
Modelling responses to a smallpox epidemic taking into account uncertainty

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SUMMARY

Epidemiology and modelling are currently under pressure to build consistent scenarios of control in case of deliberate release of biological weapons. In order to assess the key parameters for the control of a smallpox outbreak in a large city (2 million inhabitants), we built a stochastic model to simulate the course of an epidemic controlled by ring vaccination and case isolation. Assuming a reference scenario with 100 index cases and implementation of intervention 25 days after the attack, the model forecasts an epidemic of 730 cases with an epidemic duration of 240 days. Setting intervention 20 days later would result in an almost fourfold increase in the epidemic size. A multivariate sensitivity analysis has selected three key parameters: the basic reproduction number (i.e. the number of secondary cases infected by one case in an entirely susceptible population, equal to 3 in the reference scenario), time to intervention, and proportion of traced and vaccinated contacts.

INTRODUCTION

Bacteria (*Bacillus anthracis*, *Yersinia pestis*), fungi, protozoa and viruses (Ebola virus, Influenza virus, Variola virus) are cited as potential biological weapons by the World Health Organization [1]. An aerosol release of these agents could be disastrous in terms of morbidity, mortality and cost [2]. In the case of a chemical or a toxic attack, or an attack by an agent such as bacillus anthracis, for which human-to-human transmission is rare, secondary cases would be unlikely. On the other hand, in the case of an attack with infectious agents such as smallpox, serial human-to-human transmission is likely to occur. In order to assess the key parameters for the control of a smallpox outbreak we developed a stochastic version of a deterministic SEIR model (susceptible,

exposed, infectious, removed from the chain of transmission) proposed in a recent work by Gani and Leach [3] and we performed a multivariate sensitivity analysis on the different parameters with a Latin Hypercube Sampling (LHS) method [4]. We simulated the consequences of a bioterrorist attack on a city of 2·15 million inhabitants (the size of the city of Paris, France) under different scenarios. We explored two types of intervention both recommended by the Centres for Disease Control and Prevention [5] and the French Ministry of Health: (i) ring vaccination (vaccination of the individuals who have been in contact with a case) and (ii) isolation of cases.

METHODS

Smallpox spread model

This section describes the model used to simulate different epidemics of smallpox. Individuals who had

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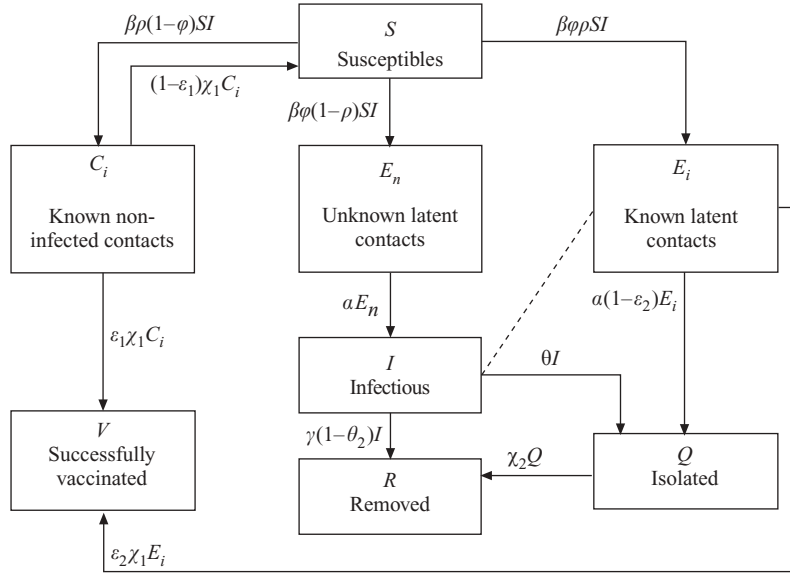


Fig. 1. Description of the model. Capital letters represent the proportion of the population in each group. Transition rates, λ_i , are indicated near arrows. S is the proportion of susceptible individuals in the population, E_n the proportion of untraced latent contacts, C_i the proportion of traced non-infected contacts, E_i the proportion of traced latent contacts, I the proportion of infectious individuals, V the proportion of successfully vaccinated individuals, Q the proportion of isolated individuals and R the proportion of recovered or dead individuals. If the number of persons isolated is limited, the dotted arrow replaces the arrow which joins E_i to Q when the threshold is raised. For parameter definitions and values see Table 2 and the Methods section.

contact with an infectious individual will be referred to as ‘contacts’.

