Available online at www.sciencedirect.com
SCIENCE DIRECT®
Mathematical Biosciences 195 (2005) 228–251
Mathematical Biosciences
www.elsevier.com/locate/mbs

Effects of behavioral changes in a smallpox attack model

S. Del Valle [a,b,*], H. Hethcote [b], J.M. Hyman [a], C. Castillo-Chavez [a,c]

[a] *Center for Nonlinear Studies (CNLS) and Mathematical Modeling and Analysis Group (T-7), Los Alamos National Laboratory, Los Alamos, NM 87545, USA*
[b] *Department of Applied Mathematical and Computational Sciences, University of Iowa, McLean Hall, Iowa City, IA 52242, USA*
[c] *Department of Biological Statistics and Department of Mathematics and Statistics, Arizona State University, PSA, Tempe, AZ 85287-1804, USA*

Received 13 January 2004; received in revised form 9 March 2005; accepted 15 March 2005

Abstract

The impact of individual and community behavioral changes in response to an outbreak of a disease with high mortality is often not appreciated. Response strategies to a smallpox bioterrorist attack have focused on interventions such as isolation of infectives, contact tracing, quarantine of contacts, ring vaccination, and mass vaccination. We formulate and analyze a mathematical model in which some individuals lower their daily contact activity rates once an epidemic has been identified in a community. Transmission parameters are estimated from data and an expression is derived for the effective reproduction number. We use computer simulations to analyze the effects of behavior change alone and in combination with other control measures. We demonstrate that the spread of the disease is highly sensitive to how rapidly people reduce their contact activity rates and to the precautions that the population takes to reduce the transmission of the disease. Even gradual and mild behavioral changes can have a dramatic impact in slowing an epidemic. When behavioral changes are combined with other interventions, the epidemic is shortened and the number of smallpox cases is reduced. We conclude that for simulations of a smallpox outbreak

* Corresponding author. Address: Center for Nonlinear Studies (CNLS) and Mathematical Modeling and Analysis Group (T-7), Los Alamos National Laboratory, Los Alamos, NM 87545, USA. Tel.: +1 201 892 4208; fax: +1 505 665 2659.
E-mail address: sara@cnls.lanl.gov (S. Del Valle).

0025-5564/$ - see front matter
doi:10.1016/j.mbs.2005.03.006

to be useful, they must consider the impact of behavioral changes. This is especially true if the model predictions are being used to guide public health policy.

Keywords: Smallpox; Mathematical model; Behavioral changes; Vaccination; Isolation; Quarantine; Sensitivity analysis

1. Introduction

Deliberate releases of biological agents such as smallpox had not been considered likely, but the terrorist attacks of September 11, 2001 altered this viewpoint. Concern that smallpox could be used as a biological weapon has prompted scientists and government officials to prepare emergency response plans in the event of a deliberate or accidental release [19]. The recent massive smallpox vaccination of US military and medical personnel suggests that the risk of a smallpox attack is not considered negligible [16]. Mass vaccination followed by control measures such as the isolation of infecteds, contact tracing, quarantine, and ring vaccination (around smallpox cases), were used in the eradication of smallpox in the 1970s [13]. The smallpox response policy of the Center for Disease Control and Prevention (CDC) includes the statement, 'Any vaccination strategy for containing a smallpox outbreak should use the ring vaccination concept. This includes isolation of confirmed and suspected smallpox cases with tracing, vaccination, and close surveillance of contacts to these cases as well as vaccination of the household contacts of the contacts' [6]. However, CDC's policy does not explicitly take into account the impact of individuals' decisions to change their behavior.

In addition to the public health interventions mentioned above, there would be changes in behavior in the affected population in response to a smallpox attack. For example, people could decide to wash their hands more frequently, wear protective masks, and avoid crowded places, fever clinics could be opened, fever checks could be instituted at transit sites; schools, theaters, bars, and libraries could be closed, social and sports events could be canceled, people could stay home from work, and businesses could close. It is surprising that the likely occurrence of these behavior changes has not been included explicitly in previous computer simulations of a smallpox epidemic. Without including behavioral changes, the simulations will predict the 'worst' possible scenario. Recent experiences with the SARS epidemics show that an outbreak of a deadly disease like smallpox would generate dramatic behavioral changes [1,8,30,35]. Lack of understanding and government planning for how people would react during a smallpox epidemic could significantly delay or eliminate the benefits of behavioral changes. Responses to an infectious disease in a community can reduce morbidity and mortality; for example, significant changes in behavior among men who have sex with men have been credited with decreases in prevalence of HIV/AIDS and other sexually transmitted diseases [17,20,24,25,41].

The transmission of smallpox has some similarities to that of SARS. Both are spread by close contacts with infected individuals, contaminated objects, or airborne virus particles. Both have high case morality rates. Transmission of both SARS and smallpox occur more frequently in households and hospitals. Fortunately in the case of smallpox, there is a relatively safe vaccine.

Smallpox vaccination side effects while rare can be serious and include postvaccinal encephalitis, progressive vaccinia, eczema vaccinatum, generalized vaccinia, and accidental infection [29]. The risks are relatively low, since for every one million smallpox vaccinations, an average of 40 people have complications and one person dies. The US policy of routine smallpox vaccination was discontinued over three decades ago. Hence the pool of susceptible individuals has increased dramatically. The smallpox virus is still kept in laboratories in the United States and Russia, and may exist in other countries [10].

Mathematical models of the transmission of infectious agents can be useful tools in understanding patterns of disease spread and assessing the effects of different interventions [20,25]. Several recent papers have used mathematical models for the dynamics of smallpox outbreaks in attempts to study the effects of various public health measures such as mass vaccination, isolation of infectives, contact tracing with quarantine and vaccination of contacts, and ring vaccination around infectives. Meltzer et al. [33] used a Markov chain model to evaluate the rates of mass vaccination and isolation of infectives needed to reduce the average transmissions per case to less than one, but they did not consider contact tracing and ring vaccination. They concluded that delays in interventions would lead to more cases and that an integrated approach that uses both quarantine and vaccination would be effective. Kaplan et al. [27] used simulations of a deterministic model in a population of 10 million people to compare the relative effectiveness of mass and ring (traced) vaccination for reducing the impact of a smallpox release. Using a model that assumed high infectivity in the prodromal period, they found that mass vaccination would lead to fewer deaths and faster eradication.

Halloran et al. [18] used a stochastic simulation of smallpox in a community of 2000 people in their efforts to compare mass and ring vaccination policies. In their model which also assumed high infectivity in the prodromal period, they found that timely mass vaccinations would be more effective than targeted vaccinations, provided that there was no preexisting immunity. However, they also noted that targeted vaccination would be more competitive in the presence of preexisting immunity. Bozzette et al. [5] used a stochastic model that kept track of adverse vaccination effects to estimate smallpox deaths under various smallpox attack scenarios. They concluded that prior vaccination of health care workers would be beneficial unless the likelihood of an attack was very low. A review article by Ferguson et al. [14] discussed the use of mathematical models in planning for smallpox outbreaks and compared the model formulations and results of the four papers above.

Eichner [12] used stochastic computer simulations to show that contact tracing and case isolation could control smallpox outbreaks. Kretzschmar et al. [28] used a stochastic branching process model to show that a policy of ring vaccination of contacts of infected people would be sufficient to control a smallpox epidemic. However, the size and duration of the outbreak could be large depending on the average time to smallpox diagnosis and the average time needed to trace and vaccinate contacts of infectives.

Castillo-Chavez et al. [2] developed a more elaborate model that incorporated the importance of transient populations on the transmission dynamics of smallpox. This model incorporated multiple environments (mass transportation). They found that control measures (vaccination) should be aimed at both local and transient populations and that delays in implementations could be catastrophic. They showed that a policy which focuses only on local populations would not be sufficient, so that global approaches would be needed.

Surprisingly, none of the mathematical models cited above incorporate behavioral changes. Consequently, they are likely to overestimate the size of an outbreak or the magnitude of the interventions necessary to control one. In this paper, the effects of population behavioral changes in conjunction with various control approaches after a smallpox release are explored. It is shown that behavioral changes alone can make a huge difference. It is also shown that the impact of standard control efforts are dramatically enhanced when the individuals affected play an active role in diminishing the likelihood of transmission.

The rest of this paper is organized as follows. The interventions are described in Section 2 and the model is formulated in Section 3. An expression for the effective reproduction number is derived in Section 4 and parameters are estimated in Section 5. Section 6 contains the simulation results showing the impact of intervention strategies and behavioral changes. The results of sensitivity analyses to determine the effects of changes in the values of model parameters are given in Section 7. Section 8 is devoted to discussion and conclusions.

2. Smallpox interventions

The CDC smallpox response strategy suggests that the highest priority is isolation of confirmed smallpox cases [6]. Isolation usually means that people infected with smallpox either stay home where they have minimal contacts with other people or are placed in isolation centers where careful procedures are followed to prevent or reduce transmission. Isolation is simulated in our model by moving a fixed proportion of the infectious class containing confirmed cases of smallpox to the isolated class each day.

The next priority in the CDC smallpox response strategy is tracing, vaccination, and close surveillance of contacts of the smallpox cases. The 'tracing ... and close surveillance part' corresponds to using quarantine, which is the identification by contact tracing and separation of people who might be infected because they may have had a contact with a person infected with smallpox. This separation could be achieved by requiring these people to stay home and avoid unnecessary contacts or by placing them in special quarantine centers. However, quarantine is likely to be maintained with the least restrictive measures possible to minimize the burden of quarantine and to facilitate compliance [3]. Because smallpox has a long incubation period, quarantined people might be allowed to conduct their normal daily activities as long as they make daily reports on their body temperature. The 'isolation of ... suspected cases' in the CDC smallpox response strategy could correspond to immediate isolation of quarantined people who are suspected to have smallpox (e.g. those with a fever). Thus the goal of quarantining with daily surveillance is to identify and isolate new infecteds before they can infect others. In our simulation model the quarantine class contains individuals in the incubation period, who were infected during a contact with a smallpox infective and found by contact tracing. People who were suspected of having a contact with a smallpox infective and were found by contact tracing, but did not become infected, remain in the susceptible class. Thus in the simulations the number quarantined is the total of the infected and uninfected people who were quarantined after being found by contact tracing.

