



Case Isolation and Contact Tracing Can Prevent the Spread of Smallpox

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Fears that terrorist groups may have gained access to variola virus have led to widespread discussions on how to prevent the reintroduction of smallpox by vaccination and on the availability of sufficiently large amounts of vaccine. In this paper, the author examines how the spread of smallpox is affected by isolating overt cases and taking their contacts under close surveillance for up to 3 weeks. The author assumes that case detection gradually improves from initially 7 days to 3 days. This intervention should be accompanied by vaccination, but its outcome does not depend on the vaccine's efficacy. It may, therefore, be especially important in controlling outbreaks caused by pathogens whose immunologic properties have been modified by genetic engineering. Using stochastic computer simulations, the author demonstrates that contact tracing and case isolation can extinguish smallpox outbreaks in highly susceptible populations within less than half a year without causing totals of more than 550 secondary cases per 100 index cases. The author also derives simple approximate expressions that allow prognostication on how efficiently an outbreak can be controlled by the described measures alone and prediction of the expected number of cases in an outbreak and the number of people that must be taken under surveillance.

bioterrorism; computer simulation; contact tracing; models, theoretical; patient isolation; population surveillance; quarantine; smallpox

Besides mass and ring vaccination, contact tracing and case isolation decisively contributed to eradicating smallpox in many countries (1), but these measures have been widely neglected in the recent discussion on the prevention of bioterrorism that focused predominantly on vaccination strategies (2–5). A close follow-up of known contacts and the isolation of emerging cases have the same epidemiologic effect as quarantine but allow persons to move freely (6). People under surveillance should be vaccinated as postexposure vaccination has been reported to alleviate the course of disease, although it does not necessarily prevent it (1, 7).

Two key parameters determine the spread of an infection through a population. The first one is the basic reproduction number R_0 (8, 9). It is defined as the average number of secondary cases that are infected by a single index case in a completely susceptible population (10). A basic reproduction number of 6.5 was derived from Daniel Bernoulli's estimates of the age-specific equilibrium prevalence of people immune to smallpox in Paris in 1760 (11, 12). Analyses of historical data from 1721 to 1973 yielded estimates for R_0 from 3.4 to 5.8 after discounting hospital-associated cases (13, 14). Evaluation of a smallpox outbreak in a religious

community in Nigeria that refused vaccination and other medical interventions yielded an estimate of 6.9 (15). This means that an outbreak in a completely susceptible population should result in an initial geometric progression, where each new wave of cases is about 3.4–6.9 times as large as the previous one if no interventions are performed. This contrasts strikingly with recent smallpox attack scenarios in which epidemic waves were assumed to grow exponentially by factors of 10–100 in spite of vaccination (2–5). The second key parameter is immunity. The United States terminated routine vaccination against smallpox in 1972, so that over 40 percent of its present population grew up without smallpox vaccination (4). Unfortunately, for vaccinated individuals it is not known how long immunity lasts (16, 17).

A mathematical model for smallpox outbreak scenarios was published by Meltzer and other members from the Centers for Disease Control and Prevention (18). It considers case isolation and vaccination as possible interventions and predicts smallpox epidemics of thousands or even millions of cases if 100 infections were introduced in the United States. This led the authors to recommend stockpiling about 40 million doses of vaccine. Their model did not consider

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TABLE 1. Model assumptions*

	Mean (days)	SD† (days)	Percentile		CV‡ (%)
			5%	95%	
Period before fever	$\mu_I = 11.6$	$\sigma_I = 1.90$	8.62	14.9	16.4
Period from fever to rash	$\mu_F = 2.49$	$\sigma_F = 0.88$	1.32	3.80	35.3
Period with rash	$\mu_R = 16.0$	$\sigma_R = 2.83$	11.7	20.9	17.7
Time at infection of close contacts‡	$\mu_C = 3.0$	$\sigma_C = 0.87$	1.7	4.5	29.0
Time for case detection‡					
Initially	$\mu_D = 7.0$	$\sigma_D = 1.75$	4.4	9.9	25.0
Finally	$\mu_D = 3.0$	$\sigma_D = 0.75$	1.7	4.4	25.0

* I employ a basic reproduction number of $R_0 = 5$, a susceptible fraction of $S = 80\%$, and a fraction of $C = 75\%$ close contacts. The time needed for case detection starts with 7 days, decreases exponentially at a rate of $\alpha = 2.31\%$ per day, and approaches 3 days. The fraction T of traceable infections among casual contacts depends on the average number N of people per case who are taken under surveillance and is limited to $T_{\max} = 70\%$ (see Appendix 1 for details).

† SD, standard deviation; CV, coefficient of variation.

‡ Infection of close contacts and case detection start at the beginning of the infectious period.