At any given time, the population is divided in eight groups: susceptible individuals (denoted S), untraced latent contacts (E_n), traced latent contacts (E_i), traced non-infected contacts (C_i), infectious individuals (I), isolated cases (Q), successfully vaccinated contacts (V), dead or recovered individuals (R). Individuals can move from one group to another (Fig. 1). This model assumes that contacts are homogeneous in the population, which tends to overestimate the epidemic size [6].

In the simulated population, β is the rate of contacts per infectious individual per day and φ is the probability that a contact is infected. When infected, a contact has a latency and prodromal period of α^{-1} days after which he becomes infectious during γ^{-1} days.

Two types of intervention were modelled: ring vaccination and isolation of cases. When traced, contacts are vaccinated with vaccine efficacy of ε_2 for latent individuals and ε_1 for non-infected individuals. After being vaccinated, non-infected contacts are released into the population at a rate χ_1 . We assumed that the contact-tracing intervention allows identification of

a proportion, ρ , of the contacts. The isolation period lasts χ_2^{-1} days. Unlike Gani and Leach, we considered that untraced contacts would not be isolated just after developing fever [3]. In our model, traced latent contacts are isolated before becoming infectious whereas untraced latent contacts become infectious and a fraction, θ , of them are isolated. We allowed for the limitation of: the maximum number of individuals isolated at the same time; the number of doses of vaccine administered per day; and the total number of persons isolated per day. We assumed that if the traced latent contacts (E_i) are not isolated they become infectious.

We have used the Gillespie stochastic algorithm to simulate epidemics [7, 8]. As can be seen in Figure 1, eleven transitions between groups are allowed. A transition rate, depending only on the present state of the population, is allocated to each transition allowed, λ_i (see Fig. 1). In a time interval $[t; t+dt]$, the probability that transition i occurs is $\lambda_i dt$. The time between two successive transitions is exponentially distributed with the mean equal to the inverse of the sum of the transition rates ($\lambda = \sum \lambda_i$). The probability P_i that the next transition is of type i is λ_i/λ .

Table 1. *Values and definitions of parameters for the stochastic SEIR model**

Ref. scenario	Bounds	Parameter definition
$R_0 = 3$ [3, 6, 15]	1.5–20 [14, 24]	Basic reproduction number
Index = 100 cases	1–1000	Number of index cases
Time = 25 days [16]	7–45 [16]	Time to onset of intervention
$\theta = 0.6$	0–1	Proportion of untraced infectious individuals isolated
$\rho = 0.8$	0–1	Proportion of traced and vaccinated contacts
$\beta = 10 \text{ days}^{-1}$	—	Number of contacts potentially infected
$\alpha = 0.0685 \text{ days}^{-1}$ [3]	—	Inverse of the duration of the latency + prodromal period
$\chi_1 = 0.06 \text{ days}^{-1}$ [3]	—	Rate of release of non-infected contacts in the population
$\chi_2 = 0.04 \text{ days}^{-1}$ [3, 9]	—	Inverse of the duration of the isolation period (25 days)
$\varepsilon_1 = 0.975$ [3]	—	Vaccine efficacy among non-infected individuals
$\varepsilon_2 = 0.3$ [3, 9]	—	Vaccine efficacy among infected individuals
$\gamma = 0.116 \text{ days}^{-1}$ [3]	—	Inverse of the duration of the infectious period (8.6 days)

* Ref. scenario, reference scenario; Bounds, bounds of the sensitivity analysis.

Parameter values

We denote the basic reproduction number (R_0), i.e. the number of secondary cases infected by one single case in an entirely susceptible population.

For the reference scenario, we assumed a R_0 of 3 and an initial exposure of 100 persons. Considering that the first case would not be diagnosed before the appearance of a rash and that it could be misdiagnosed initially, we considered that intervention would be effective 25 days after the attack. We considered that 80% of the contacts would be traced. Among these, 100% would be vaccinated and 100% of those developing a rash would be isolated. A fraction of untraced contacts would develop smallpox, 60% of those would be isolated after having developed a rash (Table 1). In the reference scenario, we have also assumed that the maximum number of individuals in isolation at the same time, the number of persons vaccinated per day and the total number of persons isolated per day are unlimited.

