

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

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Concerns over bioterrorism and emerging diseases have 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 such effects, we used Bayesian statistics to rigorously estimate the uncertainty in the parameters of an epidemic model, focusing on smallpox bioterrorism. We then used a vaccination model to translate the uncertainty in the model parameters into 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 show that the uncertainty in the model parameters is remarkably high and that this uncertainty has important implications for vaccination strategies. For example, under one plausible scenario, the most likely outcome is that mass vaccination would save $\approx 100,000$ 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 thus has the advantage of preventing outcomes that are only slightly less likely but that are substantially more horrific. Rigorous estimates of uncertainty thus can reveal hidden advantages of public health strategies, suggesting that formal 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 predictions of epidemic models are widely used in planning for public health responses to both bioterrorism and emerging diseases (1). An important source of uncertainty in such predictions is uncertainty in parameter values. Even simple epidemic models can capture disease dynamics remarkably well (2, 3), however, so most modeling studies have relied on informal methods for quantifying uncertainty in parameter values (3–9). In this article, we formally estimate the uncertainty in the parameters of a model of smallpox bioterrorism, and we show how such uncertainty estimates can reveal hidden risks of public health decisions.

To describe the dynamics of smallpox, we use the well known susceptible-exposed-infected-removed (SEIR) model (2):

$$\begin{aligned} \frac{dS}{dt} &= \frac{-R_0\gamma}{N} SI, \\ \frac{dE}{dt} &= \frac{R_0\gamma}{N} SI - \alpha E, \\ \frac{dI}{dt} &= \alpha E - \gamma I, \\ \frac{dR}{dt} &= \gamma I. \end{aligned} \quad [1]$$

R_0 is the number of secondary infections produced by a single infected individual, γ is the rate at which infectious individuals I cease to be infectious because of recovery or death, and N is the population size, here assumed to be of a single city. Hosts begin in the uninfected, nonimmune class S and move to the exposed but not yet infectious class E at a rate $R_0\gamma$. Exposed but not yet infectious individuals move to the infectious class at rate α . To fit the model to mortality data, we also introduce the parameter μ , the fraction of removed individuals that die of the disease.

The SEIR model has several useful features for estimating uncertainty in the predictions of epidemic models. First, because the model is based on assumptions that are approximately true for many diseases (2), it can be used for diseases other than smallpox (7, 9, 10), emphasizing the generality of our approach. Second, although the SEIR model has only four parameters, it provides a good fit to data for historical smallpox epidemics (3). The number of parameters in our model is important because concerns over the complexity of disease spread have caused some researchers to instead construct complex models with tens to hundreds of parameters (4–6). Estimating the values of a large number of parameters, however, requires a large amount of data, making it impractical to formally quantify parameter uncertainty for complex models. Because the SEIR model in contrast includes only four parameters, estimating the overall uncertainty in its parameters is relatively straightforward. Moreover, as we discuss further below, uncertainty in model predictions is likely to be even higher for models with many parameters.

A common method of quantifying the effects of parameter uncertainty on the predictions of epidemic models is sensitivity analysis, in which one or a few parameters are varied, whereas the others are held constant (4, 6). Sensitivity analysis, however, generally underestimates overall parameter uncertainty. We therefore instead use Bayes’ Theorem, which allows us to formally take into account uncertainty in all parameters (see supporting information, which is published on the PNAS web site):

$$P(R_0, \alpha, \gamma, \mu, \sigma^2 | \text{data}) \propto \pi(R_0) \pi(\alpha) \pi(\gamma) \pi(\mu) \pi(\sigma^2) \mathcal{L}(\text{data} | R_0, \alpha, \gamma, \mu, \sigma^2). \quad [2]$$

Here, σ^2 represents the random variation in the data beyond what can be explained by the SEIR model. The uncertainty in the model’s parameters then is represented by the spread in the posterior distribution of the parameters given the data, $P(R_0, \alpha,$

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

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Table 1. Prior and posterior medians (with 95% central credible intervals, the Bayesian counterpart to the frequentist's confidence interval) of parameters 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)
σ_e	—	0.021 (0.017, 0.032)	0.021 (0.017, 0.026)
σ_u	—	0.146 (0.110, 0.222)	0.139 (0.110, 0.185)
% Fatality, μ_e	0.14 (0.03, 0.35)*	0.12 (0.08, 0.19)	0.12 (0.09, 0.16)
% Fatality, μ_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.

