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Population-level differences in disease transmission: A Bayesian analysis of multiple smallpox epidemics

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ABSTRACT

Estimates of a disease's basic reproductive rate R_0 play a central role in understanding outbreaks and planning intervention strategies. In many calculations of R_0, a simplifying assumption is that different host populations have effectively identical transmission rates. This assumption can lead to an underestimate of the overall uncertainty associated with R_0, which, due to the non-linearity of epidemic processes, may result in a mis-estimate of epidemic intensity and miscalculated expenditures associated with public-health interventions. In this paper, we utilize a Bayesian method for quantifying the overall uncertainty arising from differences in population-specific basic reproductive rates. Using this method, we fit spatial and non-spatial susceptible-exposed-infected-recovered (SEIR) models to a series of 13 smallpox outbreaks. Five outbreaks occurred in populations that had been previously exposed to smallpox, while the remaining eight occurred in Native-American populations that were naïve to the disease at the time. The Native-American outbreaks were close in a spatial and temporal sense. Using Bayesian Information Criterion (BIC), we show that the best model includes population-specific R_0 values. These differences in R_0 values may, in part, be due to differences in genetic background, social structure, or food and water availability. As a result of these inter-population differences, the overall uncertainty associated with the "population average" value of smallpox R_0 is larger, a finding that can have important consequences for controlling epidemics. In general, Bayesian hierarchical models are able to properly account for the uncertainty associated with multiple epidemics, provide a clearer understanding of variability in epidemic dynamics, and yield a better assessment of the range of potential risks and consequences that decision makers face.

1. Introduction

Answers to questions about disease dynamics often require that we determine how a disease will spread through a population (Anderson and May, 1991; Kermack and McKendrick, 1927; Keeling and Grenfell, 2002; Rohani et al., 1999). One way to quantify disease spread is via the basic reproductive rate of spread (R_0) based on compartmental models, such as the susceptible-exposed-infected-recovered (SEIR) model (Anderson and May, 1991; Kermack and McKendrick, 1927). When temporal data sets are available for multiple outbreaks, these models have often been fitted to each outbreak separately, with individual outbreak R_0 values summarized via a range from the lowest to the highest estimate (Gani and Leach, 2001; Smith et al., 2008; Giraldo and Palacio, 2008) or as quantile intervals (Mills et al., 2004; Valleron et al., 2010). The differences in R_0 estimates in individual outbreaks may be due to a variety of factors, including environmental issues associated with each outbreak, or biological or societal characteristics of the populations. Indeed, social characteristics such as contact rates between individuals are known to have important consequences for disease spread (Mossong et al., 2008; Hethcote, 2000). Such an approach, however, produces only a range of estimated values for the data at hand, and is not able to provide a measure of uncertainty surrounding the population-average estimates of key disease characteristics. Bayesian hierarchical methods, on the other hand, present a statistical framework that can readily provide not only an estimate of R_0, but also quantify the uncertainty around it via the credible intervals (O'Neill, 2002; Jewel et al., 2009). The uncertainty estimates can then be used to predict the best- and worst-case scenarios in the event of a future epidemic, providing information that public-health officials may use to help guide policy decisions.

In this paper, we use a Bayesian hierarchical framework to estimate R_0 based on a set of smallpox (*Variola major*) outbreaks that accounts for the variability among individual outbreaks. This paper extends our earlier work which outlined a basic approach for quantifying uncertainty in R_0 based on data from multiple epidemics

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Table 1
List of epidemics used in the smallpox outbreak models.

Epidemic	Date(s)	Population size	Cumulative mortality	No. of susceptibles (S_0)	No. of data points (n)
San Francisco Xavier, Chihuahua	8/1780 – 12/1780	261	110	260	6
San Buenaventura, NM	11/1780 – 4/1781	501	137	500	6
Santa Clara, NM	12/1780 – 6/1781	627	218	626	7
Saint Lawerence, NM	1/1781 – 4/1781	215	75	214	5
Santo Domingo, NM	1/1781 – 5/1781	578	272	577	6
Pojoaque, NM	1/1781 – 3/1781	270	62	269	4
Rosalia, Baja Sur	1/1781 – 4/1781	133	58	132	5
Santo Domingo de la Frontera, Baja	8/1781 – 3/1782	119	41	118	8
Boston	1721	10,565	844	6739	8
Burford	1758	1520	182	1519	5
Chester	1774	12,009	202	3063	13
Warrington	1773	7000	211	2250	13
Mauritius	1891	37,110	492	11,504	14

Native-American mission initially susceptible population size was derived from the census of 1777 (Adams and Chavez, 1956) and 1778 (Archivo General de Indias, 1778). Forecasting of population size up to the time of the epidemic was carried out using background birth and death rates from literature sources (Jackson, 1983, 1981, 1994; Archivo General de Indias, 1778). The main source for the description of the mission epidemics is from Fenn (1999).

(Elderd et al., 2006) into an approach which quantifies the overall uncertainty in R_0 while explicitly modeling variability and spatial relationships between epidemics. By using a hierarchical approach to properly quantify the uncertainty, we can obtain more realistic estimates of disease spread and transmission, which can then be used to answer fundamental questions regarding epidemics and applied questions regarding disease control.

2. Methods

2.1. Smallpox data

In previous work, we used Bayesian techniques to show that fitting standard disease models to historical data of smallpox (*Variola major*) outbreaks leads to highly uncertain parameter estimates (Elderd et al., 2006). Here, we extend that work to consider additional models that incorporate a variety of spatial and non-spatial processes. The data set comprises 13 separate epidemics, eight of which occurred in Native-American populations and five of which occurred in mixed populations of European/African descent (Table 1). The Native-American populations were located at Jesuit missions in what is now the southwestern United States and Mexico, and, in every case, the host population had not previously experienced a smallpox outbreak. In every population of European/African descent, there was at least some history of exposure to smallpox. Due to this dissimilarity, in our analyses we allow for differences between Native-American (*NA*) populations and populations of European/African-descent (*EA*).

The mission populations in particular were in close spatial proximity of each other, and the epidemics occurred at roughly the same time (Fig. 1). This allowed us to ask not only whether population-level differences matter but also whether these outbreaks were spatially correlated. For instance, the populations at different missions consisted of different Native American tribes each with different genetic backgrounds and societal customs. Additionally, some missions were occupied seasonally while others were occupied year-round, depending upon location and on how climate affected local food production (Jackson, 1994). Each of these factors could and most likely did contribute to population-level differences in disease transmission. In the populations of European/African-descent (Table 1), there may also have been underlying differences due to age-structure (Creighton, 1891) or other environmental factors that can affect disease dynamics (Keeling and Rohani, 2008). Our analyses show that these dissimilarities between populations lead to dramatic and important differences in estimates of the transmission parameter R_0.