The results presented below concerning the size and the duration of the epidemic, the number of doses required and the number of patients isolated were estimated with 200 simulations of the epidemic for each parameter set.

Sensitivity analysis and Poisson regression model

In order to assess the key parameters of the control of the epidemic, taking into account the uncertainty of the different parameters, we performed a sensitivity analysis with a LHS scheme [4] on the following parameters (see Table 1): the time to intervention, defined as the time lag between the attack and effective




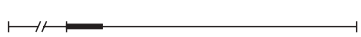

intervention; the efficiency of tracing (i.e. proportion of contacts traced); the efficiency of isolation (proportion of untraced infectious individuals isolated); the R_0 and the number of index cases. Two hundred sets of parameters were simulated using uniform distributions for all parameters except for R_0 for which we chose a probability density function constant between 1.5 and 6 and decreasing linearly between 6 and 20. To represent the low likelihood of high R_0 values, this density was 10 times higher when R_0 was equal to 6 than when it was equal to 20. Bounds of the distributions are presented in Table 1.

In order to evaluate the influence of the different parameters of the model, we built a Poisson regression model with generalized estimating equations to explain the simulated epidemic size with the ranks of the parameters as covariates in order to avoid differences between the scales of the variables. For each parameter, the regression coefficient and its 95% confidence interval was used as a measure of sensitivity between this parameter and epidemic size (Table 2). We also provided the regression coefficients computed with the values of the parameters (and not their ranks) which give an idea of the scale of the variations. We present the exponential of the regression coefficients for both the model using ranks and the classic model for ease of interpretation. In the sensitivity analysis, 100 simulations were done for each set of parameters.

RESULTS

According to the model, using the reference scenario, the epidemic would last 240 (190–310) days and

Table 2. Influence of the different parameters of the model as regards epidemic size

Parameter	Regression coefficient* (ranks)	95% confidence interval
Basic reproduction number, R_0	1.0191	
Time to onset of intervention	1.0079	
Proportion of contacts not traced ($\rho_2 = 1 - \rho$)	1.0072	
Proportion of untraced infectious individuals not isolated ($\theta_2 = 1 - \theta$)	1.0023	
Number of index cases	1.0016	

* We provide the exponential of the regression coefficient.

730 (550–910) persons would be infected. With this scenario, 5440 (3910–6840) doses of vaccine would be needed and 550 (410–690) individuals would be isolated amongst whom 230 (170–300) would be in isolation the same day. If 1000 persons were initially infected instead of 100, 7200 (6570–7770) cases would occur when it was assumed that there was no limitation on the number of doses and persons isolated per day. If the number of doses administered per day and the number of persons isolated per day were each limited to 200, the initial infection of 1000 persons would lead to 21 340 (8650–107 080) cases among which 3590 (2645–5020) would be in isolation the same day. If the maximum number of beds occupied was also limited to 2000 then 108 640 (107 815–109 000) cases would occur.

The parameter with the highest regression coefficient was R_0 (Table 2). Figure 2a shows the variation of the epidemic sizes when R_0 ranges from 2 to 12 and the values of the other parameters are those of the reference scenario. With a R_0 of 6, the forecasted size was more than 5 times larger than with a R_0 of 3. However, it is not possible to control the R_0 by an intervention unlike the three parameters of the model concerning the efficacy of intervention (time to intervention, efficacy of tracing and efficacy of isolating). Concerning these three parameters, the multivariate sensitivity analysis suggested that time to intervention and the proportion of contacts traced have the highest regression coefficient (see Table 2). Figure 2b represents the variation in the epidemic size depending on the time to onset of intervention when the values of the other parameters are those of the reference scenario. If intervention was delayed to 45 days after the attack, the epidemic size would be nearly 4 times larger [2780 (1960–3770)]. In this case, 19 700 (13 700–27 600) doses of vaccine would be needed.

The regression coefficient, computed with the values of the parameters (and not their ranks), was 1.2 (1.18; 1.23) for R_0 , 1.04 (1.03; 1.06) for the time to onset of intervention, 0.23 (0.14; 0.39) for the proportion of contacts traced, 0.63 (0.43; 0.91) for the proportion of untraced infectious individuals isolated, and was not significant for the number of index cases. Although these coefficients give an idea of the scale of the variations, as the relation between the size of the epidemic and these parameters is not linear, they should be interpreted cautiously.