transmission to household contacts or contact tracing. This also applies to the “Dark Winter” smallpox attack simulation of the US Center for Civilian Biodefense Strategies and other organizations (4). Transmission to close contacts is highly important, as Fenner et al. stated in their definitive work on smallpox: “Comparisons of the intra-familial and extra-familial spread of smallpox [...] demonstrated that the overwhelming majority of secondary infections occurred in close family contacts of overt cases of smallpox, especially in those who slept in the same room or the same bed. Next in frequency were those who lived in the same house; residents of other houses, even in the same compound (who would often visit the house of the patient), were much less likely to become infected [...] Long distance movements by train or bus of patients suffering from smallpox with an overt rash used to occur frequently, yet infection of casual fellow-travelers was rare indeed—so rare that instances of it were deemed worthy of special reports” (1, p. 191). Kaplan et al. have published a mathematical model to compare mass vaccination with traced vaccination campaigns that considered contact tracing, quarantine, and case isolation, and they found that “mass vaccination results in both far fewer deaths and much faster epidemic eradication over a wide range of disease and intervention policy parameters” (19, p. 10935), but their results strongly depend on the assumption that smallpox infections spread abundantly before the appearance of the rash, which contradicts common textbook knowledge (1) and recent parameter estimates (15). In spite of their assumption that people who have developed the typical smallpox rash are immediately isolated, they predict tremendous epidemics, because they assume that only 50 percent of each case’s contacts can be traced and subsequently vaccinated (19). Likewise, Halloran et al. (20) assume in their individual-based stochastic model that smallpox is highly contagious during the prodromal period, but they conclude that, under all scenarios, targeted vaccination prevented more cases per dose of vaccine than did mass vaccination when they considered residual immunity of those vaccinated

before 1972. Epstein et al. (21) studied the spread of smallpox with individual-based computer simulations and emphasized the importance of case isolation and vaccination of family members, but they included neither contact tracing nor postvaccination surveillance. Bozzette et al. (22, 23) described a decision-making model to compare the outcomes of various vaccination strategies for a variety of different attack scenarios and concluded that, for acceptable results, vaccination of contacts must be accompanied by effective isolation of cases, but they did not consider postvaccination surveillance of contacts.

In this paper, I use stochastic computer simulations to examine how case isolation, contact tracing, and surveillance impede the spread of smallpox in a highly susceptible population. Identified cases are immediately isolated, and all household members and other close contacts are traced, vaccinated, and put under continuous surveillance for up to 3 weeks. The surveillance comprises regular examinations of the contacts and includes taking their temperature twice a day, so that any sign of infection could be detected at the earliest possible time (24). As soon as clinical symptoms appear, the person under surveillance is isolated to prevent any further spread of the infection. Some casual contacts elude tracing and can, therefore, continue to spread the infection until they themselves are detected and isolated.

MATERIALS AND METHODS

I perform stochastic computer simulations that start with 100 infections in a population where 80 percent of the people are susceptible. I assume that each infected individual would generate on average $R_0 = 5$ secondary cases if the population was completely susceptible and if no interventions were performed. The durations of the latent and infectious period and other parameter values are given in table 1; for a detailed description of the simulation algorithm, see Appendix 1. I assume initially that 7 days are needed to detect and confirm overtly sick cases and that this duration drops exponentially

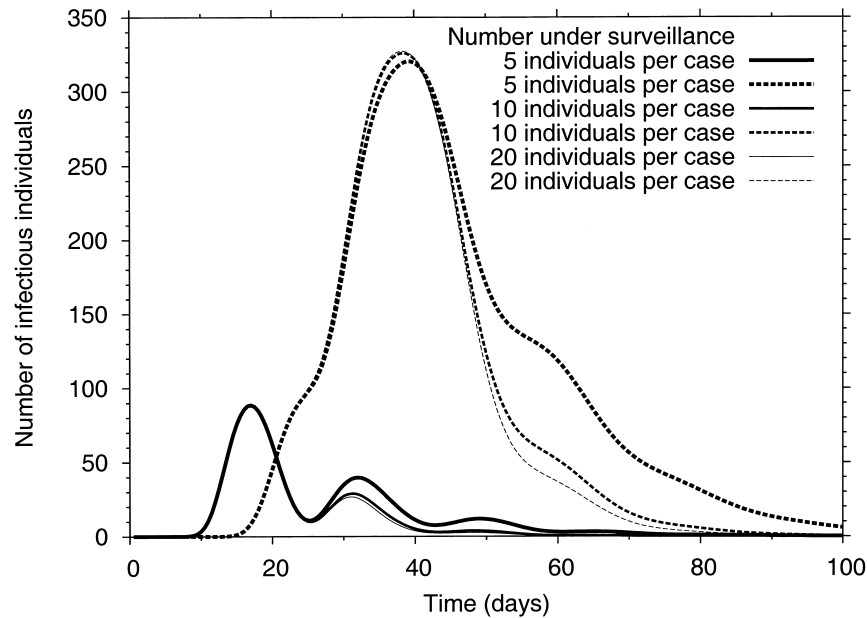


FIGURE 1. Average number of individuals infected with smallpox in a simulated outbreak that is caused by 100 index cases in a population with 20% immune. For each case, $N = 5, 10,$ or 20 people taken under surveillance for up to 3 weeks; basic reproduction number $R_0 = 5$; fraction of close contacts is $C = 75\%$; 10,000 simulations for each value of N (for other parameter values, see table 1).

to 5 days after 1 month and to 4 days after 2 months, finally approaching 3 days. Each newly detected case is immediately isolated and asked to supply a list of contact persons who will then be vaccinated and put under close surveillance.

It is assumed that postexposure vaccination ameliorates only the course of disease but does not prevent it (1, 7). Any individual under surveillance who becomes feverish or develops a rash is immediately isolated before he or she can spread the infection. Casual contacts may elude detection and can, therefore, spread the infection until they are detected and isolated themselves.

