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# Containing a large bioterrorist smallpox attack: a computer simulation approach

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Patient isolation;
Population surveillance;
Smallpox;
Vaccine

**Summary**
*Background:* A bioterrorist release of smallpox is a constant threat to the population of the USA and other countries.
*Design:* A stochastic simulation model of the spread of smallpox due to a large bioterrorist attack in a structured population was constructed. Disease natural history parameter estimates, time lines of behavioral activities, and control scenarios were based on the literature and on the consensus opinion of a panel of smallpox experts.
*Results:* The authors found that surveillance and containment, i.e., isolation of known cases and vaccination of their close contacts, would be sufficient to effectively contain a large intentional smallpox release. Given that surveillance and containment measures are in place, preemptive vaccination of hospital workers would further reduce the number of smallpox cases and deaths but would require large numbers of prevaccinations. High levels of reactive mass vaccination after the outbreak begins would further reduce smallpox cases and deaths to a minimum, but would require even larger numbers of vaccinations. Reactive closure of schools would have a minimal effect.
*Conclusion:* A rapid and well-organized response to a bioterrorist attack would be necessary for effective surveillance and containment to control spread. Preemptive vaccination of hospital workers and reactive vaccination of the target population would further limit spread, but at a cost

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of many more vaccinated. This cost in resources and potential harm due to vaccination will have to be weighed against the potential benefits should an attack occur. Prevaccination of the general population is not necessary.


## Introduction

The intentional release of smallpox remains a threat to the American population.[1,2] Our earlier work[3] showed that for a small attack involving around five initial infectives, post-release targeted vaccination of close contacts of identified infected people would be sufficient to control the epidemic. Our result is supported by other investigators using a simpler model.[4] There is modeling evidence that a large attack may be difficult to contain.[5] A stochastic model of a large smallpox attack indicates that targeted vaccination combined with early detection may be effective without resorting to mass vaccination.[6] Other work, not based on a dynamic epidemic model, suggests that given the small probability of a bioterrorist smallpox attack, preemptive mass vaccination is not a good strategy as opposed to reactive containment strategies.[7]

Our earlier work also showed that preemptive voluntary vaccination to increase herd immunity could increase the effectiveness of a surveillance and containment control strategy, but further investigation would be needed for the case of a large attack. Currently there is virtually no effort to vaccinate the civilian population in the USA. The federal government goal to vaccinate 5–10 million first responders and hospital personnel preemptively by the summer of 2003 was not achieved.[8] Even the more modest plan to vaccinate 500 000 medical personnel has not been achieved.[9] As of October 31, 2005, about 40 000 people had been vaccinated,[10] and many states had paused their smallpox vaccination program pending further federal government guidance. Routine vaccination against smallpox in the USA was stopped in 1972, currently leaving at least 43% of the population of the USA completely susceptible. However, evidence suggests that substantial residual immunity remains in those previously vaccinated,[11] and such immunity would give partial protection against severe disease and death given infection.[12]

In this work, we address the question of whether post-release surveillance and containment, i.e., isolation of detected smallpox cases, and location and vaccination of their close contacts, would be sufficient to contain even a large smallpox release, given the current level of background immunity to smallpox in the population of the USA. We also examine the added benefit of prevaccination of hospital workers, reactive mass vaccination of the population after an attack has been detected, and reactive closing of the schools.

## Materials and methods

Many of the parameters and scenarios of our model were determined by the Smallpox Modeling Working Group, The Secretary's Advisory Council on Public Health Preparedness, Department of Health and Human Services.[13] Parameter values and modeling decisions made by the working group were based on the group's collective knowledge of smallpox epidemiology and on information from Chapter 4 of *Smallpox and its eradication* by Fenner et al.[14] The simulation model developed here is a direct extension of our previous model,[3] but for a larger population and potential attack. In addition, through the working group, we were able to derive a more accurate set of natural history parameters than for the previous model. The smallpox natural history and human behavior patterns that we give in the next section represent a blending of values from the literature and expert opinion that may be the most comprehensive description up to this time.

