# Uncertainty in predictions of disease spread and public health responses to bioterrorism and emerging diseases

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**Concern over bioterrorism and emerging diseases has led to the widespread use of epidemic models for evaluating public health strategies. Partly because epidemic models often capture the dynamics of prior epidemics remarkably well, little attention has been paid to how uncertainty in parameter estimates might affect model predictions. To understand and quantify such effects, we used Bayesian analysis to rigorously estimate the uncertainty in the parameters of an epidemic model, focusing on smallpox bioterrorism. We then used the estimated vaccination model to run a large number of uncertainty in the model parameters in order to quantify uncertainty in which of two vaccination strategies would provide a better response to bioterrorism, mass vaccination, or vaccination of social contacts, so-called "trace vaccination." Our results have remarkably high and hitherto uncertainty in the model parameters with important implications for vaccination strategies. For example, under one plausible scenario, the most likely outcome with mass vaccination would save ≈100,000 more lives than trace vaccination. Because of the high uncertainty in the parameters, however, there is also a substantial probability that mass vaccination would save 200,000 or more lives than trace vaccination. In addition to providing the best response to the most likely outcome, mass vaccination has the advantage of preventing outcomes that are only slightly less likely but that are substantially more horrific. Rigorous estimates of uncertainty, which can reveal hidden advantages of public health strategies, suggesting that uncertainty estimation should play a key role in planning for epidemics.**

susceptible-exposed-infected-removed model | trace versus mass vaccination | host–pathogen interaction | Bayesian hierarchical model

The (1). A (2, 3), (3, 4).

( ) (2)

$$\frac{dS}{dt} = \frac{-R_0\gamma}{N} SI,$$

$$\frac{dE}{dt} = \frac{R_0\gamma}{N} SI - \alpha E,$$

$$\frac{dI}{dt} = \alpha E - \gamma I, \qquad [1]$$

$$\frac{dR}{dt} = \gamma I.$$

$R_0$ , $\gamma$ , , , $N$ , $S$ $E$ $R_0\gamma$ , $\alpha$, $\mu$, (2), (7, 9, 10), . (3). (4, 6). (4, 6). ( )

$$P(R_0, \alpha, \gamma, \mu, \sigma^2| \quad ) \propto \pi(R_0)\pi(\alpha)\pi(\gamma)\pi(\mu)\pi(\sigma^2)L( \quad |R_0, \alpha, \gamma, \mu, \sigma^2). \qquad [2]$$

, $\sigma^2$ , $P(R_0, \alpha,$

Author contributions: B.D.E. and G.D. designed research; B.D.E. and V.M.D. performed research; B.D.E. and V.M.D. analyzed data; and B.D.E., V.M.D., and G.D. wrote the paper.

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Abbreviation: SEIR, susceptible-exposed-infected-removed.

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**Table 1. Prior and posterior median (with 95% central credible interval, the Bayesian counterpart of the frequentist confidence interval) of parameter for the SEIR model of smallpox**

| Parameter | Prior | Posterior (SEIR model) | Posterior (SEIR with heterogeneity) |
|---|---|---|---|
| $R_{0,e}$ | 4 (0.7, 23.7) | 7.1 (5.0, 15.3) | 6.8 (5.4, 10.4) |
| $R_{0,u}$ | 4 (0.7, 23.7) | 17.5 (5.9, 59.5) | 16.3 (7.2, 36.6) |
| $\sigma_e$ | — | 0.021 (0.017, 0.032) | 0.021 (0.017, 0.026) |
| $\sigma_u$ | — | 0.146 (0.110, 0.222) | 0.139 (0.110, 0.185) |
| % Fatality, $\mu_e$ | 0.14 (0.03, 0.35)* | 0.12 (0.08, 0.19) | 0.12 (0.09, 0.16) |
| % Fatality, $\mu_u$ | 0.45 (0.08, 0.95)* | 0.37 (0.30, 0.50) | 0.36 (0.30, 0.43) |
| Latency period–up to prodromal | 12.1 (7.9, 17.6) | 10.3 (6.3, 15.9) | 8.8 (5.8, 13.1) |
| Latency period–prodromal | 2.5 (1.3, 4.3) | 2.3 (1.2, 3.9) | 2.1 (1.1, 3.7) |
| Infectious period, $1/\gamma$ | 15.8 (10.9, 22.0) | 13.4 (8.8, 19.6) | 11.5 (7.7, 16.1) |
| Old World heterogeneity $k_e$ | 2.8 (0.10, 14.8) | — | 358 (198, 976) |
| New World heterogeneity $k_u$ | 2.8 (0.10, 14.8) | — | 2,712 (415, 17,579) |

Note that, although the 95% central credible interval on $R_0$ has a smaller range for the heterogeneity model than for the model without heterogeneity, the median value is approximately the same for the two models. The similarity of the medians suggests that the major effect on the marginal distribution of $R_0$ of allowing for heterogeneity in susceptibility is a reduction in the long tail, which is confirmed by an examination of the full distribution (see supporting information). Also, following standard terminology (2), the heterogeneity parameter $k$ is the inverse of the squared coefficient of variation of the distribution of susceptibility. The large values shown here therefore indicate very low levels of heterogeneity. SEIR with heterogeneity refers to a version of the SEIR model that includes heterogeneity in susceptibility (see supporting information). The prodromal period occurs between the onset of fever and the beginning of a rash. The subscript *e* stands for exposed, Old World populations, whereas the subscript *u* stands for unexposed, New World populations.