DISCUSSION

According to the model we have presented here, an epidemic beginning with 100 infectious individuals in a city of 2.15 million people would produce around 730 cases in a reference scenario assuming that the intervention of vaccinating contacts and isolating cases would be initiated 25 days after the attack. If intervention was set 45 days after the attack, an epidemic of approximately 2800 cases would occur. The sensitivity analysis gives a quantitative view of the extent to which the information on R_0 is important for predicting the size of the epidemic with accuracy. It also shows the importance of the impact of the time to intervention and the proportion of contacts traced on the size of the epidemic.

The quantitative results of our analysis are well in line with a final remark stated by Gani and Leach: ‘significant epidemics could result, particularly if there were delays in detecting the first cases or in setting up effective public health interventions’ [3]. If an attack with smallpox occurred, the first case would develop the first symptoms around 12–14 (7–17) days (mean and range of the duration of the latency period) after the attack [9]. Because smallpox was eradicated in 1979, lack of experience could lead physicians to

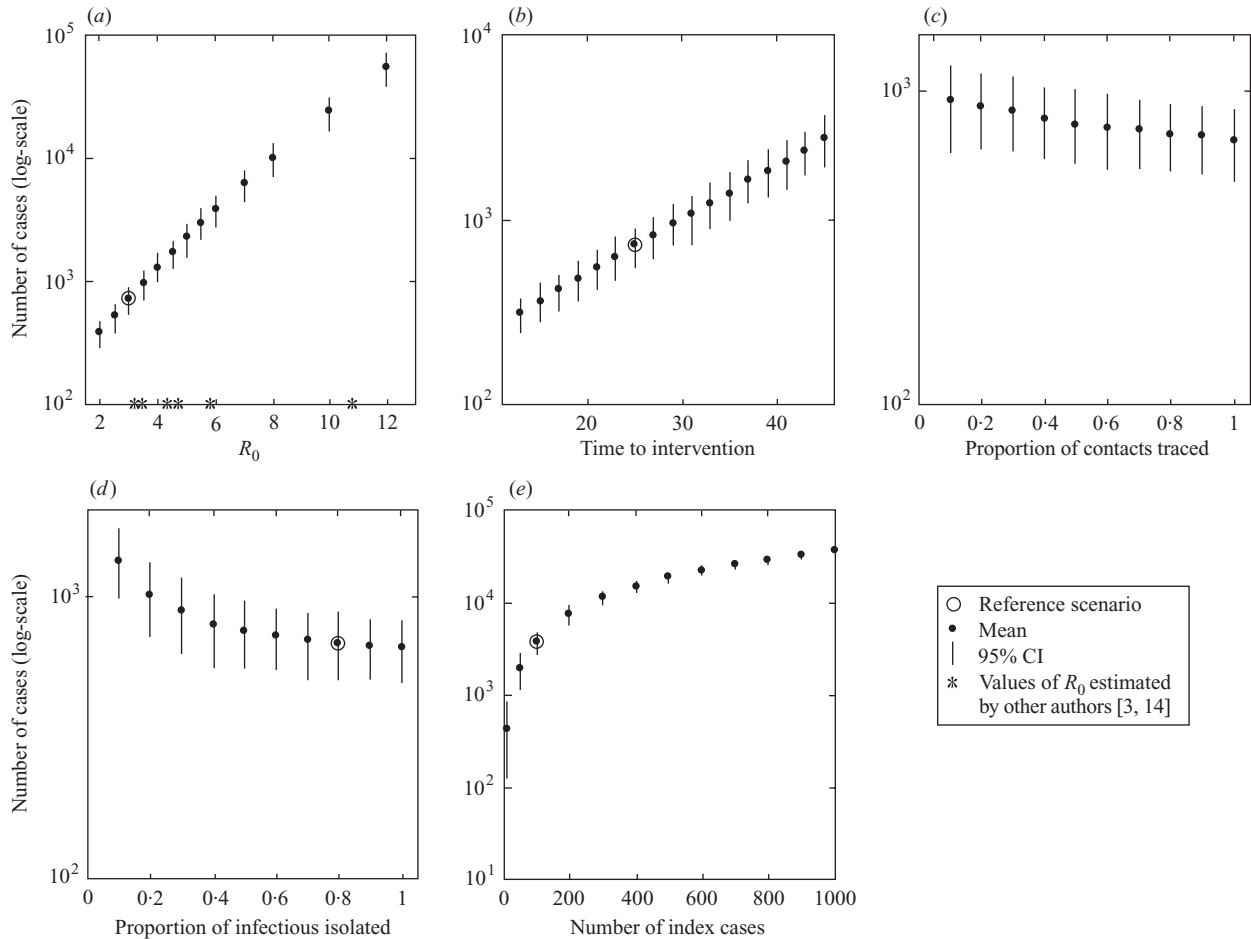


Fig. 2. Variation of the epidemic size: (a) for R_0 ranging from 2 to 12; (b) for time to intervention ranging from 13 to 45 days after the release; (c) for the proportion of contacts traced ranging from 10 to 100%; (d) for the proportion of infectious individuals isolated each day ranging from 10 to 100%; (e) for the number of persons initially infected ranging from 10 to 1000. For each graph, one parameter varies and the other parameters have the values of the reference scenario.

Table 3. Comparison with other published data

Authors	Size of the population	Number of index cases	Attack rates found by the authors (%)	Attack rates found with our model (%)
Kaplan et al. [6]	10 million	1000	3.7	0.02
Halloran et al. [15]	2000	5	13	2.55
Bozette et al. [23]	290 million	350	5.2×10^{-4}	46×10^{-4}
This paper (ref. scenario)	2.15 million	100		0.03

misdiagnose smallpox initially, delaying intervention [10, 11]. Thus we assumed that time to intervention ranged between 7 and 45 days and was fixed at 25 days in the reference scenario.

As noted above, we found that R_0 , the value of which is much debated in the literature, had the most important impact on the accuracy of the forecasted

size of the epidemic. Gani and Leach's estimates from past epidemics which occurred in Europe ranged between 3.5 and 12 [3, 12] but other authors [13, 14] have suggested that this value could be smaller, nearly 1, arguing that only large outbreaks (with high R_0) have been reported in the past and that smaller outbreaks may have occurred without being documented. For