### Natural history, behavior, and control measures

We described the natural history of smallpox in terms of three time lines (Figure 1): (1) disease symptoms and recognition, (2) infectiousness, and (3) behavior of infected people. We also partitioned smallpox cases into three categories: (1) ordinary smallpox (Figure 1), (2) modified smallpox (Figure 2), and (3) hemorrhagic smallpox (Figure 3). For those who have never been vaccinated, we assumed that 95% would develop ordinary smallpox if infected, and the remaining 5% would develop hemorrhagic smallpox if infected. For those people over 32 years of age who were vaccinated before 1971, we assumed that 10% would be fully protected against smallpox infection, 30% would develop a less severe modified case of smallpox if infected, and the remaining 60% would develop non-modified smallpox if infected. Among that 60%, 95% of the cases would be ordinary smallpox and 5% hemorrhagic smallpox. About 57% of the population of the USA was born before 1971. We divided our simulated outbreaks into two periods. The first period is before recognition of smallpox, while the second period is after the first case of smallpox is recognized.

Figure 1 shows the natural history for ordinary smallpox. The incubation period distribution was assumed to vary from 7 to 17 days with a mean of 11.48 days. The incubation period was assumed to end with the onset of fever, followed by a macular rash on the 4th day of fever, with subsequent onset of papules and then vesicles. Before smallpox is known to be present, smallpox cases would not be recognized as such until the onset of vesicles, seven days after the onset of fever. After smallpox is known to be present, cases would be recognized at the onset of papules, six days after the onset of fever. Thirty percent of the cases would die 7–14 days after the onset of fever. People have varying degrees of transmission capabilities over the course of their infectious period, as shown in Figure 1. According to this pattern, 92% of an infected person's infectiousness occurs after the onset of the macular rash, an assumption consistent with a recent statistical analysis of smallpox infectivity.[15] Figure 1 shows that 47.5% of the cases would withdraw to the home at the end of the first day of fever, and 47.5% would go to the hospital at that time. The remaining 5% would continue to circulate but go to the hospital at the end of the third day of fever.