2.2. The general model

To carry out inference about smallpox transmission, we began with a relatively simple disease model, the SEIR model (Anderson and May, 1991):

$$\frac{dS}{dt} = -\frac{R_0\gamma}{N}SI, \tag{1}$$

$$\frac{dE}{dt} = \frac{R_0\gamma}{N}SI - \alpha E, \tag{2}$$

$$\frac{dI}{dt} = \alpha E - \gamma I, \tag{3}$$

$$\frac{dR}{dt} = \gamma I. \tag{4}$$

Here, R_0 represents the number of secondary infections produced by a single infected I individual entering a completely susceptible S population (Anderson and May, 1991), while γ is the rate at which infectious individuals recover. N equals the total number of individuals in the population, which is assumed to be constant over the course of the epidemic. We, thus, assume that the epidemic moves through the population rapidly enough that births and non-disease-related deaths do not matter (Keeling and Rohani, 2008). Parameter α represents the rate at which individuals leave the latent class E and enter the infectious class I. For smallpox, the latency period, $1/\alpha$, is the time between contracting the disease and becoming infectious. The latency period actually consists of two distinct stages, a non-contagious period during which the individual exhibits no symptoms and a second non-contagious period during which the infected individual develops a fever and other flu-like symptoms (Fenner et al., 1998). The latter is considered the prodromal period, which we assume, as have others (Eichner and Dietz, 2003; Fenner et al., 1998), is part of the latency period. The infectious period begins when the individual develops the classic "pox"-like rash associated with the disease, and ends with the disappearance of the rash (Fenner et al., 1998). Note that the inverse of α is the average latency period length, while the inverse of γ is the average infectious period length. Individual latency and infectious periods are assumed to be exponentially distributed.

We further assume that a fraction μ of the recovered R individuals die. The individuals who have died comprise the historical outbreak data that we use in our analysis. In general, the SEIR model has been shown to provide a good fit to data for historical smallpox epidemics (Gani and Leach, 2001; Elderd et al., 2006) and has formed the basis for several models used to assess public-health intervention (Kaplan et al., 2002; Eichner, 2003; Elderd et al., 2006).

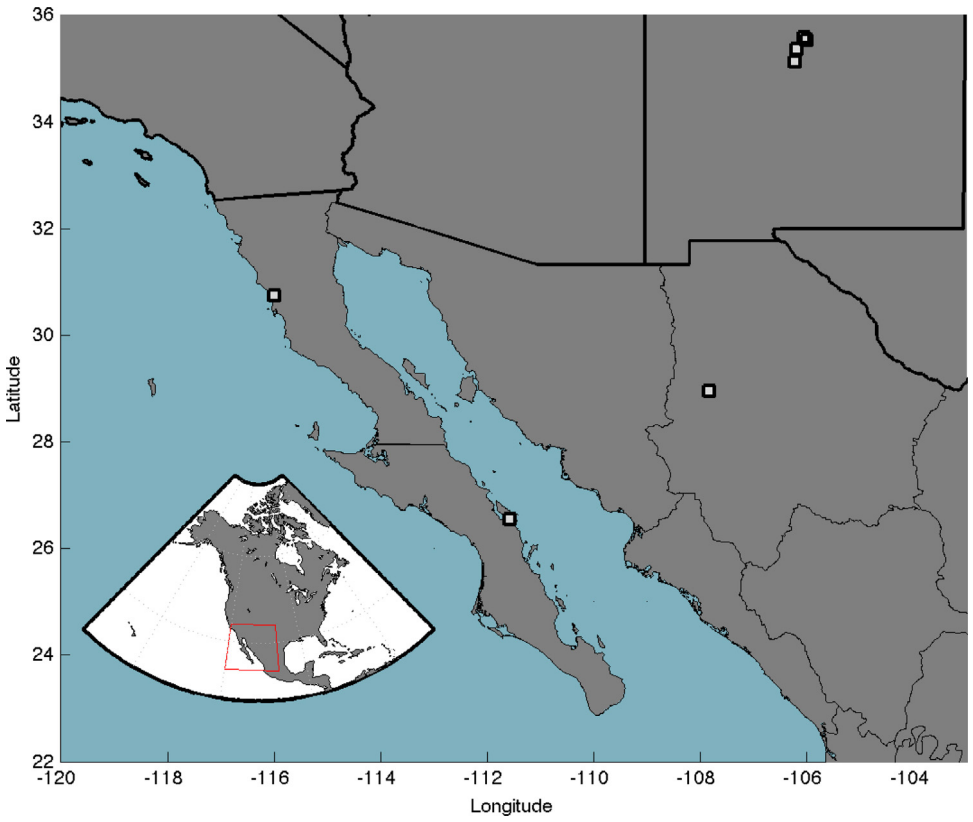

Fig. 1. Map of the locations of the eighteenth century Native-American mission epidemics. The squares represent the locations of the missions. Note the close proximity of the five missions in central New Mexico. The square in the inset shows the location of the missions on a broader scale.

2.3. Bayesian approach

Bayesian approaches to inference in epidemics have been been growing in popularity over the past two decades (O'Neill and Roberts, 1999; O'Neill, 2002; Elderd et al., 2006; Jewel et al., 2009), partly because it provides a number of advantages compared to a frequentist approach (Gelman et al., 2003). Moreover, these advantages apply to many epidemiological problems and are not limited to the problem we consider here. To explain these advantages, we first consider Bayes' theorem:

$$P(\Theta|\text{data}) \propto \pi(\Theta)\,\mathcal{L}(\Theta|\text{data}), \tag{5}$$

which states that the posterior probability of the model parameters Θ given the data, $P(\Theta|\text{data})$, is proportional to the prior information of the parameters, $\pi(\Theta)$, times the likelihood, $\mathcal{L}(\Theta|\text{data})$, which is a function of the parameters conditional on the data. Proportionality holds as long as the likelihood is integrable with respect to the prior. The likelihood can be based on data from a single outbreak or from multiple outbreaks. Prior knowledge about the parameters in the model, described by the prior density $\pi(\Theta)$, can be derived from expert opinion as well as from external information such as hospital records or case studies of the natural course of the disease (Elderd et al., 2006). When little or no prior information is available, the prior should have little or no influence on the posterior probability (Gelman et al., 2003). However, when prior information is available, the Bayesian approach provides an advantage for analyzing epidemics because it allows us to explicitly combine information in the epidemic data with prior (external) sources of information. Moreover, the Bayesian framework allows for a formal quantification of uncertainty in all model parameters jointly. This is a substantial advantage over sensitivity analyses for epidemic models that have been conducted using informal methods (Bozzette et al., 2003; Halloran et al., 2002). In such cases, quantification of overall uncertainty in model predictions or decisions based on those predictions, has been limited.

The Bayesian approach also naturally facilitates different ways of modeling variability in the data. The underlying idea is that if the values of the disease's basic reproductive rate, R_0, vary between different smallpox epidemics, these epidemics will vary in severity. In our simplest model, a single global R_0 for the thirteen epidemics is described by a log-normal probability distribution (Fig. 2A). This reflects the belief that the epidemics would be more severe if the R_0 value happens to be in the upper tail of the distribution, and that the epidemics would be milder if the R_0 value happens to be in the lower tail.

We compare this simple model to a more complex model, where each of the 13 outbreaks (populations) has its own value of R_0, denoted R_i for the ith population. The difference between this and the simpler model is that in the simpler model each outbreak has the same R_0, whose uncertainty is described by a global distribution of R_0 values, whereas in the more complex model each outbreak has a different R_0 (R_i), assumed to be a randomly drawn value from the global R_0 distribution and with uncertainty described by its own separate distribution (Fig. 2B). In the more complex model, we therefore estimate both the "population average" or R_0 across all populations and the population-specific R_i values, whereas in the simpler model we estimate only the single R_0 across all populations. As we will show, the model that allows for population-specific R_i values provides a much better explanation for the data. The typical assumption that there is a single common R_0 for all populations can therefore result in an underestimate of the uncertainty in the global value of R_0.