In the second priority in the CDC smallpox response strategy, 'vaccination ... of contacts of the smallpox cases' is usually called ring vaccination. The 'vaccination of the household contacts of

the contacts' in the CDC smallpox response strategy is a type of second order ring vaccination. This seems to be part of the CDC concept that the size of the ring around a case or contact may be modified by expansion or contraction, depending on epidemiological and logistical factors [6]. In our simulations ring vaccination corresponds to vaccination of infected and uninfected quarantined cases who have been found through contact tracing.

The CDC smallpox response strategy gives five reasons for not using 'indiscriminate mass vaccination,' but their priority list of the type of people who should be vaccinated is very broad. CDC lists health care and laboratory personnel, law-enforcement and fire personnel, people entering hospitals where smallpox cases are isolated, etc. [6]. Because other modelers have considered mass vaccination, it is included in the simulations here, so that it can be compared with the other interventions.

We live in a society where communications can be extremely fast and effective. After the terrorist attack on September 11, 2001, airports were closed and bridges and tunnels in New York City were closed to incoming traffic [39]. If a smallpox attack occurs, then personal and community behavioral changes will occur and will be managed by public health officials. People will be urged to avoid crowded places, travel will be restricted, schools will be closed, and public events will be canceled. The large number of effective actions that individuals or communities can take in order to reduce the risk of smallpox transmissions after a smallpox release may be crucial in stopping the epidemic. Three possible conservative levels of behavioral change (high, medium, and low) are included in our model simulations. These behavioral changes are incorporated into our simulation model through the transfer of normally active individuals to a less active class in which people have fewer daily contacts. Since people and community officials would respond to media information about smallpox, the rates of behavioral change are functions of the number of smallpox cases in the community. Because the smallpox epidemic is assumed to occur in a short time, the simulation model does not include flow from the less active class back to the normally active class.

Thus we use a simplified model of a single epidemic outbreak that includes behavioral changes modeled by the permanent transfer of individuals during the outbreak to a less active class with transfer rates that depend on people's knowledge of the outbreak as measured by the number of identified cases. The intervention strategies for controlling a smallpox outbreak considered in our model are summarized below.

- *Isolation*: Separation and confinement of people known to be infected with smallpox to prevent them from transmitting the infection.
- *Quarantine*: Separation or restriction of movement of people who are identified through contact tracing as having been exposed to a smallpox infective.
- *Ring vaccination*: Vaccination of people who are identified through contact tracing as having been exposed to a smallpox infective (i.e. quarantined people).
- *Mass vaccination*: Vaccination of people chosen at random from the population.
- *High behavioral change* (HBC): A high percentage (2.3% per day) of people reduce their daily number of contacts by a factor of 10.
- *Medium behavioral change* (MBC): A medium percentage (2% per day) of people reduce their daily number of contacts by a factor of 10.
- *Low behavioral change* (LBC): A low percentage (1.6% per day) of people reduce their daily number of contacts by a factor of 10.

3. Formulation of the model

The population is divided in two subgroups: normally active group (subscript n) and the less active group (subscript ℓ). People move to the less active group (reducing their average number of contacts) in response to information about smallpox cases in the community. Individuals in each activity group ($j = n$ or ℓ) are characterized by their epidemiological status: susceptibles S_j, exposed E_j (i.e. people who are infected but not yet infectious), and infectious individuals I_j. People move to the V class when they are vaccinated, to Q when they are an exposed (infected, but not yet infectious) person who was traced as a contact of an infective and quarantined, and to W when they are identified as an infective and are isolated. Infectious individuals can move to the class D when they die from the infection or move to the recovered class R upon recovery. Definitions of the eleven epidemiological classes are summarized in Table 1 and the transfers between epidemiological compartments are shown diagrammatically in Fig. 1. Because we are interested in the effects of behavioral changes and interventions in a short time, births and natural deaths are not included. This model extends previous epidemic models by allowing susceptible people to transfer into a less active class [17,22].

As seen in Fig. 1, the transfer rates of people from the exposed classes E_n and E_ℓ to the infectious classes I_n and I_ℓ are ωE_n and ωE_ℓ. Because people in Q are exposed (but are quarantined and being watched), it is assumed that when they become infectious, they are moved to the isolated class W, modeled here via the transfer rate ωQ. People in the infectious classes I_n and I_ℓ are moved to the isolated class at the rates θI_n and θI_ℓ, die at the rates μI_n and μI_ℓ, and recover at the rates δI_n and δI_ℓ. Similarly, people in the isolated class W either die at the rate μW or recover at the rate δW. Without behavioral changes, the mean times in the infectious classes I_n and I_ℓ are $1/(\theta + \mu + \delta)$. Hence, the infectious fraction $\theta/(\theta + \mu + \delta)$ are eventually isolated, the infectious fraction $\delta/(\theta + \mu + \delta)$ recovers, and the infectious fraction $\mu/(\theta + \mu + \delta)$ dies as consequence of this disease. The mean time in the isolated class W is $1/(\delta + \mu)$, so that the isolated fraction $\delta/(\delta + \mu)$ recovers while the remaining isolated fraction $\mu/(\delta + \mu)$ dies.

We assume that the contact activity of all people in the population is normal before a smallpox attack occurs and that the activity levels remain normal until people are notified that a smallpox case has been identified in the community. The first people who become infected during a smallpox release enter the exposed class E_n. Some time later after these initial infecteds become

Table 1
State variables for the model in Fig. 1

Variable	Definition
V	Number of vaccinated individuals
S_j	Number of susceptible individuals in group j
Q	Number of quarantined individuals
E_j	Number of exposed individuals in group j
I_j	Number of infectious individuals in group j
W	Number of isolated individuals
R	Number of recovered individuals
D	Number of dead individuals

The subscript refers to normally active individuals ($j = n$) or less active individuals ($j = \ell$).

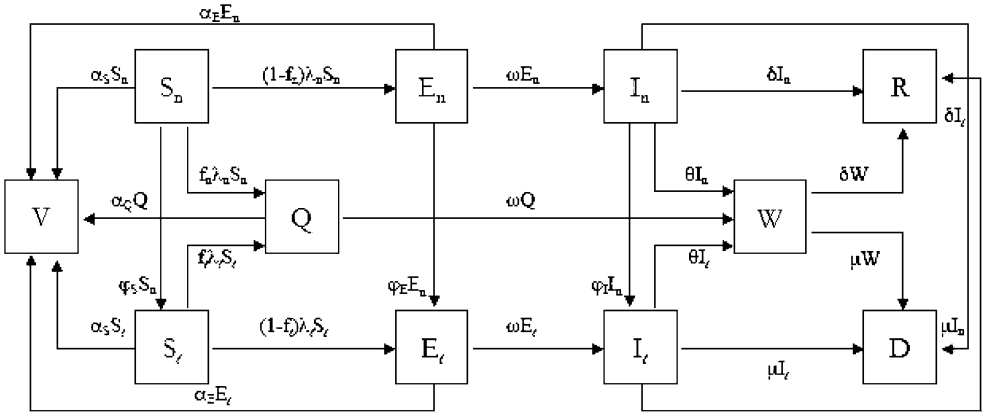

Fig. 1. Schematic relationship between normally active and less active individuals ($j = n, \ell$) for smallpox infection. The arrows that connect the boxed groups represent movement of individuals from one group to an adjacent one. Susceptible individuals (S_j) can become exposed (E_j), be quarantined (Q) or vaccinated (V). Exposed individuals (E_j) can either become infectious (I_j) after an incubation period or be vaccinated (V). Quarantined individuals (Q) can either be vaccinated (V) or isolated (W). Infectious individuals (I_j) can be isolated (W) or can either recover (R) or die (D). Similarly, isolated individuals (W) can either recover (R) or die (D).

infectious and move into the I_n class, one or a few of them will be identified as a smallpox infectives, triggering a control response. We define t_0 as the time, after the smallpox release, when public health interventions start. We assume that the public is notified at that time that smallpox cases have been identified in the community, so that behavioral changes also start at time t_0.

Of those in the susceptible classes S_n and S_ℓ who become exposed (infected, but not yet infectious), the fractions identified by contact tracing and quarantined are f_n and f_ℓ, respectively. The vaccination rates in the susceptible classes S_n and S_ℓ are $\alpha_S S_n$ and $\alpha_S S_\ell$, respectively. The rate constant α_S corresponds to successful vaccination, so it is the product of a slightly higher actual vaccination rate constant and the very high smallpox vaccine efficacy. Vaccination of exposed individuals within a few days (i.e., vaccination on days 0–4 of the incubation period) after exposure prevents illness in about 80% of people vaccinated, and later vaccination may ameliorate symptoms and the infectiousness of infected individuals [32,34]. Thus some exposed people in the E_n, E_ℓ, and Q classes who are vaccinated move to the vaccinated class V. The exposed vaccination rate constants are α_E and α_Q, so the vaccination rates are $\alpha_E E_n$, $\alpha_E E_\ell$, and $\alpha_Q Q$. Without behavioral change, the mean time in the exposed classes E_n and E_ℓ is $1/(\alpha_E + \omega)$, so that the fraction $\alpha_E/(\alpha_E + \omega)$ are vaccinated and the fraction $\omega/(\alpha_E + \omega)$ become infectious. The mean time in the quarantined class Q is $1/(\alpha_Q + \omega)$, so that the fraction $\alpha_Q/(\alpha_Q + \omega)$ are vaccinated and the fraction $\omega/(\alpha_Q + \omega)$ become isolated.