RESULTS

Simulation results

I will now examine the average course of an outbreak that starts with 100 infections. Averaged simulation results are shown for surveillance coverage of $N = 5, 10,$ and 20 contacts per index case, respectively. Within a period of 1–2 weeks after infection, the 100 index cases develop clinical signs of smallpox and start infecting others (figure 1, solid curves). As case detection initially takes 1 week on average, many family members and several casual contacts become infected before the index cases are isolated (figure 1, dashed curves). As soon as the index cases are detected and isolated (figure 2) and their close contacts are taken under surveillance (figure 3), the number of cases who can still spread the infection drops drastically. Suspected and overt cases among those people under surveillance are isolated before they can spread the infection (figure 4). About 4 weeks after the initiation of the outbreak, a second wave of cases results from

infections that could not be traced (figure 1, solid curves). These cases are also isolated and their contacts are taken under surveillance, which again depletes the number of infectious individuals in the population. Thus, the third and fourth waves of the outbreak become smaller and smaller until the last infected individual is isolated. After a median duration of 113, 89, and 84 days, respectively, the last infected individual loses infectivity and the outbreak is over. The median numbers of secondary cases in the outbreak are 534, 408, and 386, respectively. Figures 5 and 6 show selected quantiles of the total number of secondary cases and of the duration of the outbreak, respectively, for a wide range of basic reproduction numbers (assuming that $N = 10$ contacts per case are taken under surveillance).

I performed sensitivity analyses in two ways to evaluate the effect of the timing and number of close contacts. 1) Reducing the average time of infection of close contacts from $\mu_c = 3$ days to 1 day did not substantially change the above results (median number of secondary cases = 416 for $N = 10$), but increasing it to 6 days led to smaller outbreaks (median number of secondary cases = 269) because more infections of close contacts were prevented by isolation of the index cases. 2) Reducing the fraction of close contacts from $C = 75$ percent to 50 percent or 25 percent led to median numbers of secondary cases of 413 and 403, respectively (using $N = 10$).

Expected number of smallpox cases and of people under surveillance

I will now derive simple approximate expressions that allow us to determine how efficiently an outbreak can be controlled by case isolation alone, how many cases must be

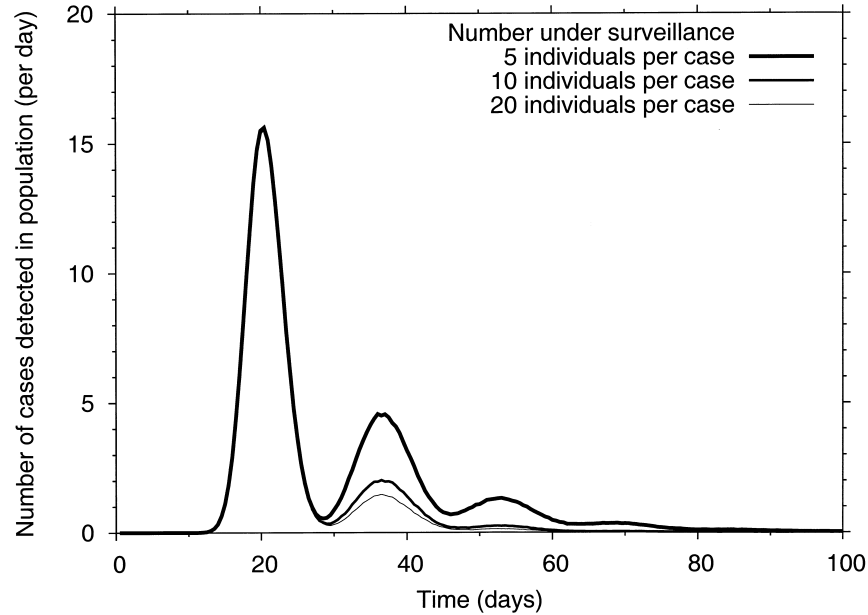


FIGURE 2. Incidence of smallpox case detection in the population for the smallpox outbreak simulation described in figure 1.

expected in an outbreak, and how many people have to be taken under surveillance. The key question is how many of such secondary cases X who can transmit the infection are generated on average by a single index case. If this value is larger than one, the number of cases will increase exponentially until the number of susceptible individuals will locally become exhausted; if it is less than one, each case causes less than one successor and the number of infections decreases.

To calculate X , I make the following assumptions: 1) each case has on average $R_0 = 5$ sufficiently close contacts during the whole course of the infectious period; 2) the susceptible fraction of the population is $S = 80$ percent; 3) the average fraction of close contacts is $C = 75$ percent; 4) in addition to all close contacts, a fraction $T = 20$ percent of the casual contacts of the case are taken under surveillance when the case is detected and isolated; and 5) the case is detected and

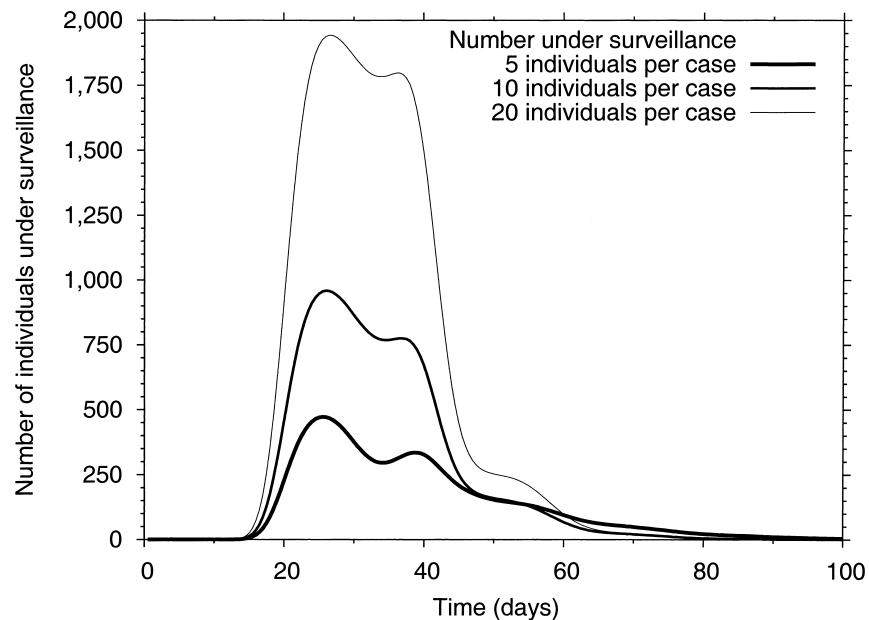


FIGURE 3. Number of individuals under surveillance for the smallpox outbreak simulation described in figure 1.