γ , μ , σ^2 | data), which depends on the prior uncertainty in the parameters, $\pi(R_0)$, $\pi(\alpha)$, $\pi(\gamma)$, $\pi(\mu)$, and $\pi(\sigma^2)$, and on the likelihood of the data, $L(\text{data} | R_0, \alpha, \gamma, \mu, \sigma^2)$.

We used Bayes' Theorem in the following way. First, we constructed priors for the parameters from literature data on smallpox progression (*Methods* and supporting information). Second, we calculated the likelihood of the parameters from data on 13 past smallpox epidemics (listed in Table 3). Third, we combined the likelihood and the priors to calculate the joint posterior distribution of the parameters, according to Bayes' Theorem, Eq. 2. We thus allowed for uncertainty in all model parameters, and we combined information from all available data. Although alternative approaches also might have allowed us to combine data, such approaches are generally less efficient (see supporting information). Similarly, although previous researchers also have used multiple data sets, in so doing they have assumed that the uncertainty in some (5, 7, 8, 11) or all (3, 9) other parameters is zero. As we will show, this assumption leads to serious underestimates of parameter uncertainty. Also, in estimating a single value of R_0 from multiple epidemics, we are effectively assuming that contact networks were the same in different populations. Although this assumption is undoubtedly unrealistic, allowing for population-specific values of R_0 very likely would lead to even more uncertainty in the parameters. Because our intent is to demonstrate that uncertainty is high, assuming a common value of R_0 thus is conservative.

To show how uncertainty in parameter values can lead to uncertainty in evaluations of public health responses to epidemics, we translated parameter uncertainty into uncertainty in the relative efficiency of two different vaccination strategies. The two strategies are mass vaccination, under which the entire population is vaccinated at the beginning of the epidemic, and trace vaccination, under which vaccinations are given only to those who contact infected individuals. Although mass vaccination is the policy of the U.S. and U.K. governments (12, 13), trace vaccination was used in the final stages of smallpox eradication (12, 14) and, recently, some researchers have argued that it will be as effective as mass vaccination while, of course, being cheaper (4, 5). These two strategies are not the only possibilities,

but they allow us to clearly show how uncertainty in parameters is translated into uncertainty in strategy evaluations.

The particular vaccination model that we used was developed by Kaplan *et al.* (11). For our purposes, this model is convenient because it is essentially the SEIR model with the addition of either mass or trace vaccination (see *Supporting Text* for details of the Kaplan *et al.* model). The Kaplan *et al.* (11) model thus inherits assumptions of the SEIR model, such as exponential sojourn times in each stage and homogeneous mixing of individuals, that are not necessarily realistic. We therefore emphasize that we use this model not because it is necessarily the best model, but because our aim is to illustrate the effects of parameter uncertainty on evaluations of vaccination strategies rather than to identify the best of all possible strategies. We therefore compared the two vaccination strategies in the following way. First, we drew a large number of sets of parameter values from the posterior distribution of the SEIR parameters. Second, we used each set of parameters in simulations of the Kaplan *et al.* (11) model, first under trace vaccination and second under mass vaccination, to calculate the difference in the number of people dying between the two strategies for each parameter set. Our evaluation of the relative efficiency of the two strategies thus considers both the most likely difference in the number dead and the uncertainty in the difference in the number dead.

Results and Discussion

Our results show that the overall uncertainty in the parameters of the SEIR model is remarkably large (Table 1). Part of the reason is that, when fitting the model to the epidemic data, it becomes harder to distinguish among epidemic curves as R_0 increases (Fig. 1). The prior uncertainty in the parameters, however, also contributes substantially to the overall uncertainty. To illustrate this effect, in Fig. 2 we show that the marginal distribution of R_0 is much wider when we allow for uncertainty in all parameters than it is when we allow for uncertainty only in R_0 and the error parameter σ^2 .