After they become aware of smallpox cases in their community at time t_0 , some normally active people change their behavior. The behavioral changes in these individuals are modeled via the transfer of normally active people to the less active categories. The transfer rates are assumed to depend on the prevalence of infected individuals in the population. Let $\varphi_S S_n$, $\varphi_E E_n$, and $\varphi_I I_n$ be the transfer rates from the S_n, E_n, and I_n classes to the S_ℓ, E_ℓ, and I_ℓ classes, respectively. The rate coefficients (i.e. the per-capita transfer rates) are modeled by the non-negative, bounded, monotone increasing functions given by

$$\varphi_i = \varphi_i(I_n + I_\ell) = \frac{a_i(I_n + I_\ell)}{1 + b_i(I_n + I_\ell)} \frac{1}{\text{day}} \tag{1}$$

for $i = S$, E, I [21]. In other words, the rate at which normally active individuals change their behavioral rises as the disease prevalence increases, leveling off at a plateau given by a_i/b_i. The parameters a_i and b_i are positive constants that modulate the rate of change. The 1/day factor balances the units of the Eq. (1). We assume that infected individuals are more likely to change their behavior (and thus reduce the average number of contacts) because of their physical condition, that is $\varphi_S < \varphi_E < \varphi_I$. The impact of vaccine complications is assumed to be small and hence neglected in the model. Models that incorporate vaccine-induced deaths have been studied by Castillo-Chavez et al. [2], Halloran et al. [18], Kaplan et al. [27], and others.

Using the transfer diagram in Fig. 1, we arrive at the following non-linear system of differential equations:

$$\begin{aligned}
\dot{V} &= \alpha_S(S_n + S_\ell) + \alpha_E(E_n + E_\ell) + \alpha_Q Q,\\
\dot{S}_n &= -\lambda_n S_n - (\varphi_S + \alpha_S)S_n,\\
\dot{S}_\ell &= -\lambda_\ell S_\ell + \varphi_S S_n - \alpha_S S_\ell,\\
\dot{Q} &= f_n\lambda_n S_n + f_\ell\lambda_\ell S_\ell - (\omega + \alpha_Q)Q\\
\dot{E}_n &= (1 - f_n)\lambda_n S_n - (\varphi_E + \omega + \alpha_E)E_n,\\
\dot{E}_\ell &= (1 - f_\ell)\lambda_\ell S_\ell + \varphi_E E_n - (\omega + \alpha_E)E_\ell,\\
\dot{I}_n &= \omega E_n - (\varphi_I + \mu + \delta + \theta)I_n,\\
\dot{I}_\ell &= \omega E_\ell + \varphi_I I_n - (\mu + \delta + \theta)I_\ell,\\
\dot{W} &= \theta(I_n + I_\ell) + \omega Q - (\mu + \delta)W,\\
\dot{R} &= \delta(I_n + I_\ell + W),\\
\dot{D} &= \mu(I_n + I_\ell + W),
\end{aligned} \tag{2}$$

where λ_n and λ_ℓ are the forces of infection (defined below). The definitions of the parameters are summarized in Table 2.

We define λ_n and λ_ℓ, by dividing the population into three categories: normally active people (A_n), less active people (A_ℓ), and confined people (A_c), who are quarantined or isolated. We assume that recovered and vaccinated people have contacts at normal levels. Thus the sizes of the three active subgroups are $A_n = S_n + E_n + I_n + R + V$, $A_\ell = S_\ell + E_\ell + I_\ell$, and $A_c = Q + W$. Let γ_n, γ_ℓ, and γ_c be the average contact rates or contact activity levels of individuals in the three subgroups. In our simulations it is assumed that the average number of contacts of normally active people is 10 times higher than the average number of contacts of less active people ($\gamma_n = 10\gamma_\ell$) [20]. Furthermore, we assume that quarantine and isolation procedures are effective, and the average number of contacts of less active people is 10 times that of confined people ($\gamma_\ell = 10\gamma_c$). The average transmission probability per contact, β, incorporates both the average infectiousness of infecteds and the average susceptibility of susceptibles.

We assume that the mixing is homogeneous within each subgroup, but is heterogeneous among subgroups [2,24,27]. Specifically, we assume proportionate mixing [20], so that the contacts γ_n and

Table 2
Parameter definitions and values that fit the cumulative number of cases for the model

Parameter	Description	Dimension	Baseline	Range	Reference
$\Re_{\text{unc}}$	Effective reproduction number (uncontrolled)	1	3	1.5–20	[12,15]
β	Transmission rate	1	0.1	0–1	[33]
δ	Recovery relative rate	Day^{-1}	$(16)^{-1}$	0–1	[13,23,36]
θ	Isolation relative rate	Day^{-1}	$(5)^{-1}$	0–1	[13]
μ	Death relative rate	Day^{-1}	0.0268	0–1	[13,23,26]
ω	Incubation relative rate	Day^{-1}	$(15)^{-1}$	0–0.2	[13,36,38]
α_S	Vaccination relative rate for susceptible individuals	Day^{-1}	0.01	0–1	[19,27]
α_E	Vaccination relative rate for exposed individuals	Day^{-1}	0.015	0–1	[19,27]
α_Q	Vaccination relative rate for quarantined individuals	Day^{-1}	0.0167	0–1	See text
φ_S	S_n behavioral change relative rate	Day^{-1}	0.076	0–1	[1,4,35]
φ_E	E_n behavioral change relative rate	Day^{-1}	0.082	0–1	[1,4,35]
φ_I	I_n behavioral change relative rate	Day^{-1}	0.089	0–1	[1,4,35]
f_n	Fraction of $\lambda_n S_n$ found by contact tracing and quarantined	1	0.8	0–1	[27]
f_ℓ	Fraction of $\lambda_\ell S_\ell$ found by contact tracing and quarantined	1	0.8	0–1	[27]
N	Population size	People	1 million	0–7 billion	See text
E_{0n}/N	Initially infected fraction of the population	1	0.00001	0–1	See text

γ_ℓ of people in the n and ℓ activity level classes are distributed among the three subgroups in proportion to their fractional activity levels ψ_k for $k = n$, ℓ, and c given by

$$\psi_k = \frac{\gamma_k A_k}{\gamma_n A_n + \gamma_\ell A_\ell + \gamma_c A_c}.$$

The denominator is the total number of contacts of the three activity subgroups per unit time. The fractions of people in subgroups n, ℓ, and c that are infectious are I_n/A_n, I_ℓ/A_ℓ, and W/A_c, respectively. Thus the fractions of contacts with infectious people in subgroups n, ℓ, and c are $\psi_n I_n/A_n$, $\psi_\ell I_\ell/A_\ell$, and $\psi_c W/A_c$. Incorporation of the probability of transmission per contact β gives the forces of infection for the normally active and less active groups ($j = n$ and ℓ):

$$\begin{aligned}\lambda_j &= \gamma_j \beta\left(\psi_n \frac{I_n}{A_n} + \psi_\ell \frac{I_\ell}{A_\ell} + \psi_c \frac{W}{A_c}\right)\\ &= \gamma_j \beta\left(\frac{\gamma_n I_n + \gamma_\ell I_\ell + \gamma_c W}{\gamma_n A_n + \gamma_\ell A_\ell + \gamma_c A_c}\right).\end{aligned} \tag{3}$$

These forces of infection and appropriate initial conditions complete our model formulation.

4. The effective reproduction number $\Re_{\text{eff}}$

Often the effectiveness of control efforts is measured by their ability to reduce the spread of a disease in a given population. A common measure of the transmissibility of a disease is the effective reproduction or replacement number $\Re_{\text{eff}}$, which is the average number of secondary cases

produced by a typical infectious individual during its infectious period [22,40]. In an epidemic model the magnitude of the effective reproduction number $\Re_{\text{eff}}$ determines whether or not an epidemic occurs and if so, its severity. The number of infections grows when the effective reproduction number is greater than one, so that there is an epidemic outbreak, but there is no outbreak when the effective reproduction number is less than one. In the absence of interventions or behavioral changes, the model has an initial effective reproduction number $\Re_{\text{unc}}$ (i.e. uncontrolled) given by

$$\Re_{\text{unc}} = \frac{\beta\gamma_n}{\delta+\mu}\frac{S_{0n}}{N_0}. \tag{4}$$

This $\Re_{\text{unc}}$ is the product of the contact rate γ_n, the fraction β of contacts that result in transmission, the average infectious period $1/(\delta+\mu)$, and the initial susceptible fraction S_{0n}/N_0, where the initial population size without controls is $N_0 = S_n + E_n + I_n + R$.

The 'next-generation operator' approach [40] can be used to find an expression for the effective reproduction number $\Re_{\text{eff}}$ for our epidemic model when isolation, quarantine, vaccination, and behavioral changes are implemented in the population. The computation is done by linearizing system (2) around the disease-free steady state and by identification of conditions that guarantee growth in the infected classes. The disease-free steady state has Q, E_n, E_ℓ, I_n, I_ℓ, and W equal to zero with S_{0n}, R_0, V_0, and $S_{0\ell}$ positive. But since we are not considering residual immunity from previous smallpox vaccination, then R_0 and V_0 are also equal to zero. The resulting six dimensional linearized system is of the form $\dot{\mathbf{X}} = (\mathbf{F}-\mathbf{V})\mathbf{X}$, where

$$\mathbf{X} = [\,Q \quad E_n \quad E_\ell \quad I_n \quad I_\ell \quad W\,]^{\mathrm{T}},$$

$$\mathbf{F} = \frac{1}{\rho}\begin{bmatrix} 0 & 0 & 0 & f_n\gamma_n^2\beta S_{0n} + f_\ell\gamma_n\gamma_\ell\beta S_{0\ell} & f_\ell\gamma_\ell^2\beta S_{0\ell} + f_n\gamma_n\gamma_\ell\beta S_{0n} & f_n\gamma_n\gamma_c\beta S_{0n} + f_\ell\gamma_\ell\gamma_c S_{0\ell} \\ 0 & 0 & 0 & (1-f_n)\gamma_n^2\beta S_{0n} & (1-f_n)\gamma_n\gamma_\ell\beta S_{0n} & (1-f_n)\gamma_n\gamma_c\beta S_{0n} \\ 0 & 0 & 0 & (1-f_\ell)\gamma_n\gamma_\ell\beta S_{0\ell} & (1-f_\ell)\gamma_\ell^2\beta S_{0\ell} & (1-f_\ell)\gamma_\ell\gamma_c\beta S_{0\ell} \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

$$\mathbf{V} = \begin{bmatrix} \eta_6 & 0 & 0 & 0 & 0 & 0 \\ 0 & \eta_4 & 0 & 0 & 0 & 0 \\ 0 & -\varphi_E & \eta_1 & 0 & 0 & 0 \\ 0 & -\omega & 0 & \eta_5 & 0 & 0 \\ 0 & 0 & -\omega & -\varphi_I & \eta_2 & 0 \\ -\omega & 0 & 0 & -\theta & -\theta & \eta_3 \end{bmatrix},$$