*Intervals based on 500,000 simulated draws from a mixture reflecting the hyperprior structure.

$\gamma, \mu, \sigma^2 \mid$ ), , , $\pi(R_0)$, $\pi(\alpha)$, $\pi(\gamma)$, $\pi(\mu)$, $\pi(\sigma^2)$, , , $L($ $\mid R_0, \alpha, \gamma, \mu, \sigma^2)$.

(*Methods* ).

13 ( 3) ,

. 2.

. A ( ). (5, 7, , 11) (3, ) A A

$R_0$

A $R_0$

$R_0$ ,

(12, 13),

(12, 14) ,

(4, 5) ,

*et al.* (11).

( *Supporting Text* *et al.*). *et al.* (11)

*et al.* (11)

## Results and Discussion

( 1).

$R_0$

( 1).

2

$R_0$

$R_0$ $\sigma^2$.

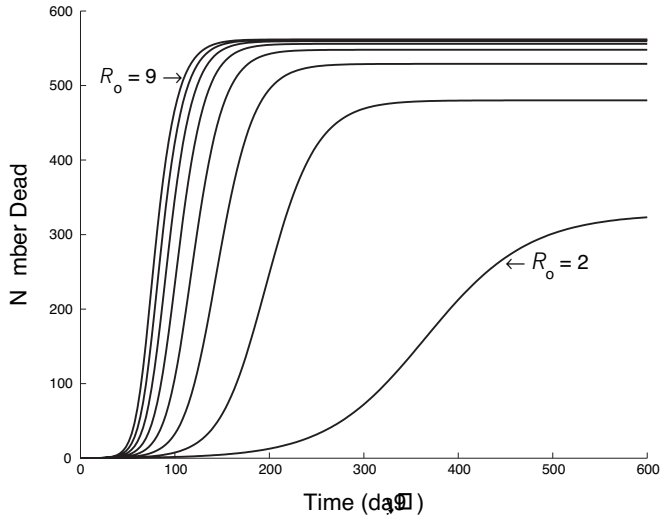


**Fig. 1.** Impact of changing $R_0$ on epidemic dynamics in the SEIR model (Eq. **1**). All other parameters are fixed. As $R_0$ increases (by ones from one line to the next), the cumulative death curves are increasingly similar.

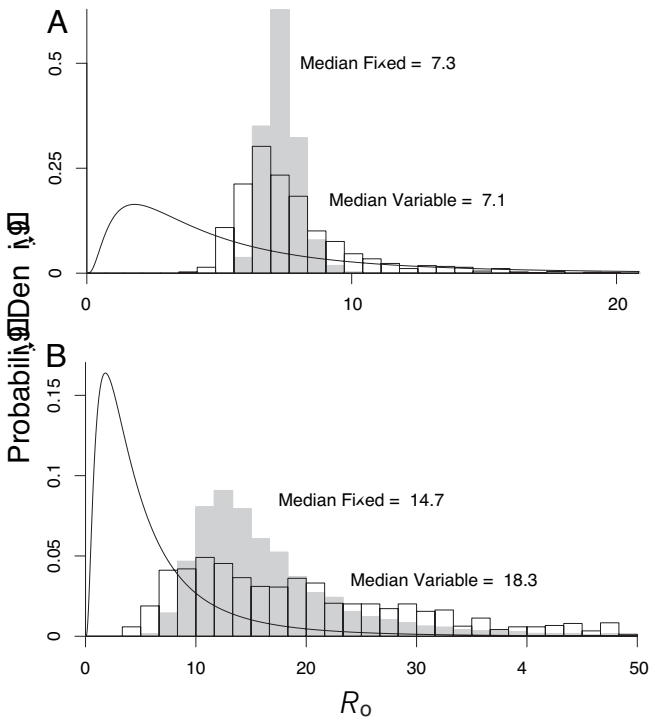


**Fig. 2.** Effects of prior knowledge on uncertainty in the disease transmission rate $R_0$. We distinguish between epidemics in Old World populations and New World populations because epidemics were more severe in New World populations, apparently because of differences in previous exposure and social structure (15). Because it is not clear which group is more similar to contemporary populations, we consider each separately. Shown are the estimated posterior density of $R_0$ for Old World and New World populations, respectively. The curved black line shows the prior distribution. The gray histogram shows the case in which we assume that there is no uncertainty in any SEIR model parameter except $R_0$ (''fixed''), whereas the black-outlined histogram shows the case in which we instead assume that all model parameters are uncertain, and we have integrated out all of the other parameters (''variable''). The gray histogram thus is equivalent to assuming that disease parameters besides $R_0$ have zero uncertainty, showing that such an assumption conceals substantial uncertainty. Note differences in scales on the axes.