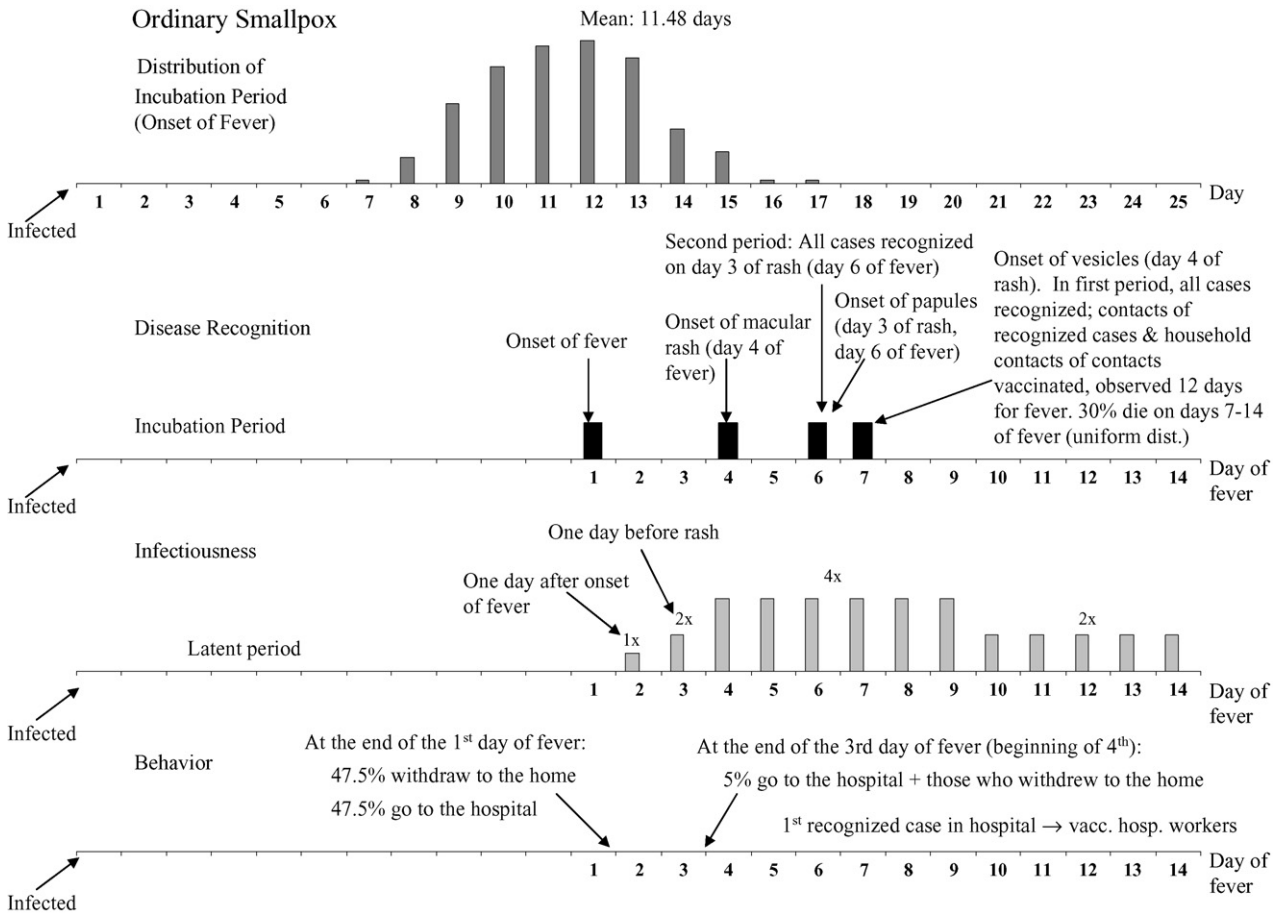


**Figure 1** The natural history of ordinary smallpox in terms of time lines. Parameter values were determined through group consensus from the Smallpox Modeling Working Group and Chapter 4 of Fenner et al.[14] The length of the incubation period follows the probability distribution shown in the top line. At the end of the incubation period, cases develop a fever, and then pass though a series of disease states. Before smallpox is recognized in the hospital (i.e., the first period), an ordinary case of smallpox would be recognized on the fourth day of rash. After this (i.e., the second period), smallpox is known to be present and all ordinary smallpox would be recognized in the hospital on the third day of rash. For infectiousness, the per contact transmission probability $x$ (Table 1), is set to $1x$ for the first day of fever, increased to $2x$ for the second day of fever, $4x$ at the onset of rash, etc., with an upper limit of 1.0. Thirty percent of ordinary smallpox cases would die between days 7 and 14, according to a uniform distribution. In the behavior time line, cases withdraw to the home or go to the hospital according to the pattern indicated. In surveillance and containment, close contacts of identified cases are vaccinated.

We modeled modified smallpox to have a similar incubation period to that of ordinary smallpox, but a milder course of disease with only a 10% case fatality rate (Figure 2). The infectiousness of people with modified smallpox would be 33% of that for people with ordinary smallpox. Hemorrhagic smallpox was modeled to have a shorter natural history and more severe disease progression than ordinary smallpox with a 100% case fatality rate (Figure 3). Infected people would begin internal bleeding four days after the onset of fever, and die on the seventh day after the onset of bleeding. Before smallpox is known to be present, we assumed that 50% of hemorrhagic smallpox cases would not be recognized and 50% would be recognized on the fifth day of fever. After smallpox is known to be present, all hemorrhagic cases would be recognized on the fourth day of fever. People with hemorrhagic smallpox would be five times more infectious than those with ordinary smallpox.

## The population

The model populations are based on a 50 000 person network of structured subpopulations of 2000 people mixing in households, clusters of households, neighborhoods, preschool groups, schools, and the community at large. The age distribution and approximate household sizes were based on the US Census 2000.[8] The subpopulations are connected through adult workplaces and high schools, and the whole population through a hospital. We include one hospital since statistics show there is about one hospital per 50 000 people in the USA.[13] The hospital has a total of 686 workers, 133 of whom can make close contact with smallpox cases until isolation measures in the hospital are instituted, based on a review of the numbers of employees having routine contact with patients.[13] Each person in the population may visit the hospital with probability 0.001 each day. They mix with all