this reason, we used a R_0 ranging between 1.5 and 20 favouring values under 6, with 3 in the reference scenario.

One of the main interests of this type of model is to perform sensitivity analysis to explore uncertainty. The seven parameters which were considered as fixed were drawn from the literature [3, 6, 9, 15, 16] although they may be prone to variation. However, we have decided to restrict our sensitivity analysis to five parameters, the values of which were the most debated or totally unknown at the current time.

For the sake of simplicity, we assumed in our work that the whole population was susceptible to variola virus. Actually, in many developed countries a proportion of the population has never been vaccinated (estimated at 43% in the United States [15] and 42% in France [17]) and the remainder received one dose more than 30 years ago [18]. The duration of immunity conferred by vaccination remains uncertain: it is expected to be 3–10 years for one dose and 20–30 years or more for secondary vaccinations [18–22]. In addition, the impact of residual immunity in the population is not clear. On the one hand, residual immunity may reduce the severity of the disease and in turn reduce its infectivity [20]. On the other hand, residual immunity may increase the mobility of the infectious individuals vaccinated in the past, enhancing the spread of the epidemic. Recently, a model considering residual immunity has been published [15] but the authors did not take into account the role of immunity on the movement of infected individuals vaccinated before 1972.

In the past 2 years, several models have been proposed to simulate smallpox attacks in order to estimate the efficacy of different interventions of control [6, 15, 16, 23]. In addition to the results presented above, in order to compare the attack rates produced by our model and the figures published recently [6, 15, 23] we have simulated epidemics in populations of various sizes and various number of index cases (see Table 3). Note that the range of published attack rates is wide, with orders of magnitude ranging from 1 to more than 1000 depending on the author. This reflects uncertainty in the most likely attack scenario and diffusion dynamics. Our figures are smaller than those proposed by the first two publications and greater than those proposed by Bozzette et al. [23]. However, these results are difficult to compare since the assumptions are different in the three models and in particular concerning the efficacy of interventions. Halloran et al. [15] and Kaplan et al. [6] made the