$\eta_1 = \alpha_E + \omega$, $\eta_2 = \mu + \delta + \theta$, $\eta_3 = \mu + \delta$, $\eta_4 = \eta_1 + \varphi_E$, $\eta_5 = \eta_2 + \varphi_I$, $\eta_6 = \alpha_Q + \omega$, and $\rho = \gamma_n(S_{0n} + R_0 + V_0) + \gamma_\ell S_{0\ell}$. The effective reproduction number $\Re_{\text{eff}}$ is the largest eigenvalue of the matrix $\mathbf{FV}^{-1}$ [40]. Hence $\Re_{\text{eff}}$ with controls called $\Re_{\text{con}}$, the only non-zero eigenvalue of the matrix above, is given by the expression

$$\Re_{\text{con}} = \frac{\beta\gamma_n^2(1-f_n)S_{0n}}{\rho}\frac{\omega}{\eta_4\eta_5} + \frac{\beta\gamma_n\gamma_\ell(1-f_n)S_{0n}}{\rho}\left[\frac{\varphi_E}{\eta_4}\frac{\omega}{\eta_1} + \frac{\varphi_I}{\eta_5}\frac{\omega}{\eta_4}\right]\left[\frac{\gamma_\ell}{\eta_2} + \frac{\theta\gamma_c}{\eta_2\eta_3}\right] + \frac{\gamma_c}{\eta_3}\left[\frac{\beta\gamma_n(1-f_n)S_{0n}}{\rho}\frac{\omega\theta}{\eta_4\eta_5} + \frac{\beta\gamma_\ell(1-f_\ell)S_{0\ell}}{\rho}\frac{\omega\theta}{\eta_1\eta_2}\right] + \frac{\gamma_c}{\eta_3}\frac{\omega}{\eta_6}\left[\frac{\beta\gamma_n f_n S_{0n}}{\rho} + \frac{\beta\gamma_\ell f_\ell S_{0\ell}}{\rho}\right] + \frac{\beta\gamma_\ell^2(1-f_\ell)S_{0\ell}}{\rho}\frac{\omega}{\eta_1\eta_2}. \tag{5}$$

We use expressions (4) and (5) to define the effective reproduction number for the model as

$$\Re_{\text{eff}} = \begin{cases} \Re_{\text{unc}} & t < t_0, \\ \Re_{\text{con}} & t > t_0, \end{cases}$$

where t_0 is the time at which the control measures are implemented and behavioral changes start. Note that when $S_{0\ell} = 0$, $\rho = \gamma_n N_0$, where N_0 is the population at the disease free steady state, so that with no controls, $\Re_{\text{con}}$ in (5) reduces to $\Re_{\text{unc}}$ in (4).

The secondary cases for $t > t_0$ can be explained as follows. The first term of (5), is the contribution from the normally active class I_n, which is the product of the effective infectivity $\beta\gamma_n^2(1-f_n)S_{0n}/\rho$, the fraction ω/η_4 through E_n that goes to I_n, and the mean residence time $1/\eta_5$ in I_n. Because of behavioral changes, there are additional possible paths to infectious classes for the fraction $1-f_n$ who go to E_n. Of those in E_n, the fraction φ_E/η_4 go to E_ℓ and then the fraction ω/η_1 of these go on to I_ℓ. Of those in E_n, the fraction ω/η_4 go to I_n and then the fraction φ_I/η_5 of these go to I_ℓ. Those in I_ℓ contribute some new infectious contacts and some in I_ℓ move on to W where they produce more contacts. Thus the total contribution to producing new infectious contacts due to behavioral change is

$$\frac{\beta\gamma_n\gamma_\ell(1-f_n)S_{0n}}{\rho}\left[\frac{\varphi_E}{\eta_4}\frac{\omega}{\eta_1} + \frac{\varphi_I}{\eta_5}\frac{\omega}{\eta_4}\right]\left[\frac{\gamma_\ell}{\eta_2} + \frac{\theta\gamma_c}{\eta_2\eta 3}\right].$$

Now consider the paths of the new cases leading to the third term (second line) in (5). Of the new cases starting in S_n, the fraction $(1-f_n)$ go to E_n with an effective infectivity of $\beta\gamma_n S_{0n}/\rho$. Of these the fraction ω/η_4 go to I_n, and the fraction θ/η_5 of those in I_n go to W, in which they have a contact rate γ_c and stay for a mean time $1/\eta_3$. The explanations for the second term in the second line is similar with γ_n, S_{0n}, f_n, η_4, and η_5 replaced by γ_ℓ, $S_{0\ell}$, f_ℓ, η_1, and η_2. Thus the total contribution to producing infectious contacts of these new cases is

$$\frac{\gamma_c}{\eta_3}\left[\frac{\beta\gamma_n(1-f_n)S_{0n}}{\rho}\frac{\omega\theta}{\eta_4\eta_5} + \frac{\beta\gamma_\ell(1-f_\ell)S_{0\ell}}{\rho}\frac{\omega\theta}{\eta_1\eta_2}\right].$$

In addition, the fraction f_n of normally susceptible individuals go to Q with an effective infectivity $\beta\gamma_n S_{0n}$, and the fraction ω/η_6 of those in Q go to W, in which they have a contact rate γ_c and stay for a mean time $1/\eta_3$. The explanations for the second term on the third line are similar with the subscripts n replaced by ℓ. Hence, the total contribution to producing infectious contacts of these new cases is

$$\frac{\gamma_c}{\eta_3}\frac{\omega}{\eta_6}\left[\frac{\beta\gamma_n f_n S_{0n}}{\rho} + \frac{\beta\gamma_\ell f_\ell S_{0\ell}}{\rho}\right].$$

The last term in (5), which is the contribution from the low infectivity class I_ℓ, is the product of the effective infectivity $\beta\gamma_\ell^2(1-f_\ell)S_{0\ell}/\rho$, the fraction ω/η_1 through E_ℓ that goes to I_ℓ, and the mean residence time $1/\eta_2$ in I_ℓ.

5. Estimation of parameter values

Here the sources are given for the baseline parameter values in Table 2 that are used in the numerical simulations. The incubation period for smallpox has been reported to be from 7 to 19 days, but the most common reported range is 10–14 days with a mean of 12 days [13,36,38]. Afterward, smallpox patients experience a prodromal phase with symptoms such as fever, malaise, prostration, headache, backache, and vomiting. This period lasts for 2–4 days with a mean of 3 days [7,13]. Data on previous outbreaks show that patients have very low infectivity during the prodromal phase [11,14,31]. Here, the prodromal phase is combined with the incubation phase. Thus the mean time in the non-infectious stages denoted by E_n and E_ℓ, here corresponding to the incubation period plus the prodromal period, has been assumed to be 15 days, so that the transfer rate constant is $\omega = 1/15$.

Patients remain contagious for a period of approximately 14–17 days with a mean of 16 days [13,23,36], so that the recovery rate constant is $\delta = 1/16$. The case fatality rate of smallpox (variola major) varies, but is reported to be about 30% among unvaccinated individuals [13,23,26]. Without behavioral change or isolation, the fraction in the model dying from smallpox is $\mu/(\delta+\mu)$. Setting this equal to 0.3 yields $\mu = 0.3\delta/0.7 = 0.0268$.

Recent estimates on the transmission of smallpox indicate that 1 infected person may infect 3–6 others [12,15]. Therefore, the product $\beta\gamma_n$ of the probability of transmission and the contact rate in the normally active population was set equal to $3(\delta+\mu)$, so that $\Re_{\text{unc}} = 3$ in a completely susceptible population. The contact rates for the normally active, less active and confined people are chosen so that a normally active individual would have 10 times more contacts then a less active person and 100 times more contacts than a confined individual. Thus $\beta\gamma_\ell = \beta\gamma_n/10$ and $\beta\gamma_c = \beta\gamma_n/100$. Other ratios are considered in the sensitivity analyses section.

A product $\beta\gamma_k$ is often called an adequate contact rate, because it is the rate of contacts that are sufficient for transmission [20]. When the numerators and denominators of the forces of infection (3) are multiplied by β, then the forces of infection depend on the products $\beta\gamma_n$, $\beta\gamma_\ell$, and $\beta\gamma_c$. Thus β does not have to be estimated independently in order to do the computer simulations of the model for transmission and control. However, a value for the probability β of transmission is needed in order to estimate quantities such as the total number quarantined and the total number vaccinated using ring vaccination. The probability of smallpox transmission during daily contacts in previous smallpox outbreaks have an average value of about 0.1 [33], so we set $\beta = 0.1$.

The baseline population size N for the community experiencing a smallpox attack is set at one million and all are initially in the normally active susceptible class S_n. Also the initial fraction E_{0n}/N is 0.00001, so that $E_{0n} = 10$, when N is one million. However, our model scales linearly, so that if the initial population size N and the initial infected fraction E_{0n} are both scaled up or down by the same factor, then the resulting solutions are also scaled by this factor. Moreover, since E_{0n} is much less than N, if E_{0n} is scaled up or down from 10 by less than an order of magnitude, then the

results are also scaled by this factor. We assume that the initially infected people enter the normally active exposed class E_n. The average time for these initially-infected people to move through the incubation class E_n and become infectious is 15 days. Then it may take about 5 days for public health officials to diagnose smallpox. Hence, we assume that interventions and behavioral change start on day $t_0 = 20$ [33].

