the impact of shortening the delay from disease onset to diagnostic confirmation. On average, a 9-day delay was reported at the early stage of the outbreak. The total number of infections by the end of 2022 was predicted for different states of the USA assuming the confirmation delay can be shortened to 5 or 3 days. (C) When simulating the effectiveness of ring vaccination, the median delay from symptom onset to confirmation was assumed to be 5 days. The efficacy of smallpox vaccines against monkeypox was estimated as 85% for both routine vaccination and ring vaccination.

32.3% by the third quarter and by 61.1% by the end of 2022. If vaccination coverage reached 40 and 60%, cumulative infections would be reduced by 78.3 and 81.8%, respectively, by the end of 2022. We observed similar effects of ring vaccination across different representative states (Supplementary Figure S3, supplementary data are available at *JTM* online).

As a further demonstration of the robustness of our model, we found that the simulated cumulative infections from 15 July to 15 August, under the scenario of 30% vaccination coverage and 5 days between onset and conformation that is in line with the real-world situation,[2] are well fitted to the reported data (Supplementary Figure S4, supplementary data are available at *JTM* online). This scenario, when compared with a 9-day delay between onset and conformation, would prevent 29.6% infections.

In summary, this epidemic modelling study recapitulated the early transmission dynamics of the 2022 monkeypox outbreak in the USA. Our model allows us to quantify the importance of shortening the delay from disease onset to diagnostic confirmation and of implementing ring vaccination so as to mitigate the spread of MPXV.

Of note, there are some limitations in this study. First, our model only considers infection numbers, but not the clinical burden related to disease severity, hospitalization or mortality. Second, we did not incorporate the number of sexual partners in transmission, since these numbers remain not available for the US epidemic setting. Third, reinfections and asymptomatic infections were also not considered. Last but not least, once the availability of vaccines increases, follow-up studies will be needed to plan optimal vaccination campaigns that prioritize different high-risk populations.

## Authors' Contributions

All authors conceptualized and designed the study; Zheng and Bao were involved in acquisition and analysis of data; Zheng, Giordano and Bao took the reponsibility of model building; Pan, Zheng and Bao led the drafting of the manuscript; Giordano, de Vries and Li revised the manuscript; Bao, Zheng, de Vries and Li were responsible for the effectiveness of analysis; Pan, Giordano and Zheng were involved in supervision.

## Conflict of Interest Disclosures

None reported.

## Funding/Support

This work was supported by the National Natural Science Foundation of China (nos. 71901132, 72134004 and 42001121), and the VIDI grant from the Netherlands Organization for Scientific Research (71 901 132).

## Role of the Funder/Sponsor

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

## Supplementary data

Supplementary data are available at *JTM* online.

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# Supplementary file

**Projecting the impact of testing and vaccination on the transmission dynamics of the 2022 monkeypox outbreak in the United States.**

## Supplementary Methods

**Epidemiological dynamical model:** Our mathematical model describes the dynamics of the monkeypox disease through seven epidemiological compartments (Figure. 1A). S: susceptible; V: protected by ring vaccination or routine vaccination, cannot be symptomatically infected; E: exposed and latent, but not infectious; I: infected and infectious, with symptoms, undetected; L: infected and infectious, with symptoms, detected (laboratory confirmed); R: recovered; D: dead.

The dynamical system describes the time evolution of the population fractions in the various compartments:

$$\dot{S}_i = -\beta I_i \frac{S_i}{N_i} - \beta' L_i \frac{S_i}{N_i} \quad (1)$$

$$\dot{E}_i = \beta I_i \frac{S_i}{N_i} + \beta' L_i \frac{S_i}{N_i} - \alpha E_i \quad (2)$$

$$\dot{V}_i = \alpha \cdot \upsilon \cdot VE \cdot E_i \quad (3)$$

$$\dot{I}_i = \alpha(1 - \upsilon \cdot VE)E_i - \eta I_i - \gamma I_i - \sigma I_i \quad (4)$$

$$\dot{L}_j = \eta I_i - \gamma L_i - \sigma L_i \quad (5)$$

$$\dot{R}_i = \gamma I_i + \gamma L_i \quad (6)$$

$$\dot{D}_i = \sigma I_i + \sigma L_i \quad (7)$$

where the subscript $i$ represents the state $i$ in the United States. Parameters $\beta$ and $\beta'$ are the transmission rates respectively due to undetected and detected infected subpopulations, where $\beta'$ is 50 times smaller than $\beta$ thanks to the isolation of detected cases [1 2]. The transmission rate $\beta$ is estimated by combining the secondary attack rate and the average number of contacts of an infected individual [3]. The secondary attack rates of close contacts and general contacts were defined by [4], and the average number of persons exposed to an infected case was obtained from a surveillance study [5], of which 45% were household or sexual (close) contacts, others were general contacts .

The efficacy of smallpox vaccines against monkeypox is assumed to be 85%. Smallpox vaccines are employed in both routine and ring vaccination campaigns [6 7]. The delay between symptom onset and laboratory testing results is reflected through the diagnosis rate $\eta$. It has been reported that the median time between

symptom onset and monkeypox virus testing was 7 days, while the turnaround time from monkeypox virus testing to result availability was 2 days at the early stage of the 2022 outbreak [8]. Therefore, the median confirmation delay in our retrospective simulation was assumed to be 9 days.