The data associated with the 13 smallpox epidemics propagate through the likelihood of the SEIR model (Eq. (1)–(4)) via Bayes'

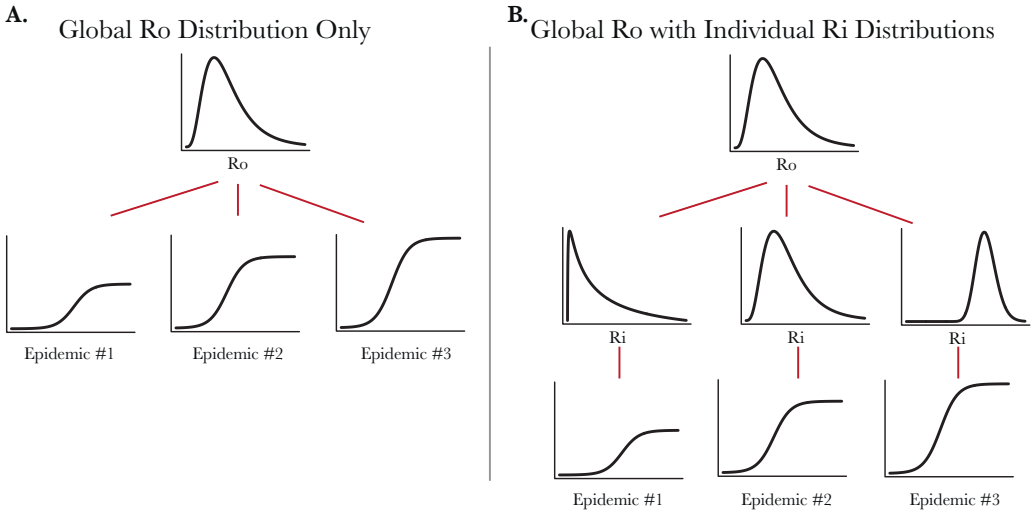

Fig. 2. Two hierarchical structures used to model the relationship between the reproductive rate R_0 and the epidemic outcome: (A) The model assumes a global distribution of R_0 and three separate instances of possible resulting epidemics, (B) the model assumes each population has its own R_0, called R_i, that is randomly sampled from a global distribution of R_0. For our data, there were two global R_0s – one associated with the populations of European/African descent and the other associated with the Native-American populations. The above sets of outbreaks were linked by shared parameters that were also allowed to vary. These parameters, such as the infectious period of the disease, are not shown for clarity.

Theorem (Eq. (5)). For the simple model, where we have a single R_0 for all epidemics, we formally update our prior knowledge about the epidemic parameters as follows:

$$P(R_0, \alpha, \gamma, \mu, \sigma^2|\text{data}) \propto \pi(R_0)\pi(\alpha)\pi(\gamma)\pi(\mu)\pi(\sigma^2)$$
$$\mathcal{L}(R_0, \alpha, \gamma, \mu, \sigma^2|\text{data}). \quad (6)$$

Here, the posterior probability of the parameters $P(R_0, \alpha, \gamma, \mu, \sigma^2|\text{data})$ is proportional to the product of the prior probability densities of those parameters, $\pi(R_0)$, $\pi(\alpha)$, $\pi(\gamma)$, $\pi(\mu)$, and $\pi(\sigma^2)$, and the likelihood $\mathcal{L}(R_0, \alpha, \gamma, \mu, \sigma^2|\text{data})$. Note that σ^2 represents the variance of the random observational errors in the data beyond what can be explained by the SEIR model. We assume that these errors are uncorrelated over time, and normally distributed with mean 0 and variance σ^2. The implied distribution of the observed number of deaths in a single population i at time t, $f(\text{data}_{it}|R_0, \alpha, \gamma, \mu, \sigma^2)$, is then also normal, based on the following:

$$\text{data}_{it} = \mu \text{SEIR}_{it} + \epsilon_{it}, \quad (7)$$

where μ is the mortality rate, SEIR_{it} is the solution of the SEIR system (Eq. (1)–(4)) for the number of recovered people in population i at time t, and $\epsilon_{it} \sim N(0, \sigma^2)$. Note that while the normality assumption in theory allows negative values for mortality counts, the variance σ^2 will usually be small enough that this does not occur in practice.

The above model assumes that each separate epidemic has the same value for each parameter in the SEIR model. While this is a reasonable assumption for parameters associated with the latency or infectious period, this is unlikely to hold true for R_0, whose value may be affected by differences in biological and societal factors (Anderson and May, 1991). Given the framework of Eq. (6), however, we can easily expand upon the model by increasing model complexity. In particular, we can account for differences between epidemics in each population and spatial autocorrelation between populations, as we outline next.

2.4. Individual smallpox epidemics

To quantify the *a posteriori* uncertainty associated with the global smallpox R_0, we used the data from 13 smallpox outbreaks that occurred before the widespread use of vaccination. Five of the epidemics took place in populations of European/African descent (Table 1). These outbreaks occurred in New England, England, and Mauritius and were both spatially and temporally distant. For instance, the outbreak on the African island of Mauritius occurred over a century after the final European outbreak in our data set. These five populations were similar in that all had been previously exposed to smallpox. There is at least some evidence, however, that there were differences in age structure between some of these populations, possibly because the populations differed in the time since previous epidemics (Anderson, 1918; Creighton, 1891). While these age differences may systematically affect R_0 values, our models do not account for age structure. This choice was made based on the difficulty with reliable estimation of age structures for the populations from historical records, estimating a large number of additional parameters, and describing the mixing and survival rates of the age classes (Keeling and Rohani, 2008). Given the absence of sufficiently detailed prior information about these rates, the identifiability of these additional parameters was expected to be very weak. However, while this historical smallpox analysis does not account for age structure, if age-structure were available, it could explain some of the systematic variation in the data.

The eight mission outbreaks, in what is now the southwestern United States and Mexico (Fig. 1, Table 1), occurred over a relatively short period (1780–1782) and in close geographic proximity. Populations in these missions were all naïve to the disease but differed in other ways. First, each mission most likely contained members of different Native American tribes. The missions of Baja California, for instance, were composed of members of nomadic hunter tribes while the missions of the Sonora region consisted of the semi-sedentary and agriculturally based Northern Pima tribe (Jackson, 1994). The difference in tribal makeup of the missions could have affected disease spread due to either biological or societal factors associated with individual tribes. The missions also experienced different environmental factors that may have affected food and water availability. The missions of Baja California, for example, were used seasonally because the greater aridity of the climate in Baja California limited food production (Jackson, 1994). This difference may similarly have affected disease transmission and spread. The period of time associated with the smallpox outbreaks, however, was too short for seasonality to have explicitly

affected transmission dynamics, like that seen in measle epidemics (Finkenstädt and Grenfell, 2000; Rohani et al., 2002).