The uncertainty in the parameters has important consequences for uncertainty in the relative effectiveness of the two vaccination strategies. When the likelihood is calculated from

$$k_e \sim \Gamma(\text{mean} = 4, \text{var} = 16),$$

$$k_u \sim \Gamma(\text{mean} = 4, \text{var} = 16).$$

Here, the hyperparameters on the fatality rate are a_e , b_e , a_u , and b_u , and Γ , LN, and Be denote gamma, log-normal, and beta distributions, respectively. Note that e stands for previously exposed Old World populations, whereas u stands for previously unexposed New World populations.

Likelihood Calculation. In fitting the SEIR model, we considered only epidemic data because of the difficulty of fitting the complex fluctuations typical of endemic data (10, 18). Also, we used only 18th and 19th century epidemics (Table 3) to avoid the complication of vaccination. In using epidemic data from previous centuries, we are implicitly assuming that parameters estimated from such data are relevant to contemporary populations. Given that R_0 in particular is likely to vary in a complex way across centuries, because, for example, of changes in social mixing or access to information regarding smallpox, it is likely that, in fact, smallpox spread rates would be different in contemporary populations. Nevertheless, as we describe in *Results and Discussion*, allowing for differences between historical and contemporary populations almost certainly would increase the uncertainty in the parameters, reemphasizing our main point. Moreover, in using historical data, we are following essentially all previous smallpox modeling studies; given that our goal is to suggest a modification to the methodology of such studies, using historical data is appropriate.

The likelihood is then based on

$$\begin{aligned} \text{Data}_{ij} &\sim \text{N}(\text{Dead}_{ij}, \sigma_I^2) \\ \text{Dead}_{ij} &= \mu_I f(R_{0,I}, \alpha, \gamma). \end{aligned} \quad [4]$$

Here, Data_{ij} and Dead_{ij} are, respectively, the observed and predicted number of individuals who died in the i th epidemic at time j , and $f(R_{0,I}, \alpha, \gamma)$ is the model's prediction of the number of individuals recovering and dying. Because of differences between Old World and New World populations, we allowed some parameters to differ between them (15), and so I indicates whether a population is Old World or New World. Note that we assume that the errors in the fit of the model to the epidemic data

are normally distributed. Our reasoning for this choice is that the population sizes in the epidemic data were in the hundreds; for such sample sizes, a normal distribution typically provides a good approximation to a binomial distribution. Moreover, the normal distribution is computationally convenient, particularly in the current Bayesian context. More generally, using a binomial distribution would be equivalent to assuming that all of the error in the fit of the model is simply binomial sampling error. A normal distribution in contrast allows the magnitude of the error to be independent of its mean size and, thus, is in this case a conservative choice.

An important feature of our likelihood calculation is that, because of the sparseness of the observations over time, we assumed that any discrepancies between the model and the data were due to independent recording errors. Because modeling the (positive) autocorrelation process probably would have increased overall uncertainty, this is a conservative assumption. We thus assumed that stochasticity in transmission was manifest between epidemics, rather than within epidemics. Previous work (22, 24) in contrast has focused on stochasticity within epidemics, particularly that due to small population sizes. The population sizes in our data set, however, were large enough that such stochasticity was probably weak (Table 3; ref. 25). A related issue is that previous Bayesian smallpox analyses have used the even simpler SIR model and have considered only single epidemics (26, 27) or exponential growth of the infected class (17). By using the SEIR model, and by considering multiple epidemics, our estimates should better reflect overall uncertainty.

The likelihood was evaluated numerically by solving the differential equations with standard methods (see supporting information). Because of the complexity of the likelihood, the posterior distribution can be formulated only up to the proportionality constant and can be evaluated only pointwise. To generate samples from the posterior, we therefore followed standard practice in using a Markov chain Monte Carlo algorithm that replaces each multidimensional random draw with a sequence of single-parameter, or at least lower-dimensional, draws (26). We assessed convergence by using standard Brooks-Gelman and Geweke criteria (28, 29).

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