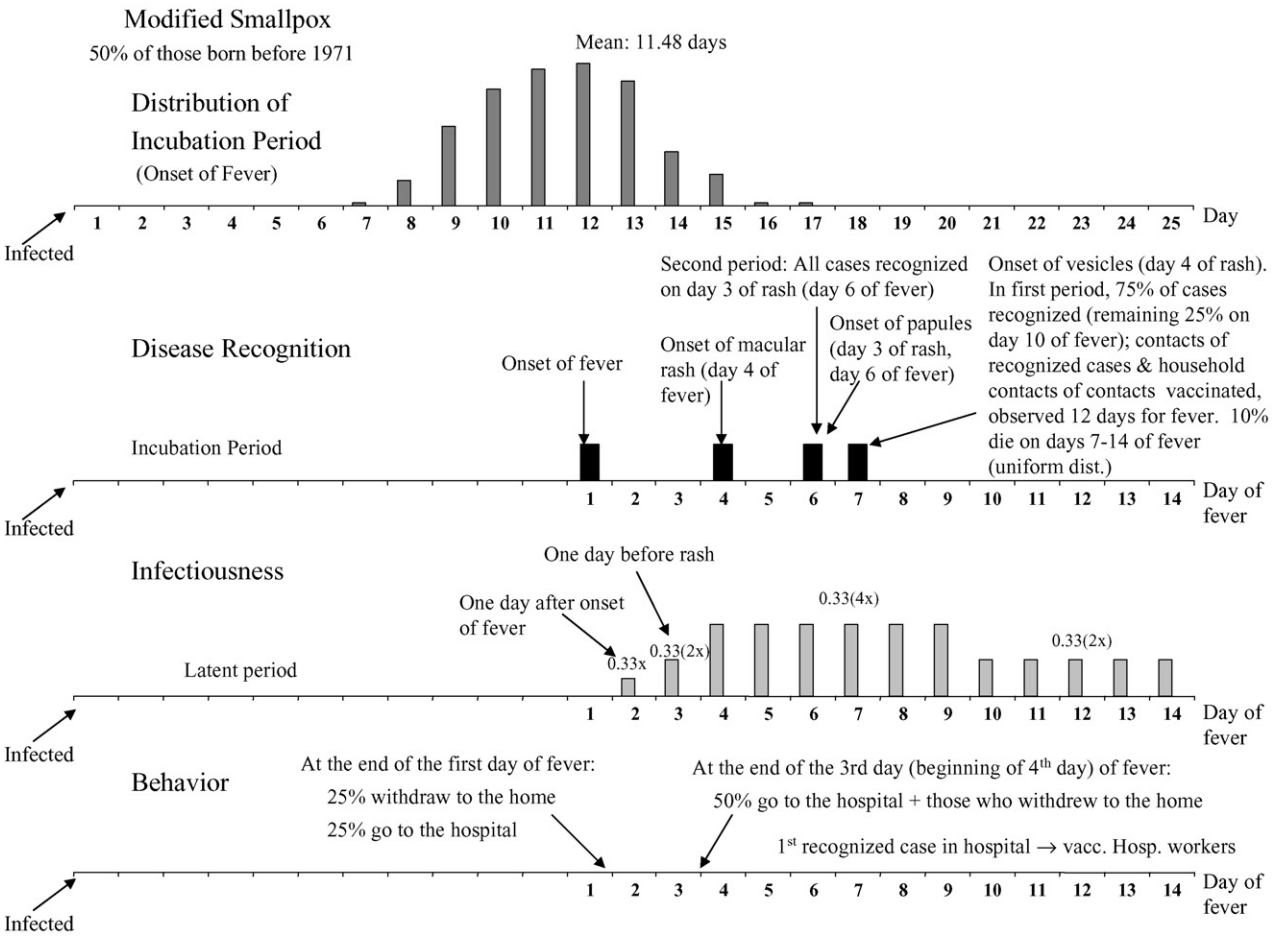


**Figure 2** The natural history of modified smallpox in terms of time lines. Modified smallpox is assumed to have the same incubation period as ordinary smallpox, but to have a milder course of disease. The infectiousness of people with modified smallpox would be 33% of that for people with ordinary smallpox, with a case fatality rate of 10%. However, it would be harder to recognize modified smallpox and cases would be slower to withdraw to the home or go to the hospital than for ordinary smallpox. Before smallpox is recognized in the hospital (i.e., the first period), 75% of cases would be recognized on the fourth day of rash and the remaining 25% on the seventh day of rash. After this, the smallpox is known to be present (i.e., the second period), and all ordinary smallpox would be recognized in the hospital on the third day of rash.

infected people in the hospital in the first period before smallpox is recognized, but only with unisolated circulating cases during the second period after smallpox is recognized. Figure 4A shows a schematic of the configuration of a subpopulation of 2000 people. Figure 4B shows how the subpopulations are connected through schools, workplaces, and a hospital to form the population of 50 000 people.

## The simulation model

We developed a discrete-time, stochastic simulation model of smallpox spread within a structured population described above. As mentioned above, the model is an extension of our previous smallpox model,[16] but for a larger population and with a more detailed disease natural history description. The model represents the number of close and casual contacts that a typical person makes in the course of a day. The basic person-to-person daily transmission probabilities, $x$, and mixing group sizes are given in Table 1. We define $x$ as the probability that an infected person with ordinary smallpox, on the second day after the onset of fever, makes sufficient contact to infect an unvaccinated susceptible person in the mixing group being modeled. For example, if a child were infected with ordinary smallpox, the probability that this child would infect an unvaccinated adult in the household, one day after the onset of fever, would be 0.05. On the third day after the onset of fever, this probability would increase to 0.10 (see infectiousness time line in Figure 1). The transmission probability would be 0.20 for days 4—9, and it would drop back down to 0.10 for days 10—14. People who complete the full course of disease without dying are considered to be immune.