The data consist of 13 monthly time series, with total number of individuals who died during each month of an outbreak in each community. The data for the populations of European/African descent are counts of smallpox deaths only (Creighton, 1891; Anderson, 1918), while the Native-American population data include all deaths during the outbreak (Fenn, 1999). Given the low background mortality rates, and the fact that not all smallpox deaths were recorded in the registries (Fenn, 1999), in addition to the relatively short duration of each outbreak, the assumption that deaths in the Native-American populations were entirely due to smallpox does not seem unreasonable. For each epidemic, we anchored the data by adding a zero time point to the time series, so that there is an initial time at which smallpox deaths had not yet begun to occur. This time point was placed at the beginning of the month before the first deaths from smallpox were recorded. Previous analyses (Elderd et al., 2006) did not make this anchoring assumption, which is the reason for slight differences in results reported in this paper as compared to those in Elderd et al. (2006).

Visual inspection of the data strongly suggested that each epidemic in our data set began with the introduction of a small fraction of individuals, and so for simplicity we assumed that the initial number of infected individuals, in each case, was one. In the populations of European/African descent, the initial number of susceptible individuals was derived from published studies (Anderson, 1918; Gani and Leach, 2001), but for Native-American populations, the number of susceptible individuals was unavailable. In these latter populations, however, smallpox was apparently spreading for the first time, and so the initial number of recovered-and-immune individuals can be safely assumed to be zero. For the data from Native-American populations, we therefore assumed that the number of susceptible individuals was equal to the total population size, minus the single infected individual who introduced the disease.

The model prediction for the number of individuals who died each month over the course of each epidemic was obtained as the number of recovered individuals, as predicted by the SEIR model (Eq. (1)–(4)), multiplied by the mortality parameter μ. Observed cumulative monthly mortality is then compared to the cumulative monthly deaths predicted by the model, with the distribution of the discrepancies described by the normal distribution. This was done to match the popular "sum of squares" approach in past analyses by numerous authors (e.g., Elderd et al., 2006; Gani and Leach, 2001; Mills et al., 2004). Note that the use of normal likelihood allows for the possibility that the monthly data may actually be recorded with error (e.g., there could be administrative or counting errors that artificially inflate or deflate the recorded counts). Alternative methods could also be used such as comparing monthly incidence to the SEIR fitted monthly incidence with a normal likelihood or using a truncated normal distribution to compare cumulative mortality to the SEIR fitted cumulative incidence.

We assume that R_0 is the most important parameter varying between populations because R_0 accounts for contact rates between individuals, which are likely to vary between populations because of biological, societal, or environmental factors. In contrast, we have little reason to believe that the other parameters in the SEIR model, such as the average time that an individual is in the latency or infectious period, should differ greatly between epidemics; the processes represented by such parameters are unlikely to be as strongly affected by biological, societal, or environmental factors that vary between populations.

2.5. Prior knowledge about epidemic parameters

A great deal of effort has been devoted to understanding and calculating the length of various smallpox stages and so there are numerous external sources of information. To make the best use of that information, we constructed informative priors from these supplementary data sets. For example, the prior distribution for the latency period was taken to be Gamma distributed which best fits the histograms of observed individual latency periods reported in the literature (Litvinjenko et al., 1973; Gelfand and Posch, 1971; Mack, 1972), while the recovery period prior was derived from Eichner and Dietz's estimates (Eichner and Dietz, 2003). For specific details, we refer the reader to the Supplementary Data, Fig. S2.

A prior distribution for R_0 was also derived from the literature. The prior median of R_0 was set to four, based on previous estimates of R_0 from immunization rates (Anderson and May, 1991). The range of the R_0 prior was derived from previously reported R_0 estimates (Gani and Leach, 2001). To summarize these values with a prior distribution, we used a log-normal distribution, which ranges from zero to infinity, with the highest 95% probability interval of R_0 values set to include all values observed in the literature. In order to make this prior relatively uninformative, the 95% probability interval of the prior distribution was left quite wide, ranging from R_0 values of 0.7 to 23.7. As we will show, the posterior estimates of R_0 were not sensitive to this relatively diffuse prior (see Supplementary Data, Table S1), which is expected as the information in the likelihood is sufficiently strong.

On the contrary, there is relatively little information in the literature about smallpox mortality (or fatality) rates. This is particularly true for the Native-American populations, which had never previously seen such epidemics. Instead, we relied on the mortality estimates reported for European/African populations (Gani and Leach, 2001; Anderson, 1918) and expert opinion for the Native-American populations (Rigau-Pérez, 1982). Since by definition the mortality fraction must be between zero and one, we used a Beta distribution for the prior. Due to the high prior uncertainty about the mortality rate, we also treated the two parameters of that Beta distribution as random variables. The parameters associated with mortality were, thus, allowed to have their own priors, known as hyperpriors (see Supplementary Data, eq. S2). The prior mean of the fatality rate for populations of European/African descent was centered around 16% with a 95% range extending from 5% to 35%. The prior mean of fatality rates for Native-American populations was centered around 49% with 95% of the probability between 8% and 90% (Table 3). The prior distribution of μ is therefore a mixture of Beta distributions over the hyperprior structure. By using a mixture of Beta distributions instead of a single Beta distribution, we allowed for greater uncertainty in these priors, reflecting our lack of knowledge about the associated parameters. Given the wide spread of these priors (Table 3 and see Supplementary Data, Fig. S3), our choice of hyperprior parameter values had little influence on the posterior estimates of μ.

The one parameter in the model for which we have no real prior information is the error variance σ^2. This is natural, however, as this parameter describes the error between the model and the data, and thus depends on both the model and the data. Note that the error variance includes not only the observation error associated with the data and initial conditions but also the error derived from the model's approximation of reality (see Supplementary Data). While some practitioners use a vague Inverse Gamma distribution to describe the prior uncertainty in the error variance, an equally suitable choice is a simple flat prior over a finite range (Gelman et al., 2003), which is what we chose to use. In our models, the error variance will be allowed to differ depending on whether the population was of Native American or European/African descent.

2.6. Candidate models

We considered a suite of nine candidate models, of varying complexity, to assess which model is best supported by the data

Table 2
Comparison of the fit of nine candidate models for estimating R_0 from the smallpox epidemics using BIC scores, ΔBIC, and BIC weights.

Model (summary)	K	BIC	ΔBIC	BIC weights
1. Native-American and European/African populations differ in R_0 – $R_{0,EA}$ & $R_{0,NA}$ only	13	−549.0	96.2	0.0
2. Same as Model 1, except including heterogeneity in infection risk	15	−540.9	104.3	0.0
3. Each population has a separate estimate of R_i	**28**	**−645.2**	**0**	**1.0**
4. Same as Model 3, except including heterogeneity in infection risk	43	−574.9	70.3	0.0
5. Same as Model 3, except R_i for Native-American populations spatially autocorrelated	29	−592.4	52.8	0.0
6. Same as Model 5, except including heterogeneity in infection risk	44	−523.7	121.5	0.0
7. Same as Model 1, except population-level differences in μ	28	−523.7	121.5	0.0
8. Same as Model 1, except population-level differences in epidemic start date	26	−520.8	124.4	0.0
9. Same as Model 3, except error variance distributed as a negative binomial	28	872.0	1572.2	0.0

The model in bold provided the best fit (i.e., the lowest BIC score). Models 3 through 6 and 9 assume inter-population differences in the reproductive rate R_i, whereas Model 1, 2, 7, and 8 assume that the reproductive rate R_0 does not differ within the European/African or Native-American populations.