The transfer rate constant of infectives into isolation is $\theta = 1/5$ per day; that is, it takes an average of 5 days to identify smallpox and isolate an infected person not found by contact tracing. Using the values of θ, δ, and μ in Table 2, we find that 69% of smallpox infectives in the infective classes I_n and I_ℓ are moved to the isolation class, 22% recover, and 9% die on our baseline simulations. Of the 69% moving into the isolation class W, 48% recover and 21% die, so that $9\% + 21\% = 30\%$ of those infected eventually die, which is consistent with the 30% case fatality rate reported for smallpox.

The proportions f_n and f_ℓ of adequate contacts of normally and less active individuals found by contact tracing and quarantined are set to 0.8 [27]. Recall that the quarantine class Q contains people who were not only quarantined after being traced as a contact of an infective, but also were latently infected. For every traced person who was latently infected due to an adequate contact and moved into Q, there are $(1 - \beta)/\beta = 9$ other people who are identified by contact tracing and quarantined, but who do not become infected since their contact with an infective was not sufficient for transmission. Note that these 9 other people were quarantined, but were left in the susceptible class, since they were not latently infected. Thus with $\beta = 0.1$, 10% of those found by contact tracing move into Q and 90% stay in S, so that there are 9 quarantined (not infected) people remaining in S for every 1 latently infected person moving into Q. Thus the total number of latently infected and uninfected people who are quarantined is 10 ($=1/\beta$) times the number moving into the quarantine class Q.

In ring vaccination we assume that people identified by contact tracing as having a contact with a smallpox infective are vaccinated. Smallpox vaccination has been reported to prevent disease if given within 4 days after infection [5]. Because people in the quarantine class were identified by contact tracing, it is high priority to vaccinate them as soon as possible. Therefore, it is assumed that 90% of quarantined people are vaccinated, but because of delays in identifying index cases and finding their contacts, only 20% of quarantined individuals are assumed to be successfully vaccinated within the first 4 days after exposure. Setting the fraction $\alpha_Q/(\alpha_Q + \omega)$ of people leaving the quarantined class by vaccination equal to 0.2 yields $\alpha_Q = 0.2\omega/0.8 = 0.0167$. For each person entering Q, there are $(1 - \beta)/\beta = 9$ other people who were identified by contact tracing and quarantined, but uninfected. Thus the total number vaccinated, successfully or unsuccessfully, is 0.90×10 times the inflow into the quarantined class Q.

The policy of mass smallpox vaccination implies that people to be vaccinated are chosen at random. Hence, it is assumed that initially an average of 10 000 randomly selected people are vaccinated a day (e.g. 100 vaccinators vaccinating 100 people per day [19]). Since 1% of the population is initially vaccinated each day, $\alpha_S = 0.01$. If 80% of those vaccinated during their first 4 days in E_n and E_ℓ become immune and the average time in E_n and E_ℓ is 15 days, then only about 20% of those randomly chosen from E_n and E_ℓ would be successfully vaccinated, so that $\alpha_E = 0.2\alpha_S = 0.002$. Because the rates α_Q, α_S, and α_E are rates of successful vaccination and the smallpox vaccine efficacy is about 95% [27], the actual vaccination rates would be slightly (5%) higher.

The relative rates $\varphi_i(I_n + I_\ell)$ given by Eq. (1) at which people change their behavior depend on the total prevalence $I_n + I_\ell$ of infected individuals in the community. Thus the behavioral change coefficients φ_S, φ_E, and φ_I increase as $I_n + I_\ell$ increases (e.g. as more cases are reported by the news), resulting in a net decrease in the total contact activity of the population [1,4,35]. The parameters a_i and b_i in the expression (1) for $\varphi_i(I_n+I_\ell)$ with $i = S$, E, or I were chosen, so that a certain percentage change in behavior was achieved at day 60. In order to have the asymptotic values a_i/b_i of the φ_i for large prevalences satisfy $a_S/b_S < a_E/b_E < a_I/b_I$, we set all $b_i = 1000$ and then chose the x in $a_S = 1000/x$, $a_E = 1000/(x-1)$, and $a_I = 1000/(x-2)$ to obtain the desired percentages. For intervention with only high behavioral change (HBC), $x = 13$ implies that 95% of the population had changed their behavior at day 60 after 40 days of behavioral change, which is an average behavioral change of 2.3% per day. Similarly when the sole intervention is medium behavioral change (MBC), $x = 23$ so that 82% of the population had changed their behavior at day 60, which is 2% per day. With low behavioral change (LBC), $x = 38$ so that 65% of the population had changed their behavior at day 60, which is an average of 1.6% per day.

6. Numerical simulation results

Sixteen intervention strategies are considered in the simulations. The eight intervention strategies considered in Table 3 are no intervention or single interventions including isolation,

Table 3
Estimates of cumulative total smallpox cases for single intervention strategies

Intervention	R_{con}[a]	60 days	180 days	365 days	Final day[b]
None	3	181	133729	966971	307
Isolation	0.9	63	179	296	1602
Isolated		35	117	198	310
Quarantine	0.6	89	204	223	318
Quarantined		634	1295	1403	1396
Ring vaccination	0.6	83	176	191	308
Quarantined		633	1284	1386	1378
Vaccinated		573	1170	1264	1256
Mass vaccination	2.9	135	1392	1640	256
Vaccinated		329544	791490	954601	895040
High behavioral change	0.8–0.3	69	107	108	166
Changed behavior		953939	999981	999986	999973
Medium behavioral change	1.3–0.3	96	298	306	208
Changed behavior		824422	998983	999934	999656
Low behavioral change	1.7–0.3	120	1345	1647	274
Changed behavior		651100	984864	999471	998352

[a] Number of infected per infectious person when interventions are present in the population.
[b] Days from infection of index cases until outbreak is controlled (when the number of cases reaches 99% of the final epidemic size).

quarantine, quarantine with ring vaccination (RV), mass vaccination (MV), high behavioral change (HBC), medium behavioral change (MBC), and low behavioral change (LBC). The first strategy in Table 4 of isolation combined with quarantine and ring vaccination corresponds roughly to the basic CDC strategy [6]. The next three strategies in Table 4 add either high, medium, or low behavioral change. The four strategies in Table 5 add mass vaccination to the four strategies in Table 4.

All simulations assume that 0.001% infected individuals in a population of 1 million people enter the incubation phase after being successfully infected during the smallpox attack. All interventions start 20 days later. One column in Tables 3–5 identifies the effective reproduction number $\Re_{con}$ for each intervention. From this column, the impact of interventions in $\Re_{con}$ are identified. The cumulative number of smallpox cases and the number of people affected by the interventions are given at 60, 180, and 365 days after the introduction of smallpox into the population. The final day in each table is the day on which the number of smallpox cases reach 99% of the final epidemic size, which is a measure of the length of the smallpox outbreak.

6.1. Single intervention strategies

The first entry in Table 3 shows that almost everyone in the population is infected with smallpox when there are no interventions. With only isolation of infectives the effective reproduction

Table 4
Estimates of cumulative total of smallpox cases for combination intervention strategies

Intervention	R_{con}[a]	60 days	180 days	365 days	Final day[b]
Isolation and RV	0.2	47	55	55	116
Isolated		31	39	39	38
Quarantined		183	211	211	209
Vaccinated		167	192	193	191
Isolation, RV and HBC	0.1–0.04	40	42	42	89
Isolated		24	27	27	26
Quarantined		95	98	98	97
Vaccinated		86	89	89	89
Changed behavior		953 741	999 850	999 858	994 933
Isolation, RV and MBC	0.1–0.04	42	46	46	92
Isolated		27	30	30	29
Quarantined		121	126	126	126
Vaccinated		110	115	115	114
Changed behavior		824 113	997 136	997 568	956 871
Isolation, RV and LBC	0.1–0.07	44	48	48	97
Isolated		28	32	32	32
Quarantined		140	149	149	148
Vaccinated		128	136	136	135
Changed behavior		650 772	974 123	977 478	867 472

[a] Number of infected per infectious person when interventions are present in the population.
[b] Days from infection of index cases until outbreak is controlled (when the number of cases reaches 99% of the final epidemic size).

Table 5
Estimates of cumulative total of smallpox cases for combination intervention strategies

Intervention	R_{con}[a]	60 days	180 days	365 days	Final day[b]
Isolation, RV and MV	0.2	45	50	50	98
Isolated		29	34	34	34
Quarantined		158	169	169	169
Vaccinated		329 881	798 113	968 190	544 456
Isolation, RV, MV and HBC	0.09–0.04	38	40	40	81
Isolated		23	25	25	24
Quarantined		80	81	81	81
Vaccinated		329 830	798 115	968 215	458 389
Changed behavior		871 356	892 705	892 706	889 765
Isolation, RV, MV and MBC	0.1–0.04	40	42	42	83
Isolated		25	27	27	27
Quarantined		103	103	103	103
Vaccinated		329 844	798 114	968 209	470 183
Changed behavior		730 278	818 525	818 564	795 056
Isolation, RV, MV and LBC	0.1–0.08	42	44	44	86
Isolated		26	29	29	28
Quarantined		119	121	121	121
Vaccinated		329 854	798 315	968 204	484 303
Changed behavior		554 902	716 709	716 992	658 561

[a] Number of infected per infectious person when interventions are present in the population.
[b] Days from infection of index cases until outbreak is controlled (when the number of cases reaches 99% of the final epidemic size).

number $\Re_{con}$ of 0.9 is just barely below one, so that the epidemic decays very slowly with 296 smallpox cases at 365 days, and a final day over 4 years. When only quarantine is used, the effective reproduction number $\Re_{con}$ is reduced to 0.6, so that the total cumulative smallpox cases of 223 is lower and the final day is reduced to 318. Ring vaccination of quarantined people, who were found by contact tracing, leads to a similar effective reproduction number $\Re_{con}$, an earlier final day of 308, and slightly fewer total smallpox cases. Mass vaccination leads to a similar final day of 256, but the total of 1640 smallpox cases at day 365 is much higher than with the other interventions and over 95% of the population of 1 million has been vaccinated on day 365.