Each day, for each susceptible, the probability of becoming infected is calculated based on his vaccination status, who is infectious in his or her mixing groups, and his or her vaccination status, as well as the mixing group-specific transmission probabilities. As an example, consider the simplest case that no one is vaccinated and we ignore the complex natural history of smallpox for illustrative purposes. An elementary school child is exposed to the number of child and adult infectives in his household $I_{hc}$ and $I_{ha}$, his household cluster $I_{kc}$ and $I_{ka}$, his school $I_s$, his neighborhood

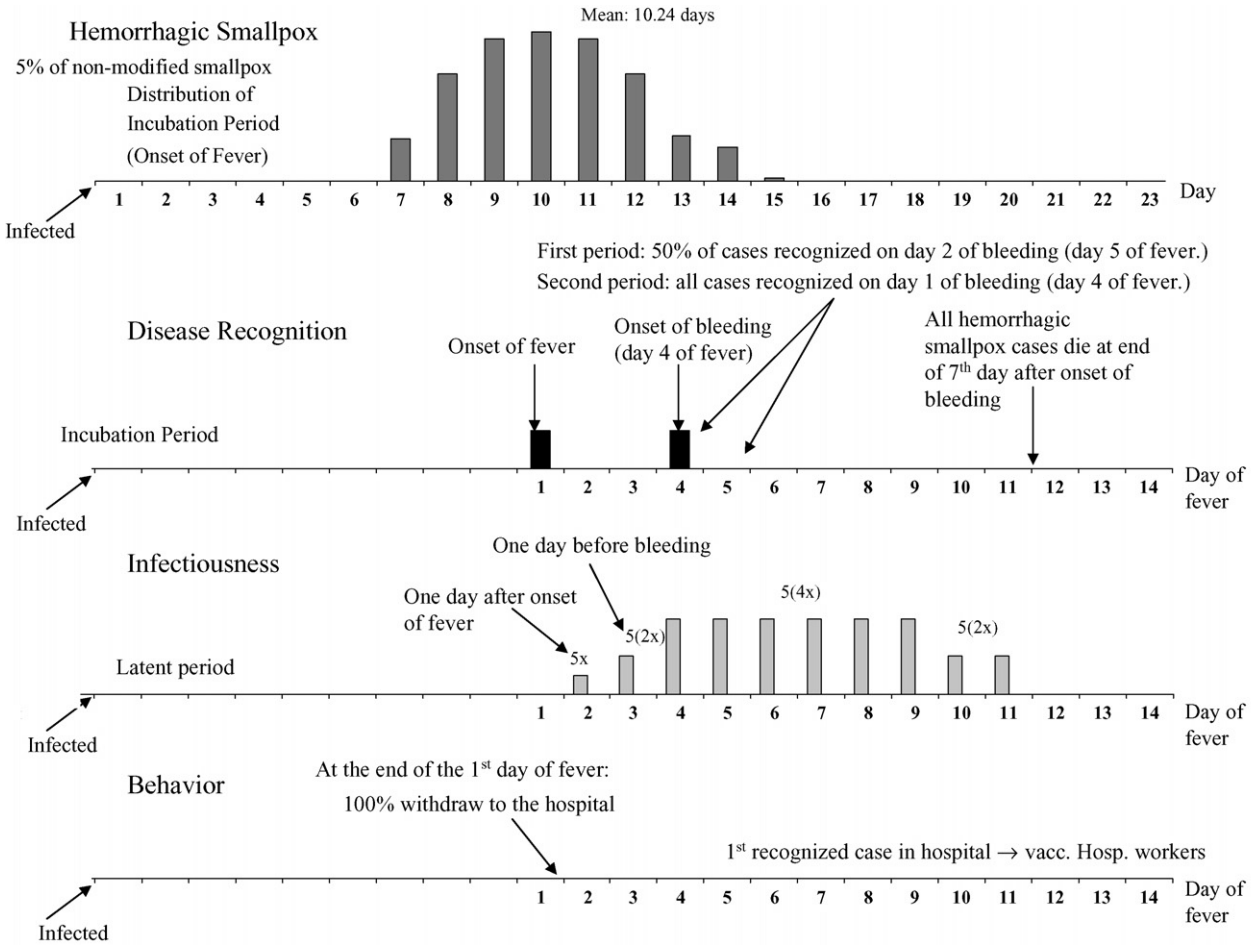


**Figure 3** The natural history of hemorrhagic smallpox in terms of time lines. Hemorrhagic smallpox is assumed to have a shorter natural history and more severe disease progression than ordinary smallpox. Infected people would begin internal bleeding four days after the onset of fever, and 100% would die on the seventh day after the onset of bleeding. Before smallpox is recognized, we assumed that 50% of hemorrhagic smallpox cases would not be recognized and 50% would be recognized on the fifth day of fever. After smallpox is recognized, all hemorrhagic cases would be recognized on the fourth day of fever.