(Table 2). The models ranged from a simple SEIR model (akin to Eq. (6)) that estimated, separately, a single R_0 and σ^2 for Native-American populations and a single R_0 and σ^2 for populations of European/African descent to a model that allowed the reproductive rate R_0 to be population-specific, with a different value of R_i for each population i (Fig. 2). The latter model assumes that each population has its own basic reproductive rate (R_i) parameter, and that those R_i parameters are distributed according to the global R_0 distribution (Fig. 2B). Due to the spatial and temporal proximity of outbreaks among the Native-American populations, we also constructed a model that allowed for R_i to be spatially correlated between the Native-American populations. For each model, we ran a suite of Markov chain Monte Carlo (MCMC) iterations to estimate parameter values (Table 2) and the uncertainty in the parameter values (see Supplementary Data). Below, we describe aspects of the models in more detail.

2.7. Heterogeneity in susceptibility

The basic SEIR model assumes that all individuals are equally susceptible. To account for potential differences in susceptibility among individuals, we modified the SEIR equations (Eq. (1)–(4)) to allow for heterogeneity in infection risk using a moment-closure approach (Dwyer et al., 1997; Lloyd, 2004; Dushoff, 1999; Elderd et al., 2006). Population-level heterogeneity in susceptibility allows for the possibility that all individuals in a population are not equally susceptible to a disease. For instance, one would suspect that individuals who are more frail may have a greater likelihood of becoming sick as compared to more robust individuals. Allowing for this variability, the susceptible and exposed equations of the SEIR model become:

$$\frac{dS}{dt} = -\frac{\overline{R_0}\gamma}{N} SI\left(\frac{S(t)}{S(0)}\right)^{1/k}, \tag{8}$$

$$\frac{dE}{dt} = \frac{\overline{R_0}\gamma}{N} SI\left(\frac{S(t)}{S(0)}\right)^{1/k} - \alpha E \tag{9}$$

where k is the inverse of the square of the coefficient of variation of the distribution of individual susceptibility. $\overline{R_0}$ is the mean value of R_0, with the mean being taken across individuals in the population. In this model, the more susceptible individuals in the population acquire smallpox earlier in the outbreak (Anderson and May, 1991). As the epidemic progresses, susceptibility of the uninfected decreases, as transmission is scaled by smaller and smaller values of $S(t)/S(0)$.

Note that the larger the value of k, the closer the model is to the homogeneous SEIR model (Eq. (1)–(4)). Models with values of $k > 200$ are nearly indistinguishable from models that assume all individuals are identical. For simplicity in comparing between models, we refer to the $\overline{R_0}$ estimates as R_0. The standard homogeneous (Eq. (1)–(4)) and heterogeneous (Eq. (8)–(9)) SEIR models form the basis for the subsequent candidate models.

2.8. Population-level differences in R_0

In these models, each population is allowed to have its own basic reproductive rate, R_i, where i denotes population (Fig. 2B). This model is commonly referred to as a random-effects (or hierarchical) model, in which populations are assumed to be heterogeneous with respect to the basic reproductive number. We examine how the model with population-level differences in rates R_i performs when using both the homogeneous (Eq. (1)–(4)) and heterogeneous (Eq. (8)–(9)) SEIR models.

2.9. Model with spatial correlation of R_i

The next set of models we present allows for spatial correlation between Native-American population reproductive rate parameters, R_i. These spatial epidemic models take advantage of the fact that the epidemics among the Native-American populations occurred over a relatively short time period (Table 1) and that the populations were located in the same region (Fig. 1). The strength of the correlation between two reproductive rates is modeled as an exponentially decaying function of geographic distance between their corresponding populations. This model assumes that the closer the populations, the stronger the correlation between their R_0 values. This is particularly appropriate when the nearby populations are more similar to each other genetically, environmentally, and/or socially than any two randomly chosen populations. While an explicit spatial model could also be constructed, note that our model here accounts for dispersal, genetic, or social similarities between the populations without explicitly defining these specific relationships. Given the lack of data regarding any of these specific relationships as well as the fact that we do not know the extent to which dispersal between populations occurred, we are only able to assess whether spatial processes were important in aggregate for understanding disease transmission in these smallpox outbreaks.

In these models, the spatial correlation between the R_i values of Native-American populations declines exponentially at rate d as the geometric distance between populations increases. We used an uninformative prior for d to reflect the lack of prior knowledge about this parameter. We therefore allowed only the data at hand to inform the estimation of d. The spatial model was analyzed with both the homogeneous (Eq. (1)–(4)) and heterogeneous (Eq. (8)–(9)) SEIR models.

2.10. Additional models

In general, we focused on the the basic reproductive rate, but population-level differences may arise in other ways. To examine the effects of heterogeneity in other parameters across populations, we constructed a suite of additional models. This included a model that allowed for population-level differences in the mortality frac-

Table 3
Prior and posterior parameter estimates with 95% posterior credible intervals (CI) for three of the candidate models.

Parameter	Models			
	Prior	Model 1 – $R_{0,EA/NA}$	Model 3 – $R_{i,EA/NA}$	Model 5 – $R_{i,EA/NA}$ spatial autocorrelation
$R_{0,EA}$	4 (0.7, 23.7)	6.2 (5.18, 7.68)	6.7 (3.17, 14.43)	6.8 (2.96, 15.21)
$R_{0,NA}$	4 (0.7, 23.7)	8.0 (4.89, 16.07)	8.1 (4.11, 15.50)	8.9 (2.69, 25.05)
μ_{EA}	0.14 (0.03, 0.35)	0.12 (0.103, 0.151)	0.12 (0.116, 0.130)	0.12 (0.116, 0.131)
μ_{NA}	0.45 (0.08, 0.95)	0.35 (0.293, 0.416)	0.39 (0.352, 0.434)	0.36 (0.292, 0.421)
σ_{EA}	–	0.015 (0.0124, 0.0187)	0.005 (0.0042, 0.0070)	0.005 (0.0043, 0.0069)
σ_{NA}	–	0.12 (0.097, 0.149)	0.070 (0.0534, 0.0961)	0.115 (0.0907, 0.1462)
Latency up to prodromal (α_1)	12.1 (7.9, 17.6)	10.5 (7.16, 14.83)	11.6 (8.17, 15.94)	11.9 (8.28, 16.62)
Latency prodromal (α_2)	2.5 (1.3, 4.3)	2.3 (1.20, 3.93)	2.5 (1.23, 4.21)	2.5 (1.31, 4.33)
$1/\gamma$	15.8 (10.9, 22.0)	13.8 (9.96, 18.78)	14.8 (10.86, 19.73)	15.2 (10.96, 21.06)

Model 1 assumes that all populations share the same R_0 depending upon whether the population is of Native-American or European/African descent. Model 3 assumes populations have different values of basic reproductive rates, R_i. Model 5 includes the effects of spatial correlation between R_i of the Native-American populations. For brevity, the other models (Table 2) are not included. For models that assume heterogeneity in infection risk, the posterior distributions are nearly identical to the homogeneous models that are their counterpart (e.g., Model 3 vs. Model 4). Note that the prior intervals for fatality fraction are based on 500,000 simulated draws from a mixture that reflects the hyperprior structure.

tion μ and a model that allowed for differences in the date on which the epidemic began. Additionally, we constructed a hierarchical model based on the negative binomial instead of the normal likelihood and allowed population-level differences in the reproductive rate of spread, R_i. Given the rather large size of each population, we used a normal approximation of the negative binomial in our model runs. All other candidate models assumed a standard normal distribution. These additional models were analyzed using only the standard homogeneous SEIR equations (Eq. (1)–(4)).