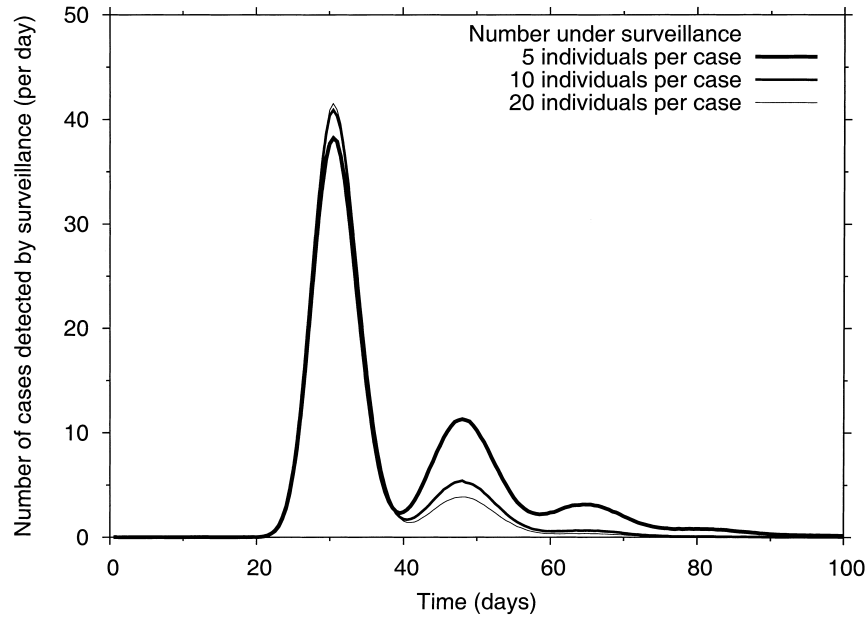


FIGURE 4. Incidence of smallpox case detection among individuals under surveillance for the smallpox outbreak simulation described in figure 1.

isolated on average $\mu_D = 4$ days after the onset of rash, which reduces the infectious period to $\mu_D/\mu_R = 4/16 = 25$ percent. As traced contacts are taken under surveillance and consequently cannot spread the infection, I calculate

$$X = R_0 S(1 - C)(1 - T)\mu_D/\mu_R, \tag{1}$$

which is 0.2 with the given parameter values (figure 7). By modifying equation 1, I calculate that the outbreak can still

be controlled if up to 21 percent of the cases are never isolated (Appendix 2). During the whole course of the outbreak, we expect a number of

$$Y = 100 \times \sum_{k=0}^{\infty} X^k = 100/(1 - X) \tag{2}$$

cases to be able to spread the infection if the outbreak starts with 100 infections and if $X < 1$. The values above result in

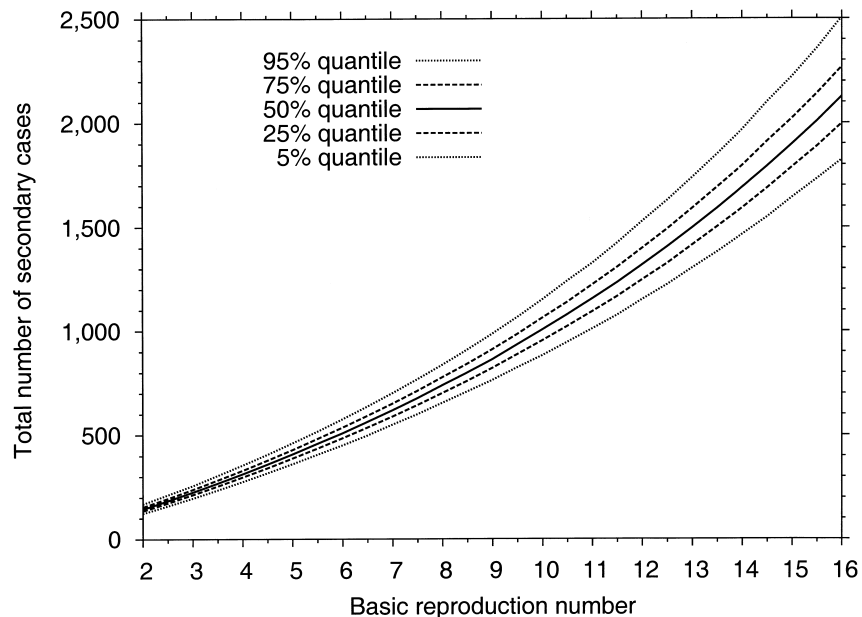


FIGURE 5. Selected quantiles of the total number of secondary cases in 10,000 simulated smallpox outbreaks as described in figure 1 (with $N = 10$ and R_0 as shown).