Before the outbreak, the total population $N_i$ is assumed to have been composed of susceptible subpopulation ($S$), constituting 70% of the total population, and vaccinated subpopulation ($V$), constituting 30% of the total population, to account for individuals born before 1980s who have been routinely vaccinated against smallpox [9] and are therefore protected against monkeypox with 85% vaccine efficacy [7].

Other parameters were also taken from verified sources [6 10].

**Scope, timeframe and data sources:** The reported monkeypox virus (MPVX) cases were obtained from an open-access database (https://github.com/globaldothealth/monkeypox) compiled from verified sources [11]. We investigated the MPXV epidemiology of the US states. The timeframe of epidemic recapitulation started from June 20 and ended on July 15, 2020. The time window of MPXV spread prediction is six months.

**Table S1. Key parameters of the mathematical model.**

| Parameter | Definition | Value | Source |
|---|---|---|---|
| $\beta$ | transmission rate due to undetected infections | 0.329 (95% CI 0.231-0.429) | [4 5] |
| $\beta'$ | transmission rate due to detected infections | 0.006 | [1 2] |
| $\nu$ | coverage of ring vaccination to exposed individuals | 0% | Assumed |
| $VE$ | vaccine efficacy of ring vaccination | 85% | [6 7] |
| $1/\eta$ | delay from symptom onset to diagnosis | 9 | [8] |
| $1/\alpha$ | incubation period | 8.5 | [12] |
| $\gamma$ | recovery rate | 4.54% | [6 10] |
| $d$ | fatality rate for infected individuals with symptoms | 0.22% | [13] |

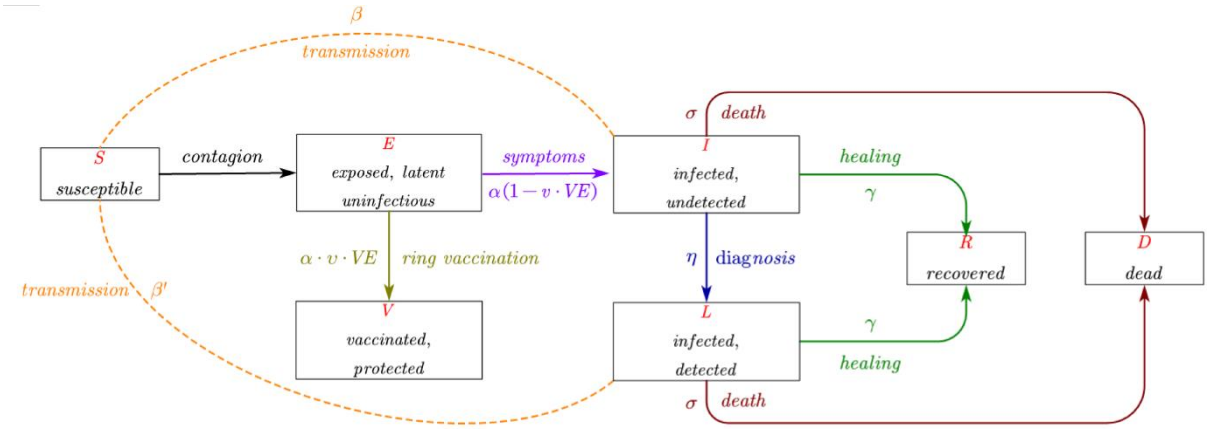


**Figure S1.** Graphical Scheme of the epidemiological model. In the mathematical model, the vaccinated subpopulation (compartment V) already includes individuals born before 1980s, who received the routine smallpox vaccination. Exposed individuals who are identified and ring vaccinated are transferred from compartment E to compartment V. The transmission rate of detected infections is assumed to be much lower than that of undetected infections, thanks to the isolation of detected cases.