2.11. Comparing candidate models

We compared models using the Bayesian Information Criterion or "BIC" (Schwarz, 1978; Gelman et al., 2003; Burnham and Anderson, 2002). BIC balances model fit with the number of parameters in the model according to:

$$\mathrm{BIC} = -2L + K\log(n), \tag{10}$$

where L is the maximum value of the log likelihood function of the model under consideration (as given in Eq. (7)), K is the number of parameters in the model, and n is the sample size. When the likelihood is normal, this criterion is based on the squared differences between the model predictions and the data. The model with the lowest BIC score thus fits the data the best. To compare models, we calculated ΔBIC, which is defined as $\Delta\mathrm{BIC}_j = \mathrm{BIC}_j - \mathrm{BIC}_{\min}$. Here j represents the model and "min" is the model with the lowest BIC score. Thus, the best fit model will have a BIC score of 0. Models more than 10 units away from the best fit model ($\Delta\mathrm{BIC} > 10$) are considered to have little support from the data (Bolker, 2008). We also compared models using BIC weights, defined as:

$$\Pr(m_j) = \frac{\exp(-0.5\Delta\mathrm{BIC}_j)}{\sum_{r=1}^{R}\exp(-0.5\Delta\mathrm{BIC}_r)}$$

where $\Pr(m_j)$ is the posterior probability of model j as compared to all models r from $1 \ldots R$ (Bolker, 2008). Although there is no single best model selection criterion (Spiegelhalter et al., 2002; Dukic and Pena, 2005; Steele and Raftery, 2010), comparable results were seen when using Deviance Information Criterion (DIC: Spiegelhalter et al., 2002), an alternative criterion popular in Bayesian modeling. Our conclusions did not change under different model-selection criteria.

3. Results

For each candidate model (Table 2), we estimated two separate values of the basic reproductive rate R_0, one for the populations of European/African descent and one for the Native-American populations. Model 1 assumed that all populations within the European/African group had a single R_0, $R_{0,EA}$, and similarly, that all populations within the Native-American group had a single R_0, $R_{0,NA}$ (Fig. 2A). This model did a much poorer job of describing the data than the best-fit model, Model 3, which assumed that each population had its own basic reproductive rate distribution R_i (Fig. 2B). This more complex hierarchical structure substantially improved the model's ability to fit the smallpox outbreak data even though the increased complexity of the model penalized the BIC score (Eq. (10)).

The best-fit model also assumed that all individuals were equally susceptible. Models that allowed for heterogeneity in susceptibility (Dwyer et al., 2000; Elderd et al., 2008), in contrast, did a poorer job of explaining the data (Table 2). Additionally, parameter estimates of heterogeneity resulted in SEIR dynamics that were indistinguishable from the homogeneous model.

The model that accounted for spatial correlation among R_0 parameters of the Native-American populations using the homogeneous SEIR model equations gave the second-best fit. Nevertheless, the differences in BIC score (ΔBIC) between the spatial model and the best model was large. The differences in BIC score for all other models, such as population-level difference in mortality fraction, were also quite large (Table 2). The model that included population-level differences in R_0 thus had overwhelming support from the data.

By comparing the model that assumed all epidemics had the same R_0 (Model 1 in Table 2, Fig. 2A) to the model that assumed that each epidemic had its own R_i (Model 3 in Table 2, Fig. 2B), we can illustrate how changes in basic assumptions about the reproductive rate of spread affect our uncertainty about global epidemic parameter values (Table 3). For populations of European/African descent, the uncertainty in the global or average R_0 increased under Model 3 (Fig. 3). Thus, assuming that there are no inter-population level differences leads to an underestimate of the uncertainty of the global R_0 values. Moreover, the posterior distribution for R_0 for Model 3 implies that the uncertainty in R_0 encompasses a much broader range of R_0 values than has been observed in previous single-epidemic studies, which have suggested a range of only 3.5–12 (Gani and Leach, 2001). The differences in estimates of R_0 for populations of European/African descent stem from the inter-population level differences in the disease's reproductive rate of spread R_i (Fig. 4). For the Native-American populations, there was

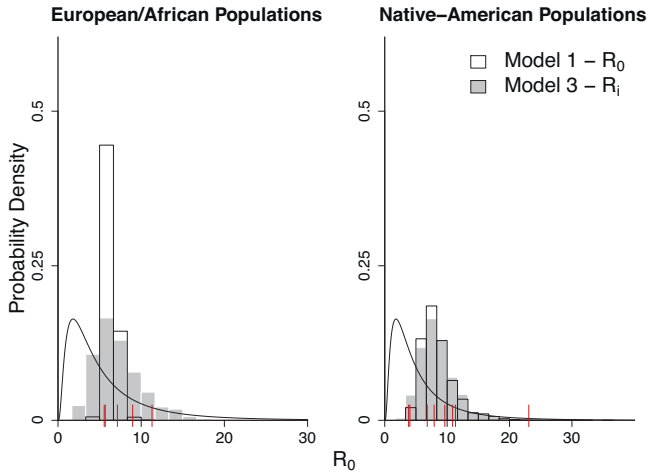

Fig. 3. Comparison of the posterior distributions of R_0 in the model in which all epidemics have the same value of R_0 (Model 1 – white) and the posterior distribution of the global R_0 in the model that assumes that each epidemic has its own value of R_i (Model 3 – gray). The solid line in the figure represents the prior. The short red lines on the x-axis are the posterior median estimates of R_i for each population using Model 3.

no appreciable change in R_0 estimates between Model 1 and 3. This was due to the wide credible interval associated with R_0 regardless of the model. Nevertheless, there were still large differences in R_i for the Native-American populations with some values close to European/African populations and others much larger (Fig. 5). This wide range of R_i estimates makes clear that differences in biological, societal, and environmental factors between populations can be of great importance when estimating a disease's basic reproductive rate.

For other parameters, uncertainty was either lower or did not change when we allowed for inter-population differences in R_0. For example, when we allowed for population level differences, disease mortality showed a decrease in uncertainty for populations of European/African descent and an increase in the median for Native-American populations (Fig. 6). For both sets of populations, there was a reduction in the median error (Fig. 7). For parameters shared by European/African and Native-American populations, such as the infectious period, there was no noticeable change (Table 3 and Supplementary Data, Fig. S1), partly because of the informative priors we placed on these parameters (Litvinjenko et al., 1973; Gelfand and Posch, 1971; Mack, 1972; Eichner and Dietz, 2003).