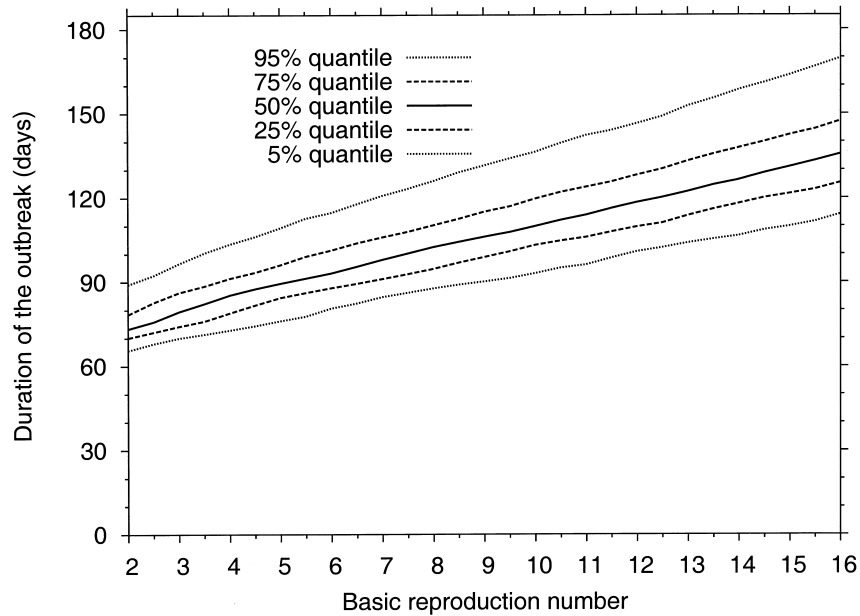


FIGURE 6. Selected quantiles of the total duration of 10,000 simulated smallpox outbreaks as described in figure 1 (with $N = 10$ and R_0 as shown).

an average of $Y = 125$ cases that can spread the infection. Before these are detected, each one of them infects an additional average number of R_0SC close contacts (here I exaggerate the infectivity to close contacts by assuming that they are infected instantaneously after the onset of rash) and $R_0S(1 - C)T\mu_D/\mu_R$ casual contacts who will also be taken under surveillance. These cases cannot spread the disease

but they contribute to the total number of cases. The expected total number of cases is, therefore,

$$Z = Y + YR_0SC + YR_0S(1 - C)T\mu_D/\mu_R, \quad (3)$$

which yields a total of 506 cases including the 100 initial cases (figure 8). Equation 3 underestimates the total number

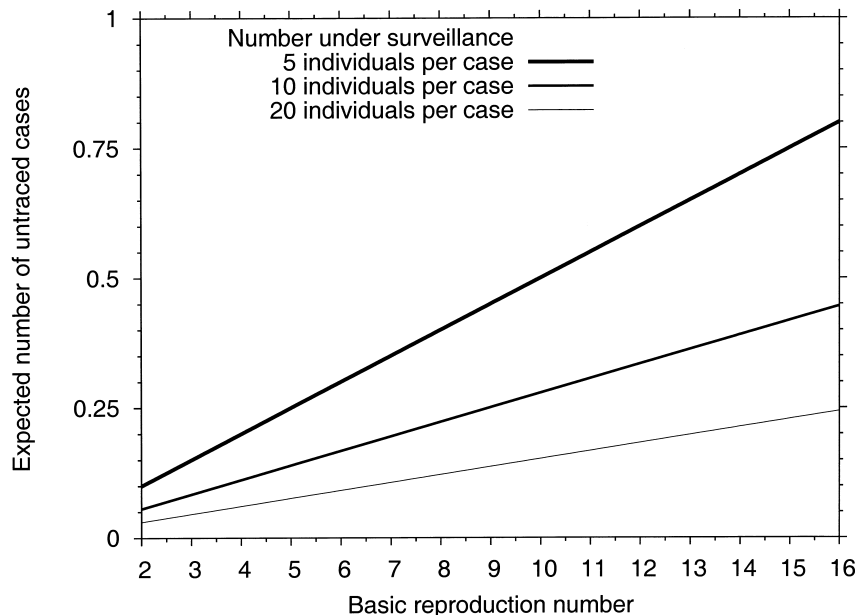


FIGURE 7. Expected number of untraced smallpox cases, X , who are infected by a single infectious person (calculated from equation 1 with the parameter values given in the text).

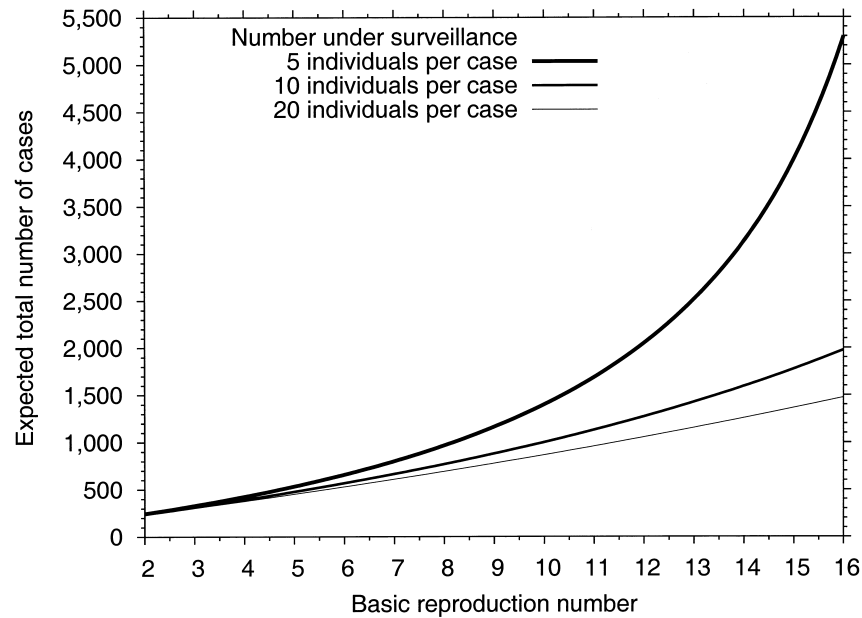


FIGURE 8. Expected total number of smallpox cases in a smallpox outbreak, Z , that is initiated by 100 index cases (calculated from equation 3 with the parameter values given in the text).