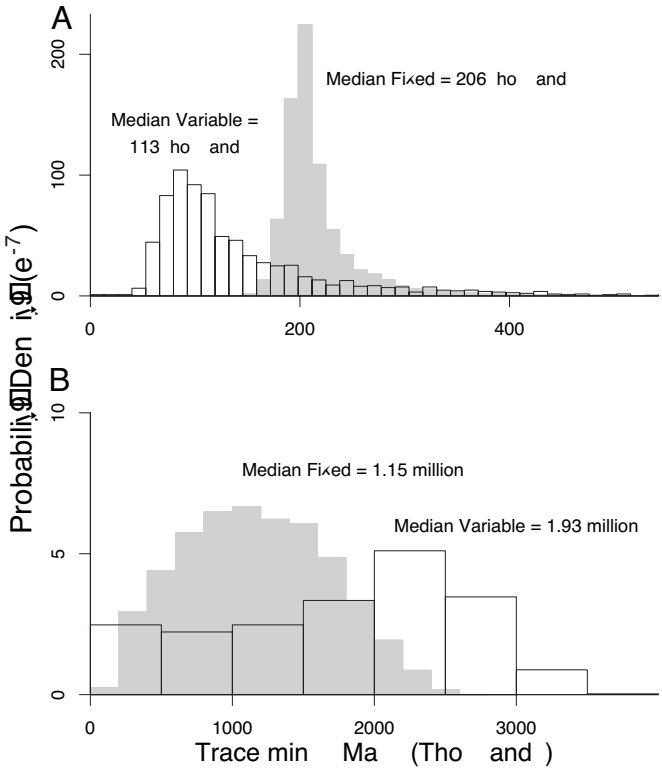


**Fig. 3.** Difference in the number of deaths between trace vaccination and mass vaccination strategies in a simulated population of 10 million. (*A*) Using parameters based on Old World populations. (*B*) Using parameters based on New World populations. As in Fig. 2, comparison of the gray- and black-outlined histograms shows the effects of neglecting uncertainty in parameters other than $R_0$ and $\sigma^2$. Note differences in scales on the axes.

## Methods

**Prior Construction.**

$$R_{0,e} \sim \mathbf{LN}(m_e, \sigma^2_{R_{0,e}}), \quad R_{0,u} \sim \mathbf{LN}(m_u, \sigma^2_{R_{0,u}}),$$

$$p(\sigma^2_e) \propto 1, \quad \sigma^2_e > 0, \quad p(\sigma^2_u) \propto 1, \quad \sigma^2_u > 0,$$

$$\alpha = \frac{1}{\alpha_1 + \alpha_2},$$

$$\begin{aligned} \alpha_1 &\sim \Gamma( \quad = 2.6, \quad = 0.6), \\ \alpha_2 &\sim \Gamma( \quad = 12.3, \quad = 6.1), \\ 1/\gamma &\sim \Gamma( \quad = 16.0, \quad = \ .0), \\ \mu_e &\sim \mathbf{Be}(a_e, b_e), \quad \mu_u \sim \mathbf{Be}(a_u, b_u), \end{aligned} \qquad [3]$$

$$\frac{a_e}{a_e + b_e} \sim \mathbf{Be}(5, 17), \quad \frac{a_u}{a_u + b_u} \sim \mathbf{Be}(4, 4.5),$$

$$\begin{aligned} a_e &\sim \Gamma( \quad = 30, \quad = 150), \\ a_u &\sim \Gamma( \quad = 4, \quad = 4), \end{aligned}$$

$$k_e \sim \Gamma(\quad = 4, \quad = 16),$$
$$k_u \sim \Gamma(\quad = 4, \quad = 16).$$

$a_e$, $b_e$, $a_u$, $b_u$, **Γ**, **LN**, **Be** $e$ $u$

**Likelihood Calculation.** (10, 1 ). A 1, 1 ( 3) $R_0$ *Results and Discussion*,

$$\quad _{ij} \sim \mathbf{N}(\quad _{ij}, \sigma_l^2)$$
$$\quad _{ij} = \mu_l f(R_{0,l}, \alpha, \gamma). \qquad [4]$$

$_{ij}$ $_{ij}$ $j$, $f(R_{0,l}, \alpha, \gamma)$ (15),

(22, 24) k ( 3 . 25). A (26, 27) (17). ( ). (26). ( , 2 ).

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