**Figure S2.** The impact of rapid diagnosis on curbing monkeypox spread in different states of the United States

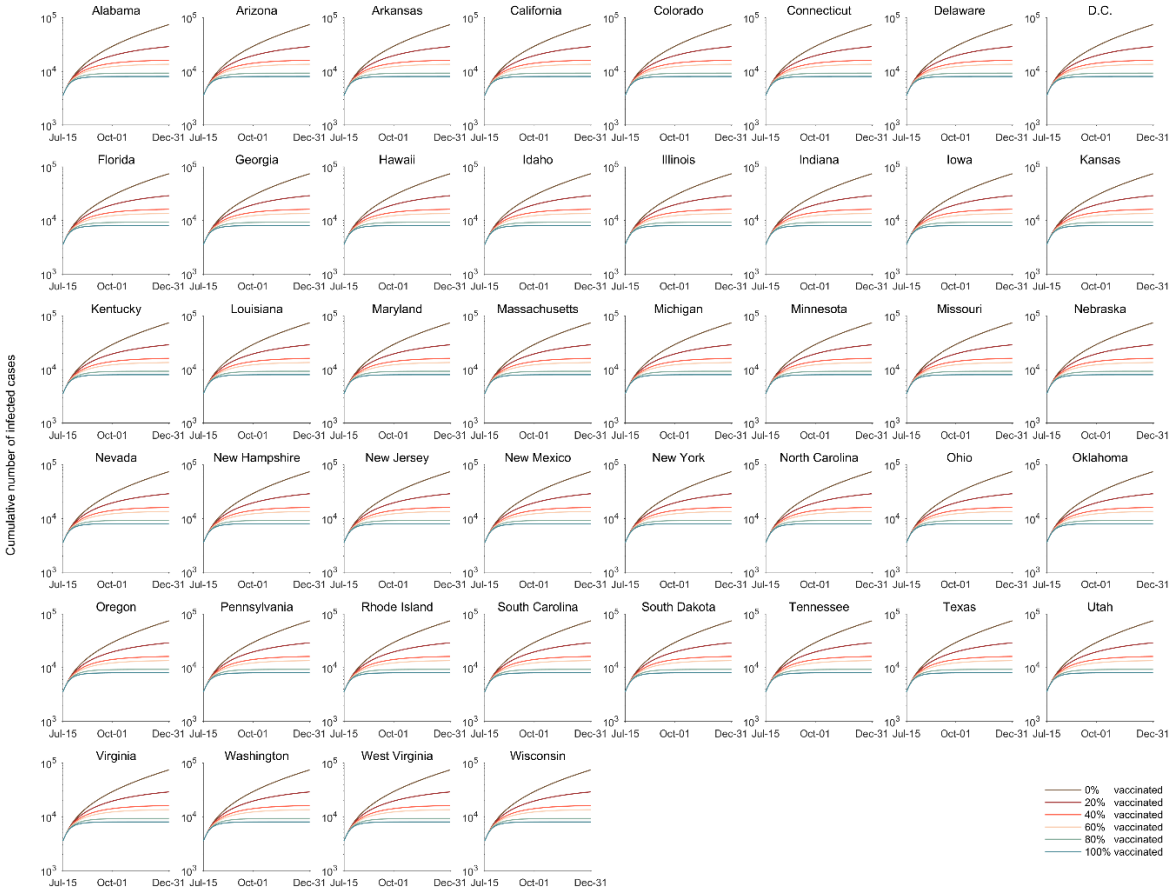


**Figure S3.** The impact of different coverage of ring vaccination on curbing monkeypox spread in different states of the United States

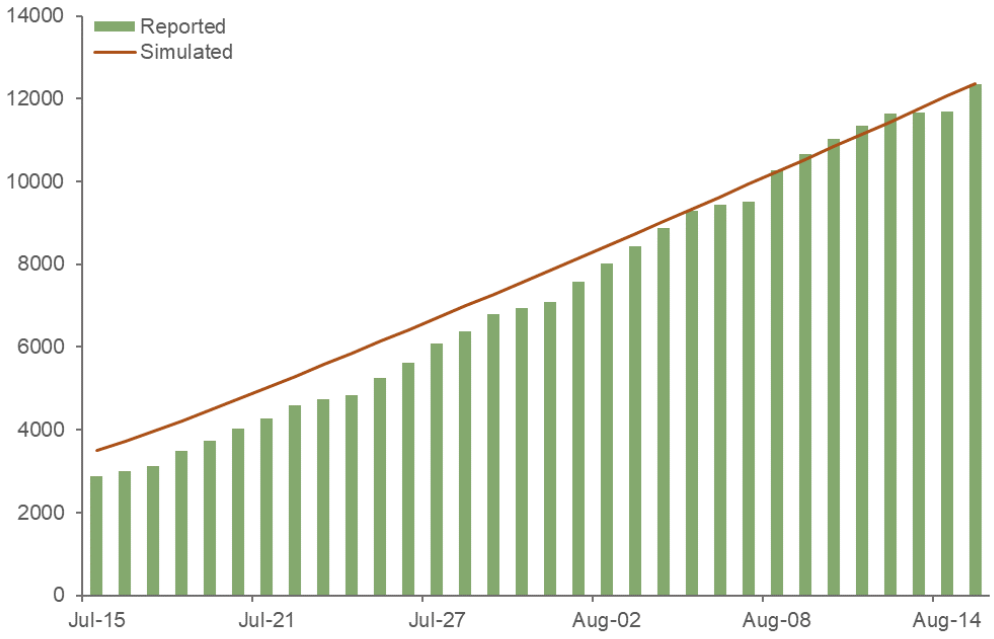


**Figure S4.** Model simulation to fit the monkeypox epidemic dynamics from 15 July to 15 August in the United States. The total coverage of vaccine of this simulation scenario is 30%, which is close to the aggregated data that 14% of persons reported receipt of pre-exposure smallpox vaccine and 14% of at-risk contacts receive vaccine [5 14]. The delay between onset and conformation was assumed to be 5 days, which is consistent with the observation from the open-access monkeypox database [15]. The reported data were obtained from US CDC [16].

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