of cases, if extremely large case-detection periods are used, as it does not consider that close contacts infect others (the simulation routine allows this). The total number of individuals who have to be taken under surveillance can be calculated from the number of cases Y that are able to spread the infection. Assuming that $N = 6$ contacts of each case are

vaccinated and taken under surveillance, we calculate a total of $YN = 750$ individuals per 100 initial infections (figure 9), which is an extremely small effort to combat the return of smallpox. For a modification of equations 1–3 that considers infections during the prodromal fever period, see Appendix 3.

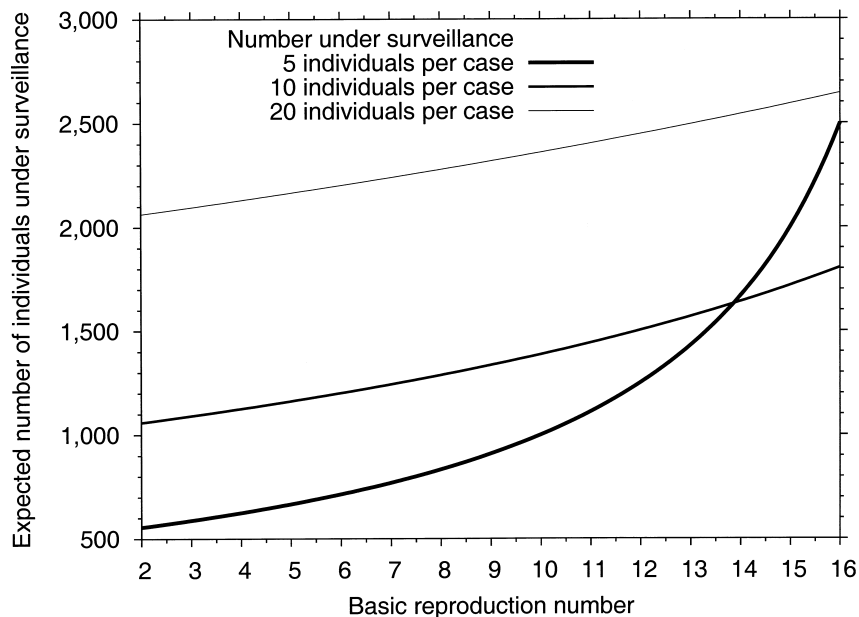


FIGURE 9. Expected total number of individuals under surveillance in a smallpox outbreak that is initiated by 100 index cases (calculated by multiplying equation 3 with N and using the parameter values given in the text).

DISCUSSION

The present investigation shows that a smallpox outbreak in a population with 20 percent immune may be controlled by means of contact tracing and case isolation alone, so that in less than half a year the outbreak is over without causing on average more than 550 secondary cases per 100 initial cases. My calculations were performed with rather pessimistic assumptions, some of which may be relaxed.

1. Although about 58 percent of the US population has been immunized against smallpox (4), I use only 20 percent for those immune in this model, as it is not well known how long protective immunity against smallpox infection and disease lasts (16, 17). The Centers for Disease Control and Prevention claim on their homepage that most estimates suggest that immunity from the vaccination lasts 3–5 years (25), but it seems unlikely that worldwide eradication of smallpox would have been achieved by using a vaccine with such weak properties. Contrary to their statement, a recent study of the Israel Defense Forces Medical Corps observed that the smallpox “titer significantly decreased during the first 3 years after the re-vaccination but remained stable for at least 30 years thereafter,” which led them to conclude that “there is probably no need for routine re-vaccinations beyond the primary and two re-vaccinations” (26, p. 446). The protective significance of antibody titers is uncertain, indicating that immunologic memory may be of higher importance (27, 28): A US group studying the duration of T-cell memory in humans recently reported that “specific vaccinia virus T-cell immunity can persist for up to 50 years after immunization against smallpox in childhood in the presumed absence of exposure to vaccinia virus” (29, p. 2627; 30).

2. The majority of estimates for the basic reproduction number of smallpox derive from data of the 18th and 19th centuries and from developing countries (12, 13, 15). Considering the fact that “variola major was almost always transmitted at the bedside of the source” (31, p. 460), one might argue that a value of $R_0 = 5$ overestimates the transmission potential in the 21st century US population. Episodes from smallpox outbreaks during the eradication campaign when individuals infected many secondary cases have been quoted (2, 4). Fenner et al. consider this fact in their book: “Sometimes one index case infected a dozen or more people These episodes however were exceptional. Epidemiologists engaged in the global smallpox eradication campaign ... agree with Dixon (1962) [(32)] that smallpox usually spread rather slowly” (1, p. 199). Some scientists argue that smallpox infections spread much more slowly than Dark Winter and other scenarios suggest and could, in many cases, be contained quite easily (31, 33).