The last three entries in Table 3 correspond to different levels of behavioral change as the sole intervention. With high behavioral change in which an average of 2.3% of those with normal activity levels reduce their daily contacts by a 10 factor during the 40 days of behavioral change, the final day of 166 is early and there are only 108 total smallpox cases, but the behavioral change is so fast that over 95% have changed their behavior after 60 days. The range 0.8–0.3 for the effective reproduction number $\Re_{con}$ means that it was initially 0.8, but then it declined to 0.3 as the average activity level in the population decreased. With medium behavioral change in which an average of 2% change their behavior per day, the final day is 208 and there are 306 total smallpox cases, but behavioral change is still extensive with over 82% changed by day 60. With low behavioral change with an average of 1.6% change per day, over 65% and over 99.9% have decreased their contact activity by days 60 and 365. In this case the final day is 274 and there are 1647 total

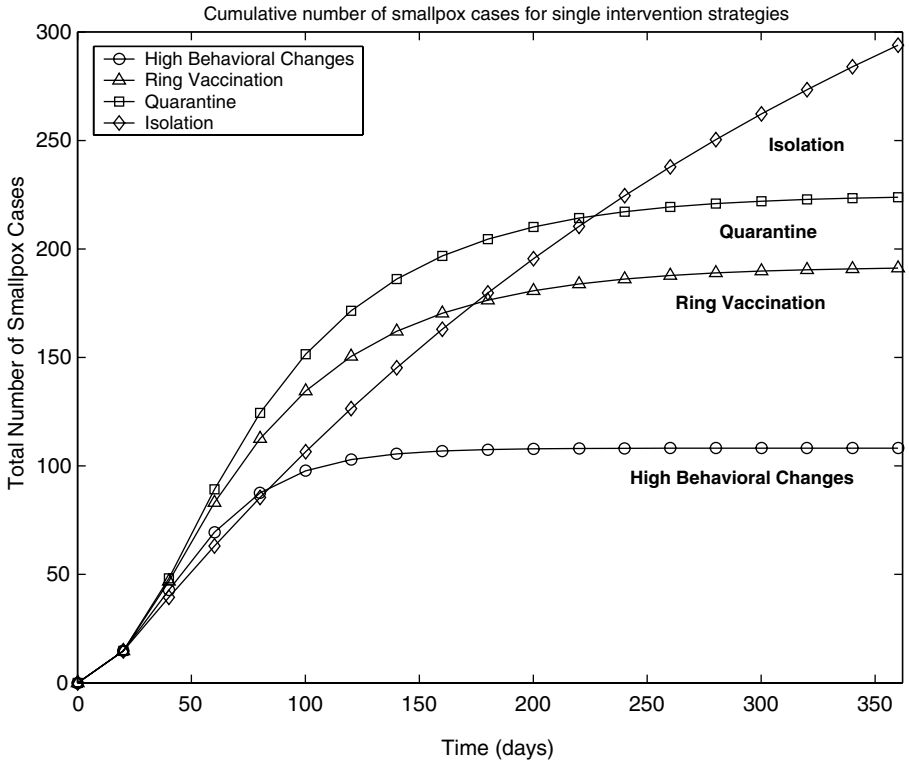

Fig. 2. Cumulative number of smallpox cases for various single intervention strategies. An intervention of high behavioral change only leads to 108 total smallpox cases (○) while ring vaccination only leads to 191 total smallpox cases (△). A quarantine only strategy leads to 223 total smallpox cases (□) and isolation only leads to 296 total smallpox cases (◇).

smallpox cases on day 365, so these values are similar to those obtained with mass vaccination. The cumulative numbers of smallpox cases for some of the interventions in Table 3 are shown in Fig. 2.

6.2. Combination intervention strategies

In Table 4 the strategy of isolation combined with quarantine and ring vaccination is quite effective with 55 total smallpox cases and a final day of 116. Moreover, there are only 209 people quarantined and 191 people vaccinated. Recall that this strategy corresponds roughly to the basic CDC smallpox response strategy [6]. When behavioral changes are added to this strategy, the results are even better. With high behavioral change the numbers quarantined and vaccinated are cut in half, the total smallpox cases are down to 42, and the epidemic is shorter with a final day of 89. The percentage who change their behavior is about 99% by day 365, so the average number of daily contacts in the population is significantly reduced. Results with medium and low behavioral change have slightly more smallpox cases and slightly longer epidemics, so they are slightly less effective.

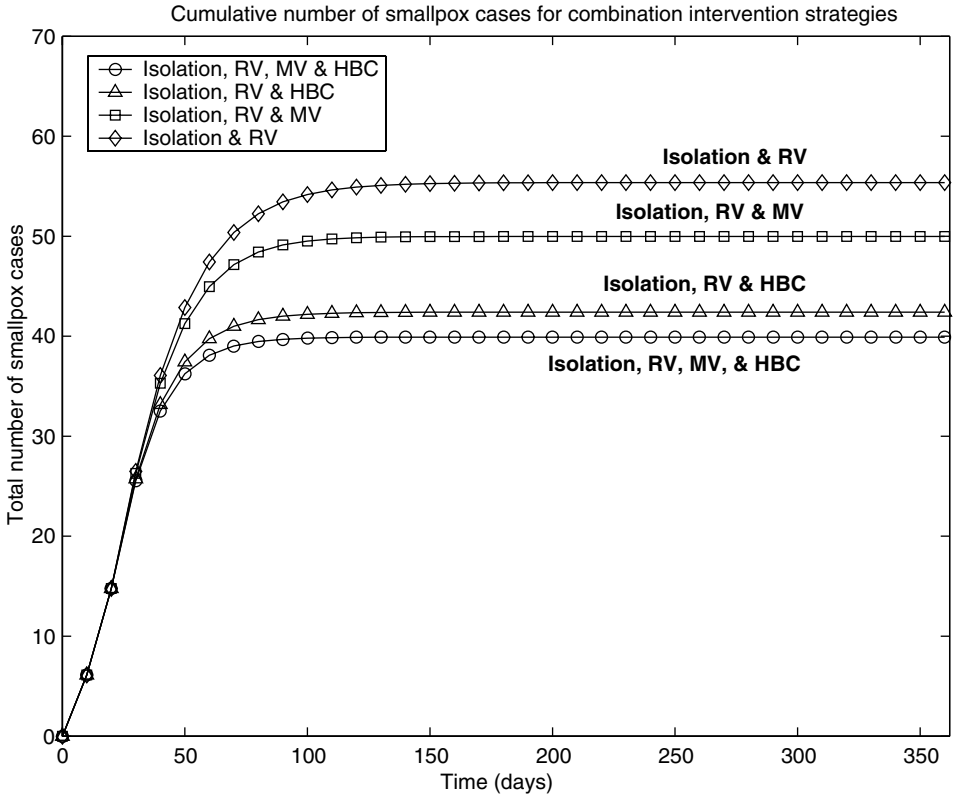

Fig. 3. Cumulative number of smallpox cases for combination intervention strategies. An intervention that combines isolation, ring vaccination (RV), mass vaccination (MV), and high behavioral changes (HBC) leads to only 40 total smallpox cases (○) while isolation, RV and HBC leads to 42 total smallpox cases (△). An intervention that combines isolation, RV and MV leads to 50 total smallpox cases (□) and a strategy that only combines isolation and RV leads to 55 total smallpox cases (◇).

Table 5 contains the same strategies as in Table 4, but with the addition of mass vaccination. The results with mass vaccination are better, since there are 2–5 fewer smallpox cases and the final days are 8–18 days earlier; however, the numbers of people vaccinated are very large, since almost half of the population has been vaccinated on the final day. The cumulative numbers of smallpox cases for some of the interventions in Tables 4 and 5 are shown in Fig. 3.

7. Sensitivity analyses

Although the parameter values were estimated from epidemiological data, there is still some uncertainty in their values. The sensitivity analyses in this section examine the effects of changes in $\Re_0$, t_0, and E_{0n} on the simulation results. We also examine the sensitivity of the single intervention simulations to changes in the values of the parameters γ_j, θ, f_j, α_S, α_E, and α_Q. Unless otherwise stated, the other baseline parameters are fixed at their values in Table 2.

Effective reproductive number: The effective reproductive number $\Re_{\text{unc}}$ determines the average number of secondary cases infected by a typical primary case during the infectious period when no control measures are present. Because the interventions are delayed by 20 days, the effective reproductive number $\Re_{\text{unc}}$ governs the initial growth of the epidemic. Recent estimates on $\Re_{\text{unc}}$ have varied widely, but the most common range is assumed to be between 3 and 6. As $\Re_{\text{unc}}$ was changed from 3 to 4, 5, and 6, the total number of smallpox cases increased significantly as shown in Fig. 4. The strategies that included high behavioral changes in conjunction with the conventional intervention strategies (Fig. 4, Part a and Part b) were the most effective in reducing the total number of smallpox cases. Note that HBC caused larger relative decreases in the total number of cases when $\Re_{\text{unc}}$ was 6 than when it was 3.