4. Discussion

Our best-supported model (Table 2) allows for dramatic differences in the basic reproductive rate of smallpox, R_i, between populations. Given the rather severe BIC penalty associated with this much more complex R_i model, it is clear that population-level differences matter. These differences may arise due to either biological, societal, or environmental factors along with their interactions. While we cannot parse which of these differences is individually most important, they are clearly important in aggregate in describing the variability in the smallpox data. For the populations of European/African descent, the differences between populations were not as great compared to the Native-American populations. This may be due to shared genetic heritage or to the fact that the

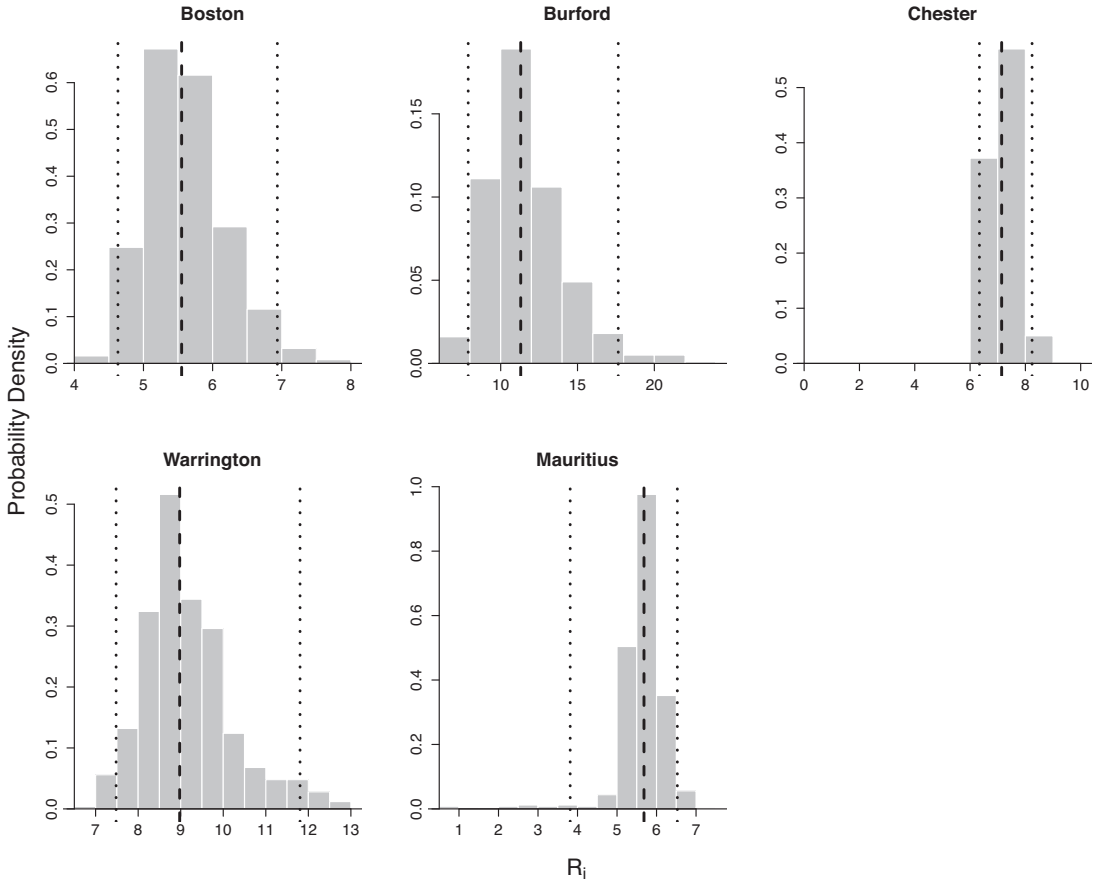

Fig. 4. Posterior distribution of the basic reproductive rates R_i for populations of European/African descent. The dashed line represents the posterior median and the dotted lines include the 95% posterior credible intervals. Note the differences in scale between the populations for both the *x* and *y* axes.

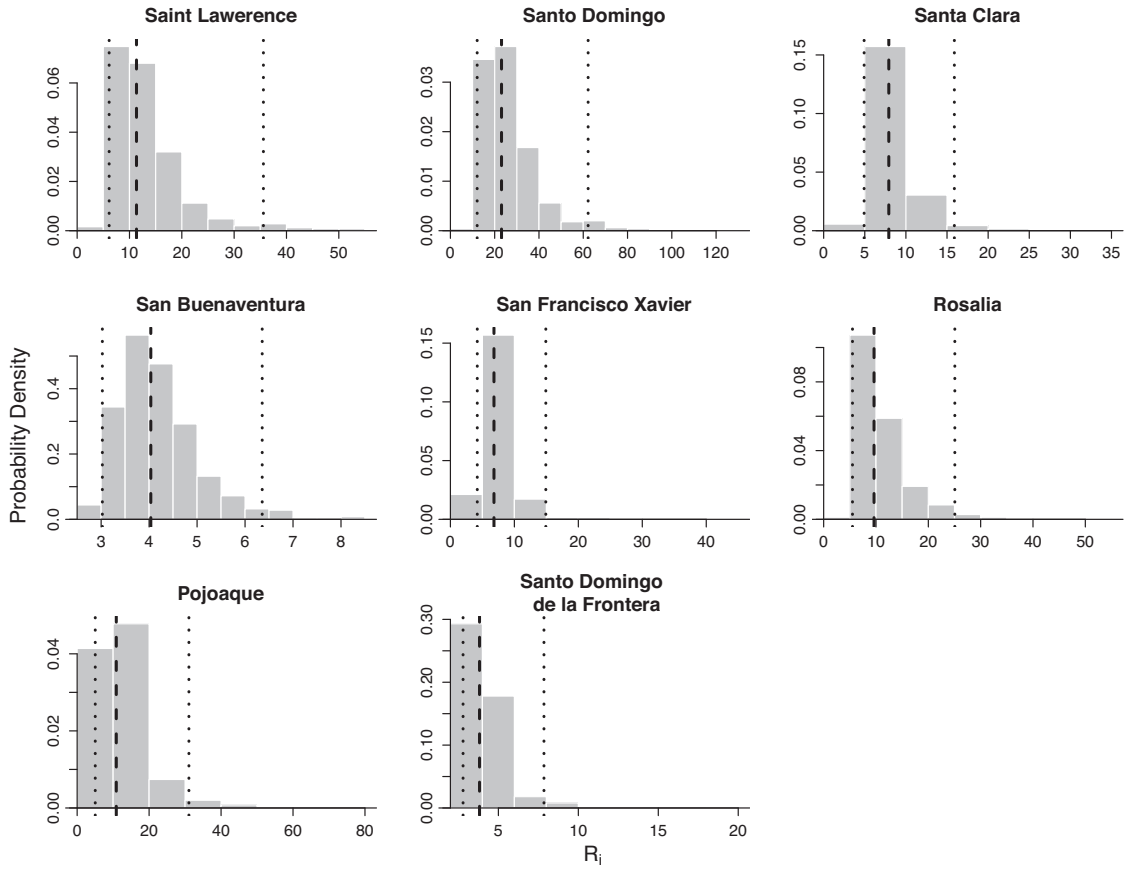

Fig. 5. Posterior distribution of the basic reproductive rates R_i for Native-American populations. The dashed line represents the posterior median and the dotted lines include the 95% posterior credible intervals. Note the differences in scale between the populations for both the x and y axes.

European/African populations had already been selectively swept by the disease. These populations nevertheless varied with respect to R_0, which may be due to other contributing factors such as differences in population age structure (Creighton, 1891). For the Native-American populations, population-level differences were much greater due to the plethora of biological, societal, and environmental factors that likely varied between missions (Jackson, 1994). In general, our results show that not accounting for differences between populations leads to a poor understanding of epidemic dynamics and R_0 estimates. When these estimates are used to determine public health responses, this could lead to lower vaccination rates than necessary to contain the outbreak. This could result in a more severe epidemic than expected.