assumptions that the prodromal period is infectious whereas we do not consider individuals in the prodromal stage to be infectious. Thus we have not simulated the assumption made by Halloran et al. [15] which could have led to simulation of larger epidemics. Further work is needed to study the impact of this assumption on the size and the duration of the simulated epidemics. Furthermore Kaplan et al. [6] considered queuing in tracing and vaccination which can explain why they have found larger epidemics. Our work indicates time to intervention as one of the key parameters for an effective control of a bio-terrorist attack with smallpox in a large city. It shows that efforts should be focused on improving early recognition of an attack (e.g. maintaining diagnosis capabilities among physicians and laboratories), and setting up contingency plans allowing for rapid implementation of intervention measures after the identification of an attack.

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REFERENCES

1. WHO. Public health response to biological and chemical weapons. WHO Guidance. 2001.
2. Kaufmann AF, Meltzer MI, Schmid GP. The economic impact of a bioterrorist attack: are prevention and postattack intervention programs justifiable? *Emerg Infect Dis* 1997; **3**: 83–94.
3. Gani R, Leach S. Transmission potential of smallpox in contemporary populations. *Nature* 2001; **414**: 748–751.
4. Blower SM, Dowlatabadi H. Sensitivity and uncertainty analysis of complex models of disease transmission: an HIV model, as an example. *Int Stat Rev* 1994; **62**: 229–243.
5. Centers for Disease Control and Prevention. Vaccination guidelines for state and local agencies: <http://www.bt.cdc.gov/agent/smallpox/response-plan/files/guide-b-part1of2.pdf>. 2002.
6. Kaplan EH, Craft DL, Wein LM. Emergency response to a smallpox attack: the case for mass vaccination. *Proc Natl Acad Sci USA* 2002; **12**: 12.
7. Gillespie DT. Exact stochastic simulation of coupled chemical reactions. *J Phys Chem* 1977; **81**: 2340–2361.

8. Cliff AD, Haggett P. Statistical modelling of measles and influenza outbreaks. *Stat Methods Med Res* 1993; **2**: 43–73.
9. Fenner F, Henderson D, Arita I, et al. Smallpox and its eradication. Geneva: World Health Organisation, 1988.
10. O'Toole T. Smallpox: an attack scenario. *Emerg Infect Dis* 1999; **5**: 540–546.
11. Madeley CR. Diagnosing smallpox in possible bioterrorist attack. *Lancet* 2003; **361**: 97–98.
12. Gani R, Leach S. Correction: Transmission potential of smallpox in contemporary populations. *Nature* 2002; **415**: 1056.
13. Kahn LH. Smallpox transmission risks: how bad? *Science* 2002; **297**: 50–51.
14. Enserink M. Bioterrorism. How devastating would a smallpox attack really be? *Science* 2002; **296**: 1592–1595.
15. Halloran ME, Longini IM Jr, Nizam A, et al. Containing bioterrorist smallpox. *Science* 2002; **298**: 1428–1432.
16. Meltzer MI, Damon I, LeDuc JW, et al. Modeling potential responses to smallpox as a bioterrorist weapon. *Emerg Infect Dis* 2001; **7**: 959–969.
17. Levy-Bruhl D, Guerin N. The use of smallpox virus as a biological weapon: the vaccination situation in France. *Euro Surveill* 2001; **6**: 171–178.
18. Henderson DA, Inglesby TV, Bartlett JG, et al. Smallpox as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. *JAMA* 1999; **281**: 2127–2137.
19. Centers for Disease Control and Prevention. Smallpox vaccine overview: <http://www.bt.cdc.gov/agent/smallpox/vaccination/facts.asp>. 2002.
20. Cohen J. Bioterrorism. Smallpox vaccinations: how much protection remains? *Science* 2001; **294**: 985.
21. el-Ad B, Roth Y, Winder A, et al. The persistence of neutralizing antibodies after revaccination against smallpox. *J Infect Dis* 1990; **161**: 446–448.
22. Frelinger JA, Garba ML. Responses to smallpox vaccine. *N Engl J Med* 2002; **347**: 689–690.
23. Bozzette SA, Boer R, Bhatnagar V, et al. A model for a smallpox-vaccination policy. *N Engl J Med* 2003; **348**: 416–425.
24. Henderson DA. Bioterrorism as a public health threat. *Emerg Infect Dis* 1998; **4**: 488–492.