3. An average duration of 7 days between the onset of rash and the intervention of public health authorities must be considered as extremely pessimistic even for the first wave of an outbreak. O’Toole (3) assumes in a detailed attack scenario that, 3 days after the occurrence of clinical symptoms of the very first case, the diagnosis of smallpox is confirmed and a contagious disease emergency is declared. Kaplan et al. (19) even assumed in their models

that overtly sick cases were isolated immediately after onset of symptoms.

Although this model uses parameter values similar to those of Meltzer et al. (18), it leads to strikingly different results. They assume that a constant fraction of overt smallpox cases are isolated every day, but they do not perform any contact tracing. Assuming a removal of $r = 25$ percent of overtly sick cases per day (which implies a case detection time of 3 days as $\mu_D < \sum_{k=1}^{\infty} (1-r)^k = (1-r)/r$), Meltzer et al. predict huge epidemics of thousands or even millions of cases unless an additional vaccination campaign reduces the spread of infection by at least 33 percent. To prevent the spread of infection by case isolation alone, they demand a daily removal of at least 50 percent of all overtly sick cases (implying a case detection time of less than 1 day). The differences between their results and the results presented here must be explained mainly by the fact that they completely neglect contact tracing and surveillance. Meltzer et al. state, “the net result of using these proxy variables to model potential scenarios is that we probably overestimate the spread of disease and the numbers infected,” but conclude, “We feel that the degree of overestimation will probably not substantially affect estimates for the total number of doses of vaccine that should be stockpiled” (18, p. 966).

Kaplan et al. (19) used mathematical models to compare the impact of traced vaccination with that of mass vaccination in case of the release of smallpox. Their model assumes that cases can spread the infection only before the onset of rash. Immediately after the onset of rash, each case is isolated and provides the names of 50 contact persons who then queue for vaccination. Although smallpox is known for spreading predominantly locally (1, 31), these 50 contacts comprise only 50 percent of the secondary cases. A detailed analysis of an historic outbreak showed that cases had 80 percent of their contacts within their own houses and a total of 93 percent among close contacts (15). Although in the models of Kaplan et al. vaccination comes too late for many of the vaccinees to prevent them from becoming infectious, the indicated contact persons are not followed up after vaccination. Only those who become feverish while queuing for vaccination are quarantined, but 37.5 percent of quarantined cases are released while still being infectious. The result of the models of Kaplan et al. that contact tracing and subsequent vaccination are inferior to mass vaccination depends critically on the authors’ assumption that, in the absence of interventions, each case would infect three others before developing the rash. A parameter inference based on historical data showed that smallpox cases can infect on average only 0.16 people in a completely susceptible population before developing the rash (95 percent confidence interval: 0, 1.3) (15), which also confirmed the statements of Fenner et al. who remarked that “it was difficult to obtain evidence of the infectivity of patients during the latter part of the incubation period or during the pre-eruptive fever” and that “epidemiological experience suggested that transmission very rarely occurred before the 1st day of the rash” (1, p.

189). Halloran et al. (20) recently applied their individual-based stochastic model to an outbreak of smallpox. Although they use the same high infectiousness during the prodromal fever period as Kaplan et al., their results favor traced vaccination if they incorporate the residual immunity of those vaccinated before 1972. A modification of equations 1–3 that considers infectiousness during the prodromal period and the application to the assumptions of Kaplan et al. and Halloran et al. can be found in Appendix 3.

Smallpox showed a distinct seasonality, with the majority of cases occurring in winter and spring (1). It has been argued that the contact rate is considerably higher in early winter (2, 4), but the large seasonal differences in smallpox incidence could also be explained as a dynamic effect of endemic transmission where the contact rate seasonally varies as little as 8 percent (34). As neighboring countries tend to have similar climatic conditions, the higher endemic incidence of smallpox during winter easily explains why smallpox was reintroduced more frequently in the cold seasons (1). A seasonal variation of the contact rate by only 1 percent can cause prevalence amplitudes of nearly 40 percent, and a variation by 10 percent may result in prevalence amplitudes to 97 percent as has been shown for measles transmission (35). Although such seasonal changes of the contact rate in the order of 1–10 percent have a huge impact on endemic transmission patterns, they have hardly any influence on the shapes of outbreak curves as shown in figures 1, 2, and 4.

It has been pointed out that the degree of population heterogeneity strongly influences the size and dynamics of infectious disease outbreaks (36). Because of the stochastic effects incorporated in this model, simulated cases have a varying number of contacts during their infectious period (95 percent reference interval: 1, 10). “Superspreaders” who come into intimate contact with many people in spite of being sick and cases who deliberately try to spread the infection should cause bigger outbreaks (22).

The simulation model presented may overestimate the number of secondary cases because it neither takes into account spatial effects (21) nor does it consider the local depletion of susceptible individuals by infection or vaccination. Since the expected number of cases grows with the initial attack size (equation 3), the described strategy is feasible only if the health system is still capable of placing the necessary number of people under surveillance, but trained personnel will certainly be supplemented from many other areas in case of a localized outbreak. Extensive outbreaks that start with many thousands of infections may demand different interventions, such as mass vaccination and geographic isolation of afflicted regions (22, 23). Barbera et al. have examined the legal and logistic issues of quarantining small or large groups of individuals in the United States and concluded that “the federal government has the authority to enact quarantine when presented with the risk of transmission of infectious disease across state lines” (37, p. 2713). It may even be considered appropriate to impose quarantine on suspect cases who are not willing to cooperate with surveillance. A country-wide smallpox vaccination campaign is expected to cause up to 4,600 serious adverse events and 285 deaths in the United States

(38), so that a smallpox outbreak that originates from relatively few infections may possibly result in less fatalities than a country-wide vaccination campaign. An eruption of smallpox would certainly lead to terror and disorder in the population that would complicate contact tracing and surveillance, but we should not underestimate the cooperativeness and resourcefulness of people, as Glass and Schoch-Spana have pointed out (39). “Contacts would seek, not avoid, medical assistance and could be efficiently kept under surveillance,” as Dr. T. Mack, one of the veterans of smallpox eradication, stated (31, p. 461). Case isolation, contact tracing, and surveillance—supported by targeted vaccination efforts—are highly effective measures that involve the public as an active and capable ally in the response to bioterrorist attacks.