$I_n$, and the community $I_m$ with corresponding transmission probabilities for each contact of $x_{hcc}$ (child-to-child), $x_{hac}$ (adult-to-child), ... respectively. Then, symbolically, the probability $P$ for that child to become infected on that day is:

$$P = 1 - (1 - x_{hcc})^{I_{hc}}(1 - x_{hac})^{I_{ha}}(1 - x_{kcc})^{I_{kc}}(1 - x_{kac})^{I_{ka}} \times (1 - x_s)^{I_s}(1 - x_n)^{I_n}(1 - x_m)^{I_m}.$$

This equation is evaluated term-by-term in order to identify the source of infection if an infection occurs. Once infected, a person passes through the natural history of the infection process (Figures 1–3). The length of the incubation period is randomly selected from the probability distributions. The rest of the disease progression follows deterministically as indicated in the Figures. Aspects of the infected person's behavior, such as if and when he or she withdraws to the home or goes to the hospital, are simulated stochastically according to the probability distributions in Figures 1–3. The model assumes the same contact structure each day of the simulation with the exception of trips to the hospital.

We created a person-to-person graph of our population by constructing a contact structure proportional to the transmission probabilities given in Table 1. The resulting weighted graph has an average clustering coefficient of 0.48, much larger than the average clustering coefficient of $10^{-3}$ of an Erdös–Rényi random graph with the same number of vertices and average degree.[17] The average shortest path was four people. This large clustering coefficient and small average shortest path, suggest that we have a small world person-to-person contact graph.[17,18] This indicates that the smallpox transmission will tend to infect close-knit groups such as households, daycare centers, and schools when introduced, and then remain confined to these groups for a few generations of transmission. After this, transmission will tend to jump to somewhat more socially distant groups in a sporadic fashion. This pattern of local clustering followed by larger jumps, makes smallpox susceptible to perifocal control efforts, such as surveillance and containment. This is in contrast to the rapid uniform transmission that would occur if the contact structure of the person-to-person graph was more like a random graph, i.e., random mixing. In this case, perifocal control measures would probably tend to fail.[5]