Start of interventions: Time is crucial when an epidemic strikes. When we changed the start of the intervention combining isolation, RV and HBC from 20 days to 30, 40, and 50 days, the

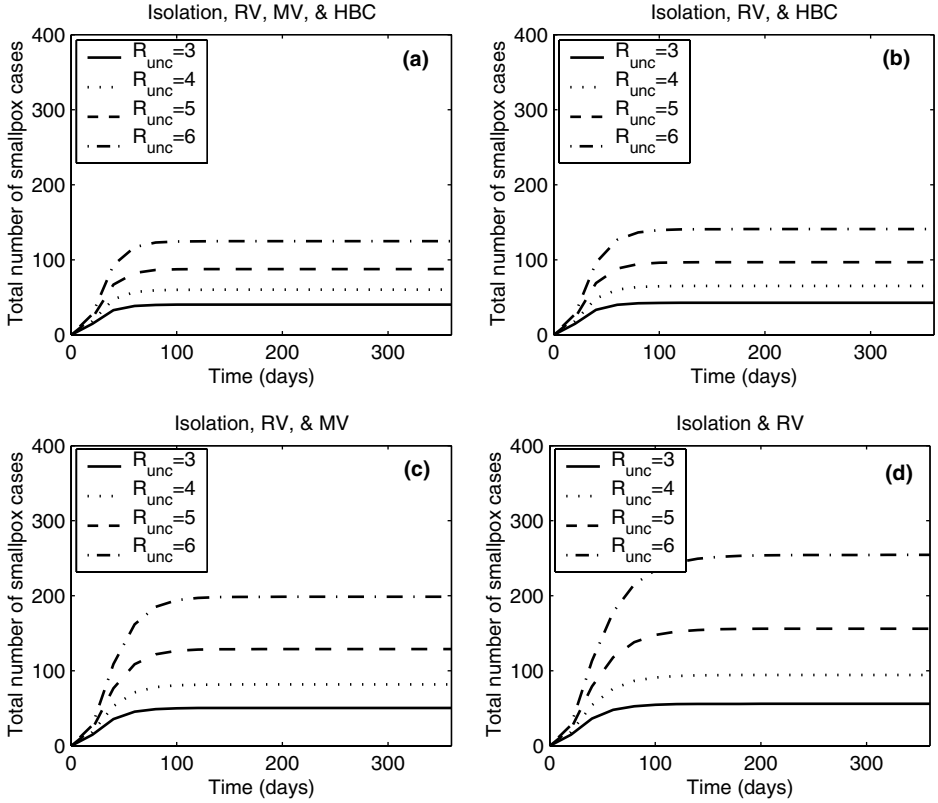

Fig. 4. Cumulative number of smallpox cases for combination intervention strategies for different values of $\Re_0$. (a) An intervention strategy that includes isolation, RV, MV, and HBC is implemented. The final epidemic sizes for $\Re_0 = 3, 4, 5,$ and 6 are 40, 60, 87, and 124, respectively. (b) An intervention strategy that includes isolation, RV, and HBC is implemented. The final epidemic sizes for $\Re_0 = 3, 4, 5,$ and 6 are 42, 65, 96, and 140, respectively. (c) An intervention strategy that includes isolation, RV, and MV is implemented. The final epidemic sizes for $\Re_0 = 3, 4, 5,$ and 6 are 50, 81, 128, and 198, respectively. (d) An intervention strategy that includes isolation and RV is implemented. The final epidemic sizes for $\Re_0 = 3, 4, 5,$ and 6 are 55, 94, 156, and 254, respectively.

cumulative cases at 365 days increased dramatically from 42 to 78, 140, and 250, respectively. Thus the epidemic is very sensitive to the delay in starting interventions and informing the population about a smallpox outbreak. Early identification of smallpox cases leading to rapid interventions and notification of the general public is very important in limiting the size and length of an outbreak.

Index cases: The number of initially exposed individuals has a major impact on an epidemic, since there are no interventions during the initial phase of the epidemic. In this model the cumulative number of cases increases linearly with the number of index cases. For example, increasing the number initially exposed by a factor of 10 increases the total number of cases at day 365 by a factor of 10.

Contact rates: We consider variations due to changes in the average contact rates γ_n and γ_ℓ for the normally active and less active populations, when high behavior change is the sole intervention. When γ_n is decreased from 10 to 9, 6, and 3, while γ_ℓ is fixed but R_{eff} decreases, the epidemic size at day 365 decreases from 108 to 85, 42, and 25, respectively. When γ_n is increased from 10 to 20, 30, and 40, while γ_ℓ is fixed but R_{eff} increases, the epidemic size at day 365 increases from 108 to 1281, 15 152, and 71 594, respectively. When the average contact rate for the less active population, γ_ℓ is decreased from 1 to 0.9, 0.6, and 0.3 while γ_n is fixed, the epidemic size at day 365 decreases slightly from 108 to 104, 96, and 90, respectively. When γ_ℓ is increased from 1 to 3, 6, and 9, while γ_n is fixed, the epidemic size at day 365 increases from 108 to 450, 253 106, and 938 163, respectively. Thus the simulation results are sensitive to changes in the average contact rates.

Isolation rate: We varied the isolation rate θ, when isolation is the only intervention. When the mean time in the infected class is increased from 5 days to 6, 7 and 8 days the epidemic size at day 365 increases from 296 to 857, 2723, and 8178, respectively. Contrarily when the mean time is decreased from 5 to 4, 3 and 2, the epidemic size at day 365 decreases from 296 to 132, 78, and 53. Therefore, the early identification and isolation of infected individuals plays an important role in slowing the spread of the epidemic.

Quarantine rates: Differences in the fraction found by contact tracing and quarantined influence the cumulative number of infected persons. As f_n and f_ℓ are decreased from 0.8 to 0.7, 0.6 and 0.5, the final epidemic size increases from 224 to 617, 4217, and 46 054, respectively. As f_n and f_ℓ are increased from 0.8 to 0.85, 0.9, and 0.95, the total number of smallpox cases decreases from 224 to 170, 139, and 120, respectively. Thus the model is moderately sensitive to decreases in the fraction of people quarantined after contact tracing.

Vaccination rates: We determined the sensitivity to changes in the vaccination rate α_Q, for a ring vaccination only strategy. When α_Q is decreased from 0.2 to 0.15, 0.10, and 0.05, the final epidemic size at day 365 increases from 191 to 199, 207, and 215, respectively. When α_Q is increased from 0.2 to 0.4, 0.6, and 0.8, the final epidemic size at day 365 decreases from 191 to 159, 128, and 97, respectively. Thus the model is slightly sensitive to changes in the vaccination rate α_Q.

Changes to the vaccination rates α_S and α_E for a mass vaccination only strategy influence the final epidemic size. As α_S is decreased from 0.01 to 0.0064 and 0.0036, while α_E is fixed, the final epidemic size at 365 days increases from 1641 to 8518 and 49 352, respectively. As α_E is decreased from 0.002 to 0.001, while α_S is fixed, the final epidemic size at 365 days increases from 1641 to 1749. When α_S is increased from 0.01 to 0.04 and 0.0225, while α_E is fixed, the final epidemic size

decreases from 1641 to 104 and 237, respectively. When α_S is increased from 0.002 to 0.005, while α_S is fixed, the final epidemic size at 365 days decreases from 1641 to 1364. Therefore, the model is moderately sensitive to changes in the mass vaccination rates α_S and α_E.

8. Discussion and conclusions

The standard intervention procedures for smallpox control are isolation, quarantine, ring vaccination, and mass vaccination. Another factor that would affect the extent and duration of a smallpox epidemic is the reduction in contacts of people in response to information about the smallpox epidemic. Based on the extensive behavioral changes that occurred during the SARS outbreaks, it is clear that similar reductions in contact rates would also occur after the deliberate release of a biological agent such as smallpox. We used a computer simulation model to examine the effects on the epidemic after a smallpox attack of the standard smallpox interventions combined with behavioral change in the population. Although the changes in behavior in our simulations are gradual and moderate, they have a dramatic impact on the size and length of the smallpox epidemic.

The model has 11 compartments with six epidemiological and eight intervention parameters. The expression in Eq. (5) for the effective reproduction number $\mathfrak{R}_{\text{con}}$ for a smallpox epidemic shows its explicit dependence on these parameter values and on the susceptible fractions in the normally active and less active populations. The derivatives of $\mathfrak{R}_{\text{con}}$ with respect to the parameters could be used to determine which parameters have the greatest effect on $\mathfrak{R}_{\text{con}}$ during the early spread of the epidemic [9,37]. We analyzed the sensitivity of the duration and final epidemic size to changes in the parameter values.

The numerical simulation results in Section 6 show that without any interventions, almost everyone is infected by the final day. This is not surprising, since with an uncontrolled reproduction number of 3, the initial growth is exponential and the final size is large. Simple interventions used alone were simulated next. Isolation of infected cases reduced the effective reproduction number just below one, so that the there were less than 300 total smallpox cases, but the epidemic took over 4 years to die out. With quarantine and ring vaccination, the total cases were around 200 and the epidemic died out in around 300 days. Random mass vaccination did shorten the epidemic to about 260 days, but there were over 1600 smallpox cases and over 90% were vaccinated by the final day. This confirms the CDC statements that indiscriminate mass vaccination is not a reasonable smallpox response strategy [6].

In the simulations, behavioral changes without any other interventions were able to control the epidemic. High behavioral changes (HBC) meant that each day, 2.3% of the population reduced their contacts by a factor of 10. Simulations with HBC led to only 108 smallpox cases with 166 as the final day. In other words, the behavioral change intervention was more effective than any other single intervention. Moreover, behavioral changes were relatively fast since over 95% reduced their daily contacts by day 60. Although global behavior change in the population was simulated, the behavioral change intervention could be applied locally, since only reductions in contact rates around those who are infected would lead to reductions in secondary cases. Medium and low behavioral changes were also effective in controlling the epidemic, but there

were more smallpox cases and the length of the outbreak was longer. Table 3 shows that the simple intervention of quarantine with ring vaccination is reasonably effective in stopping the epidemic, but the best results in the table correspond to the simulation with high behavioral change.

The combined strategy in Table 4 that consists of isolation, quarantine, and ring vaccination corresponds roughly to the basic CDC smallpox response strategy. Given that the 10 original cases are included in the final total cases and that interventions did not start until day 20, this combined strategy was reasonably effective with only 55 total smallpox cases and a final day of 116. Moreover, this combined strategy was reasonably inexpensive, since there are only 209 people quarantined and 191 people vaccinated. Thus the simulations confirm that the basic CDC strategy would be reasonably effective and would probably not be too expensive.