Interestingly, we found a negative correlation between population size and R_i for populations of European/African descent, based on the MCMC samples from the posterior distribution. The median correlation was -0.91 with the 95% credible interval of [-0.983, -0.596]. This was not the case for Native American populations

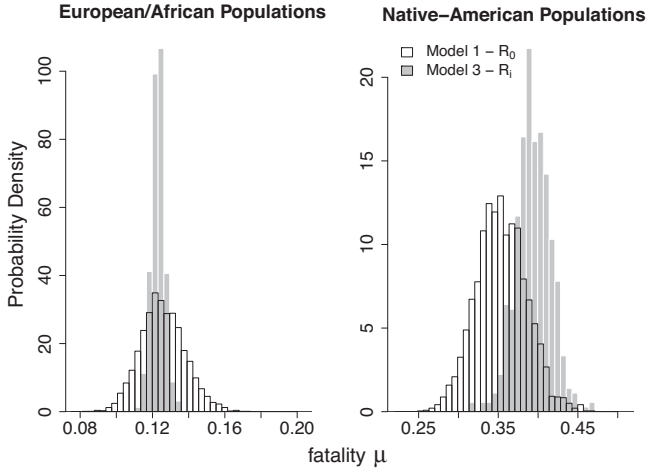

Fig. 6. Comparison of the mortality fraction μ distributions given that all epidemics have the same value of R_0 (Model 1) with a model that assumes that each epidemic has its own value of R_i (Model 3).

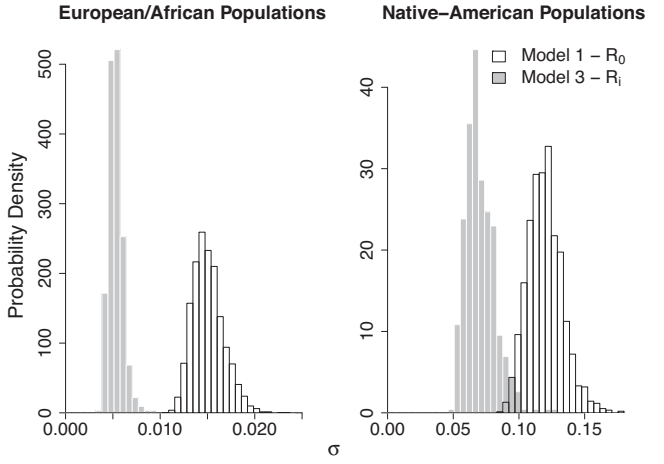

Fig. 7. Comparison of the distributions of observation error standard deviation σ given that all epidemics have the same value of R_0 (Model 1) with a model that assumes that each epidemic has its own value of R_i (Model 3).

(0.38, [−0.296, 0.785]). Whether this pattern arose from differences between the population types or due to overall population size remains to be seen. However, it does suggest a population size relationship may exist for smallpox. For other diseases, such as measles, there may be no such relationship (Bjørnstad et al., 2002).

In the best-fit model, each population has an R_i value that is drawn from a global R_0 distribution. Allowing for this hierarchical structure slightly increases the overall uncertainty in global R_0 for populations of European/African descent, but it results in a better fit of the model to the data. In particular, the improved likelihood under the R_i model (Model 3) is at least partly due to the improved fit of the European/African population data sets. By contrast, allowing for spatial correlation in R_i values for the Native-American populations did not improve model fit and the corresponding models had little relative support (Table 2). This was also true for any of the models in which we assumed that there was heterogeneity between individuals in the risk of contracting smallpox. Given that accounting for such heterogeneity provided a poorer fit to the data, building more complex hierarchical models that could explicitly incorporate age-structure (Hethcote, 2000) or super-spreaders (Riley et al., 2003) in these data is probably similarly unwarranted. A lack of data on age distributions in particular would have meant that parameter estimates in an age-structured model would have been quite uncertain.

We used a deterministic SEIR model with normally distributed errors to calculate likelihoods, and carry out the posterior inference. With faster computers, however, our overall approach could be easily extended to allow for likelihoods based on stochastic epidemic models. For data sets in which stochastic models may be appropriate for certain outbreaks (i.e., small population sizes) and deterministic models for the larger outbreaks, it would be relatively easy to combine stochastic and deterministic epidemics to derive a hybrid likelihood. By combining both stochastic and deterministic methods, the information contained in epidemic data sets for small and large populations can be easily handled. For the data at hand, however, using stochastic models for smaller population sizes would likely not yield different conclusions from the ones presented in this paper. In particular, using a stochastic model to re-calculate likelihoods at the median values of the posterior gives essentially identical results (Supplementary Data, Table S2). This was most likely because all the initial host population sizes were larger than 100 and all but two were larger than 200 (Table 1).

An advantage of the Bayesian approach is that it allows us to directly quantify the joint uncertainty associated with the data and the model parameters (Elderd et al., 2006). The approach used here formally quantifies the uncertainty associated with each population-specific parameter as all parameters are allowed to vary together. This results in a better gauge of model fit as well as a better estimate of the uncertainty associated with each parameter in the epidemic model and the overall uncertainty associated with model predictions.

Although spatial processes can be an important component of disease dynamics (Keeling et al., 2003; Ferrari et al., 2008; Grenfell and Bolker, 1998), here we find that they had little influence in aggregate, as assessed via the exponential decay model. The fact that the spatial correlation did not turn out to be supported could be either due to these spatial processes not playing an important role, or to not having enough data to detect the spatial effects via this model. Nevertheless, as data for other diseases continues to be collected over longer time periods and at varying spatial scales, methods that account for spatial processes are becoming more important. The approach that we present here could provide a simple spatial model benchmark, with relatively low data and computational requirements, to more complex network models (Ferrari et al., 2008) or agent-based models (Halloran et al., 2002).

A broader consequence of the main result of this paper is that it offers an important caveat to ongoing efforts to estimate the parameters of disease models. An implicit assumption of much of this work is that the reproductive rate of spread R_0 is a fundamental quantity, and that estimates from different populations will be relatively consistent with each other. This may be a reasonable assumption for some diseases, notably measles (Bjørnstad et al., 2002), for which inter-population differences in R_0 play less of a role. Concern over this issue led Mossong et al. (Mossong et al., 2008) to directly measure person-to-person contact rates in European populations, but their data likewise suggested that contact rates are roughly equivalent across widely separate communities. For other diseases, there is evidence that inter-population difference may be important (Valleron et al., 2010; Mills et al., 2004). These studies, however, present a range of individual estimates or quantile intervals rather than a direct estimate of R_0 along with its credible intervals. The associated distribution of R_0 rather than a simple range can play a more useful role in forecasting potential epidemic outcomes should an outbreak occur.

By showing that inter-population differences can strongly affect disease spread (see also Valleron et al., 2010; Mills et al., 2004, we have shown that smallpox epidemics may have varied greatly among populations, to the extent which may have significant public-health implications (Elderd et al., 2006). Our work thus provides an important counter-example to the assumption that R_0 is a static quantity, and argues strongly against using single estimates of R_0 when it comes to public policy decision making. In particular, given that we observed large differences in estimated R_i values between Native-American populations, our results imply that estimates of R_0 for emerging diseases in multiple communities are likely to be particularly variable. Our work thus generally emphasizes the potential importance of population-level differences for determining epidemic dynamics.

Acknowledgments

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Appendix A. Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.epidem.2013.07.001.

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