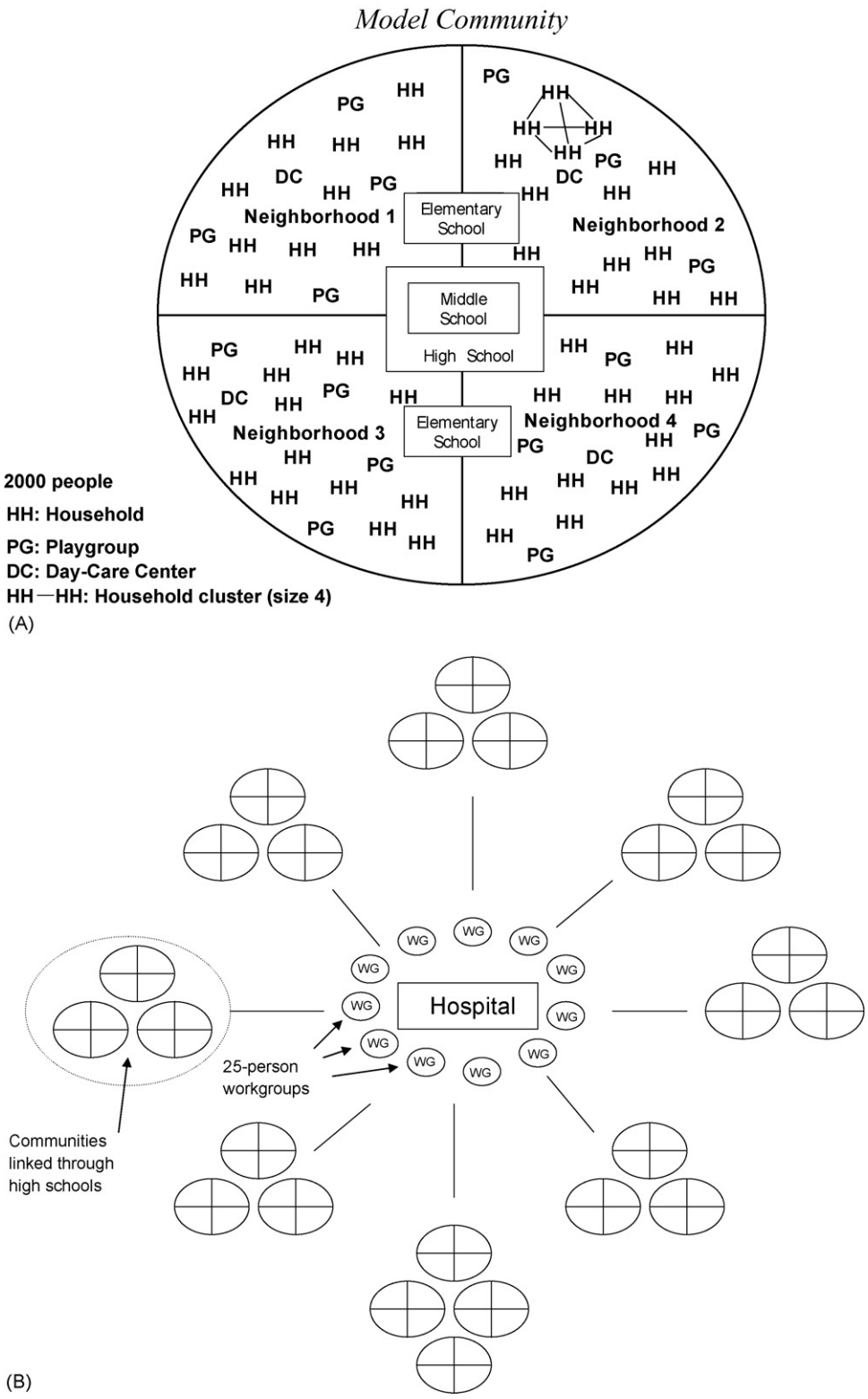


**Figure 4** Structure of the populations. (A) The 2000 person subpopulations consist of households and household social clusters depicted by the connecting lines in neighborhood 2. Each subpopulation is partitioned into four neighborhoods. Small children mix in playgroups and daycare centers within their neighborhoods. The school mixing groups link neighborhoods as shown. (B) Clusters of the subpopulations are created by allowing ten percent of high school students in each of the clusters of subpopulations to mix with high schools in other subpopulations in the same cluster. All adults who work are randomly assigned to work in mixing groups of size 25 throughout the whole population. In addition, all people can attend a single hospital.

**Table 1** Daily transmission probabilities, $x$,[a] among children and adults, by mixing group, and group sizes

| Contact group | Mean size | Children | | | | | Adults |
|---|---|---|---|---|---|---|---|
| | | Pre-school | | | School | | |
| | | Small playgroup | Large daycare | Elementary | Middle | High | |
| Small playgroups | 2.9 | 0.03000 | | | | | |
| Large day-care centers | 15.8 | | 0.02000 | | | | |
| Elementary school | 77.8 | | | 0.01000 | | | |
| Middle school | 145.3 | | | | 0.00800 | | |
| High school | 113.7 | | | | | 0.00800 | |
| Family | 2.5 | | | | | | |
| Child | | 0.03520 | 0.03520 | 0.03520 | 0.03520 | 0.03520 | 0.01240 |
| Adult | | 0.01240 | 0.01240 | 0.01240 | 0.01240 | 0.01240 | 0.01510 |
| Household social cluster | 10.1 | | | | | | |
| Child | | 0.03000 | 0.03000 | 0.03000 | 0.03000 | 0.03000 | 0.01000 |
| Adult | | 0.01000 | 0.01000 | 0.01000 | 0.01000 | 0.01000 | 0.01000 |
| Hospital | | | | | | | |
| Smallpox ward | 133.0 | | | | | | |
| Worker—worker | | | | | | | 0.00200 |
| Worker—visitor | | 0.00200 | 0.00200 | 0.00200 | 0.00200 | 0.00200 | 0.00200 |
| Patient—worker | | 0.00010 | 0.00010 | 0.00010 | 0.00010 | 0.00010 | 0.00010 |
| Patient—visitor | | 0.00010 | 0.00010 | 0.00010 | 0.00010 | 0.00010 | 0.00010 |
| Other wards | 533.0 | | | | | | 0.00050 |
| Workgroup | | | | | | | 0.01000 |
| Neighborhood | 500.0 | 0.00004 | 0.00004 | 0.00005 | 0.00005 | 0.00005 | 0.00014 |
| Community | 2000.0 | 0.00001 | 0.00001 | 0.00001 | 0.00001 | 0.00001 | 0.00003 |

[a] The probability that an infected person with ordinary smallpox, on the second day after the onset of fever, makes sufficient contact to infect an unvaccinated susceptible person in the mixing group being modeled.