For completeness, strategies that include mass vaccination are also considered. The four strategies in Table 5 with mass vaccination do yield shorter outbreaks with fewer total smallpox cases than the same strategies without mass vaccination. So the addition of mass vaccination does lead to slightly better results, but the small improvements are probably not worth the cost of vaccinating so many people. Our simulations show that following a smallpox release, mass vaccination is the least effective strategy, when cost and logistic difficulties are considered.

Although parameter values are estimated using data, there is still uncertainty associated with their values. We found that the simulation results are most sensitive to the uncertainty in the effective reproduction number $\Re_{\text{unc}}$ and the time t_0 at which interventions start. They are also sensitive to the number E_{0n} of index cases, and the isolation rate θ.

Reducing one's daily contacts in response to information about the presence of smallpox is a rational action that might be taken by many people in the community. Indeed, as the perceived threat increases, more people would change their behavior and they would make changes faster. Thus behavioral change would certainly occur without any specific actions by public health officials. Of course, public health authorities and community leaders could increase the extent and speed of these changes by actions such as encouraging people to stay home or to avoid crowded places. Table 4 shows that the addition of behavioral change to the basic CDC strategy decreases the total smallpox cases and shortens the outbreak. For example, behavioral change by 2.3% per day reduces the smallpox cases by 13 and decreases the final day by 27 days down to 89 days. With a mortality rate of 30%, the reduction of 13 cases would mean about 4 fewer deaths during the smallpox epidemic.

We conclude that for simulations of a smallpox outbreak to be useful in guiding public health policy, they must consider the impact of behavioral changes. Behavioral changes might seem inexpensive compared to isolation, quarantine, and vaccination, since there is no direct cost of behavioral changes to the public health sector. However, there would be economic costs to individuals and society related to lost work or increased school absenteeism, decreased business revenues, missed events, postponed travel, etc. Thus local, regional, and national public health officials and government leaders would need to weigh all factors before making recommendations about having people stay home, closing schools, canceling events, etc. Indeed, this planning could be done in advance, so that policies regarding recommendations on behavioral changes would become part of the smallpox response plan. The simulations here are useful in providing estimates of the effects of these recommended behavioral changes.

Acknowledgments

This research has been supported through the Center for Nonlinear Studies and the Mathematical Modeling and Analysis Group at Los Alamos National Laboratory under the Department of Energy contract W-7405-ENG-36.

References

[1] Agence France-Presse. SARS Singapore and Hong Kong both close schools. Available from: <http://www.rense.com/general36/sing.htm>.
[2] C. Castillo-Chavez, B. Song, J. Zhang, An epidemic model with virtual mass transportation: the case of smallpox in a large city, in: H.T. Banks, C. Castillo-Chavez (Eds.), Bioterrorism: Mathematical Modeling Applications in Homeland Security, SIAM, Philadelphia, PA, 2003, p. 173.
[3] J. Barbera, A. Macintyre, L. Gostin, T. Inglesby, T. O'Toole, C. DeAtley, K. Tonat, M. Layton, Large-scale quarantine following biological terrorism in the United States: scientific examination, logistic and legal limits, and possible consequences, Amer. Med. Assoc. 286 (21) (1999) 2711.
[4] R.J. Blendon, C.M. DesRoches, J.M. Benson, M.J. Herrmann, K. Taylor-Clark, K.J. Weldon, The public and the smallpox threat, New Engl. J. Med. 348 (5) (2003) 426.
[5] S.A. Bozzette, R. Boer, V. Bhatnagar, J.L. Brower, E. Keeler, S.C. Morton, M.A. Stoto, A model for a smallpox-vaccination policy, New Engl. J. Med. 348 (5) (2003) 416.
[6] Centers for Disease Control web site. What CDC is doing to protect the public from smallpox. Available from: <http://www.bt.cdc.gov/agent/smallpox/prep/cdc-prep.asp>.
[7] J. Chin, Control of Communicable Diseases Manual, 17th ed., American Public Health Association, Washington, DC, 2000.
[8] G. Chowell, P.W. Fenimore, M.A. Castillo-Garsow, C. Castillo-Chavez, SARS outbreaks in Ontario, Hong Kong and Singapore: the role of diagnosis and isolation as a control mechanism, J. Theor. Biol. 224 (2003) 1.
[9] G. Chowell, C. Castillo-Chavez, P.W. Fenimore, C. Kribs-Zaleta, L. Arriola, J.M. Hyman, Model parameters and outbreak control for SARS, Emerg. Infect. Diseases 10 (7) (2004) 1258.
[10] CIA believes four nations have secret smallpox virus stocks. Available from: <http://www.cidrap.umn.edu/cidrap/content/bt/smallpox/news/nations.html>.
[11] M. Eichner, K. Dietz, Transmission potential of smallpox: estimates based on detailed data from an outbreak, Amer. J. Epidemiol. 158 (2) (2003) 110.
[12] M. Eichner, Case isolation and contact tracing can prevent the spread of smallpox, Amer. J. Epidemiol. 158 (2) (2003) 118.
[13] F. Fenner, D.A. Henderson, I. Arita, Z. Jezek, I.D. Ladnyi, Smallpox and Its Eradication, World Health Organization, Geneva, Switzerland, 1988.
[14] N.M. Ferguson, M.J. Keeling, W.J. Edmunds, R. Gani, B.T. Grenfell, R.M. Anderson, S. Leach, Planning for smallpox outbreaks, Nature 425 (2003) 681.
[15] R. Gani, S. Leach, Transmission potential of smallpox in contemporary populations, Nature 414 (2001) 748.
[16] J.D. Grabenstein, W. Winkenwerder Jr., US military smallpox vaccination program experience, J. Amer. Math. Assoc. 289 (2003) 3278.
[17] K.P. Hadeler, C. Castillo-Chavez, A core group model for disease transmission, Math. Biosci. 128 (1995) 41.
[18] M.E. Halloran, I.M. Longini Jr., A. Nizam, Y. Yang, Containing bioterrorist smallpox, Sci. Mag. 298 (2002) 1428.
[19] D.A. Henderson, The looming threat of bioterrorism, Science 283 (5406) (1999) 1279.
[20] H.W. Hethcote, J.A. Yorke, in: Gonorrhea Transmission Dynamics and ControlLecture Notes in Biomathematics, vol. 56, Springer, 1984, p. 1.
[21] H.W. Hethcote, P. van den Driessche, An SIS epidemic model with variable population size and a delay, J. Math. Biol. 34 (1995) 177.

[22] H.W. Hethcote, The mathematics of infectious diseases, SIAM Rev. 42 (2000) 599.
[23] D. Hopkins, The Greatest Killer: Smallpox in History, The University of Chicago, Chicago and London, 1983.
[24] J.M. Hyman, J. Li, Behavior changes in SIS models with selective mixing, SIAM J. Appl. Math. 57 (1997) 1082.
[25] J.M. Hyman, J. Li, Modeling the effectiveness of isolation strategies in preventing STD epidemics, SIAM J. Appl. Math. 58 (1998) 912.
[26] H.F. Hull, R. Danila, K. Ehresmann, Smallpox and bioterrorism: public-health responses, J. Lab. Clin. Med. 142 (4) (2003) 221.
[27] E.H. Kaplan, D.L. Craft, L.M. Wein, Emergency response to a smallpox attack: the case for mass vaccination, Proc. Natl. Acad. Sci. 99 (2002) 10935.
[28] M. Kretzschmar, S. van den Hof, J. Wallinga, J. van Wijngaarden, Ring vaccination and smallpox control, Emerg. Infect. Diseases 10 (2004) 832.
[29] J.M. Lane, F.L. Ruben, J.M. Neff, J.D. Millar, Complications to smallpox vaccination, 1968: National Surveillance in the United States, New Engl. J. Med. 281 (1969) 1201.
[30] J.T.F. Lau, H. Tsui, M. Lau, X. Yang, SARS transmission, risk factors, and prevention in Hong Kong, Emerg. Infect. Diseases 10 (2004) 587.
[31] T.M. Mack, Smallpox in Europe 1950–1971, J. Infect. Diseases 125 (1972) 161.
[32] M.S. Massoudi, L. Barker, B. Schwartz, Effectiveness of postexposure vaccinations for the prevention of smallpox: results of a delphi analysis, J. Infect. Diseases 188 (2003) 973.
[33] M.I. Meltzer, I. Damon, J.W. LeDuc, D. Millar, Modeling potential responses to smallpox as a bioterrorist weapon, Emerg. Infect. Diseases 7 (2001) 959.
[34] P.P. Mortimer, Can postexposure vaccination against smallpox succeed? Clin. Infect. Diseases 36 (2003) 622.
[35] X. Pang, Z. Zhu, F. Xu, J. Guo, X. Gong, D. Liu, Z. Liu, D.P. Chin, D.R. Feikin, Evaluation of control measures implemented in the severe acute respiratory syndrome outbreak in Beijing, 2003, J. Amer. Math. Assoc. 290 (2003) 3215.
[36] A.R. Rao, E.S. Jacob, S. Kamalakshi, S. Appaswamy, Bradbury, Epidemiological studies in smallpox. A study of intrafamilial transmission in a series of 254 infected families, Indian J. Med. Res. 56 (1968) 1826.
[37] M.A. Sanchez, S.M. Blower, Uncertainty and sensitivity analysis of the basic reproductive rate, Amer. J. Epidemiol. 145 (12) (1997) 1127.
[38] S. Singh, Some Aspects of the Epidemiology of Smallpox in Nepal, World Health Organization, Geneva, 1969.
[39] Terror attack hits US. Available from: <http://archives.cnn.com/2001/US/09/11/worldtrade.crash/>.
[40] P. van den Driessche, J. Watmough, Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission, Math. Biosci. 180 (2002) 29.
[41] J.X. Velasco-Hernandez, Y.H. Hsieh, Modeling the effect of treatment and behavioral change in HIV transmission dynamics, J. Math. Biol. 32 (1994) 233.