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APPENDIX 1

Simulation Algorithm

Each simulation starts with 100 index cases. For each of them, the following actions are performed. 1) The durations of the incubation period, the fever period, and the rash and the time of detecting and isolating the case are sampled from gamma distributions with means as given in table 1. I do not consider in the simulations that cases are infectious during the prodromal fever (1, 15). The average duration μ_D after the onset of rash that is needed for case detection is initially set to 7 days and then drops exponentially to 3 days at a rate $a = 0.0231$ per day (i.e., $\mu_D = 3 + 4 \exp(-at)$). 2) To account for the much higher probability of transmitting the infection to close contacts, I assume that, in the absence of intervention, a fraction of $C = 75$ percent of infections occurs among close contacts (15) who, because of high infection pressure, are infected soon after the onset of disease. For each index case, the number of infected close contacts is sampled from a Poisson distribution with a mean R_0SC and, for each of these contacts, an infection time is sampled from a gamma distribution with a mean μ_C (table 1). 3) In addition to the infections among close contacts, infections among casual contacts occur at a daily rate of $\beta = R_0S(1 - C)/\mu_R$; that is, the waiting time between two successive infections of casual contacts is sampled from an exponential distribution with mean $1/\beta$. All infections of close and casual contacts that would have occurred after the index case's isolation are ignored. 4) At the time when the index case is isolated, all close contacts and traced casual contacts are vaccinated and taken under surveillance. I assume that an average of $N = 5$ people is sufficient to ascertain the household members and other close contacts of an index case. The traced fraction of contacts increases if more people per index case are taken under surveillance, but the additional effort to discover more cases grows exponentially. By assuming that a fraction $T = (1 - \exp(-(N - 5)/3))T_{\max}$ of infections among casual contacts is traced if $N \geq 5$ people per index case are taken under surveillance, I set the maximum fraction of all traced infections to $C + T_{\max}/(1 - C) = 92.5$ percent (table 1) (15). All individuals under surveillance are isolated at the earliest sign of clinical symptoms. They contribute to the total number of cases but cannot spread the infection. All infected casual contacts who were not traced can start a new cycle of infections and will be treated like the index cases.

APPENDIX 2

Fraction of Untraced Cases

I modify equation 1 to consider a fraction E of all close and casual cases who will never be recognized. The number X of secondary cases who can spread the infection is

$$X = R_0SE + R_0S(1 - E)(1 - C)(1 - T)\mu_D/\mu_R. \quad (\text{A1})$$

This equation can be solved for the critical fraction of E that still allows control of the outbreak by demanding $X < 1$:

$$E_{\max} = \frac{1 - R_0S(1 - C)(1 - T)\mu_D/\mu_R}{R_0S(1 - (1 - C)(1 - T)\mu_D/\mu_R)}. \quad (\text{A2})$$

Using the same values as for equation 1, we calculate that the undetected fraction of cases must remain below 21 percent to control the outbreak. This equation underestimates the maximal permissible fraction of untraced cases because it neglects any backtracing of infections; that is, all close contacts of undetected cases have to be detected and isolated independently.

APPENDIX 3

Infectivity during the Prodromal Period

To consider infectivity before the rash, I split the basic reproduction number R_0 into a fraction f during the

prodromal fever period and a fraction $1 - f$ during the rash. According to parameter estimates derived from a smallpox outbreak in Nigeria in 1967, the fraction f of contacts during the prodromal period is 2.4 (95 percent confidence interval: 0, 22.8) percent (15). Introducing this feature into equation 1, we get

$$X = R_0S(1 - C)(1 - T)(f + (1 - f)\mu_D/\mu_R). \quad (\text{A3})$$

Equation 2 is not affected by these assumptions (i.e., $Y = 100/(1 - X)$ for 100 index cases), but equation 3 needs to be changed because more casual contacts are infected if $f > 0$. The total number of cases in the outbreak is

$$Z = Y(1 + R_0S(C + (1 - C)T(f + (1 - f)\mu_D/\mu_R))), \quad (\text{A4})$$

again assuming that all close contacts are infected very quickly. If we use the same parameter values as for equation 1, we get $X = 0.21$ for $f = 0.024$ (95 percent interval: 0.20, 0.34), $Y = 127$ (95 percent interval: 125, 152), and a total number of cases $Z = 515$ (95 percent interval: 506, 621).

To evaluate how efficient contact tracing and case isolation would be under such extreme conditions as assumed by Kaplan et al. (19) and Halloran et al. (20), I set $R_0 = 3$, $S = 100$ percent, and $f = 1$ but keep the values for C and T unchanged. This leads to $X = 0.8$ (i.e., the outbreak can still be controlled with the described strategy), a total of $Y = 500$ individuals who can spread the infection (including the 100 index cases), a total number of $Z = 2,100$ cases, and a total of $NY = 3,000$ people who have to be taken under surveillance.