## Interventions

For those people who receive a fresh smallpox vaccination before they are infected, we assumed the vaccine efficacy is 0.97, and that response to vaccination is all-or-none.[19] For those who receive a fresh vaccination four days post-infection, we assumed that 90% would not develop disease and 10% would develop modified smallpox. For those vaccinated between 5—7 days post-infection, 60% would develop modified smallpox, 38% ordinary smallpox, and 2% hemorrhagic smallpox. Vaccination reduces the death rate of breakthrough infections, for old vaccinations or fresh vaccinations 4—7 days post-infection, to a very low level, i.e., 1% or less.

We evaluated a number of intervention strategies. The most basic for traditional smallpox control has been surveillance and containment, also referred to as targeted or ring vaccination, which is part of the Centers for Disease Control and Prevention response plan.[20] For this control strategy, when the first case of smallpox is recognized, all hospital workers who deal with smallpox cases would be immediately vaccinated. Recognized cases of smallpox would be placed in hospital-based isolation, and their close contacts would be vaccinated and kept under observation. These close contacts would be those people in the recognized case's household and, when appropriate, in the case's household social cluster, daycare center, school group, or workplace. Contacts in the neighborhood or the community at large would not be considered to be close contacts and not be isolated. Children under one year of age are not vaccinated.

We considered mass reactive vaccination where vaccination would begin one day after recognition of the first case of smallpox, and would take seven days to complete to a

**Table 2** Smallpox simulation scenarios

| | Scenario | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | Baseline | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Background immunity | | +[a] | + | + | + | + | + | + | + | + | + |
| Surveillance and containment | | | Isolation but no vaccination | + | + | + | + | + | + | + | + |
| Pre-emptive vaccination | | | | | | | | | | | |
| Pre-emptive vaccination (hospital-only) | | | | | 10% | 50% | 10% | 50% | 10% | 50% | 10% |
| Reactive school closure 10 days | | | | | | | + | + | + | + | + |
| Mass reactive vaccination | | | | | | | 40% | 40% | 80% | 80% | |

[a] The + indicates that the factor is present.

particular level. Smallpox cases are not vaccinated. In addition, any person freshly vaccinated through contact tracing or pre-emptive vaccination in the hospital would not be revaccinated. The schools would serve as vaccination centers and be closed for that seven-day period. A further strategy that was considered was the prevaccination of different proportions of hospital workers. We also considered reactive closing of the schools for ten days, starting one day after recognition of the first case of smallpox.

In accordance with the working group, we evaluated a range of control scenarios (Table 2). The baseline scenario involved people withdrawing to the home and others being placed in effective hospital isolation at the appropriate times, but no contact tracing or vaccination. Scenario 3 was surveillance and containment (with vaccination of close contacts) alone and then scenarios 4—10 involved surveillance and containment plus various additional control measures including pre-emptive vaccination of hospital workers, reactive mass vaccination, and reactive school closings. Scenarios 1 and 2 involved no interventions and were used to help validate the simulations.

For the attack scenario we assumed that 500 randomly selected people are initially infected. For each intervention scenario, 100 epidemics were stochastically simulated.

## Results

Calibration of the model was based on historical data available on smallpox, including household secondary attack rates,[14] relative age-specific attack rates being higher in children,[21] and the distribution of secondary cases produced by an introductory case.[14,22] We roughly calibrated the transmission probabilities in households to observed household secondary attack rates from past smallpox epidemics. These ranged from 44% to 88% to unvaccinated people in a variety of populations in Africa and South Asia in the 1960s and 1970s.[14,22] For example, we set the child-to-adult household daily transmission probability $x$ to 0.05. Using the information in Figure 1, if the infected child remained in the household over his entire infectious period, then the probability that he would infect the exposed adult would be 0.85 (i.e., household secondary attack rate of 85%). However, in reality the household secondary attack rate would be lower as the infected child would be placed in isolation when recognized as a smallpox case. Thus, 85% is the maximum household secondary attack rate. If the index infected child had modified smallpox, then the maximum secondary attack rate for child-to-adult transmission in the household would be 46%, and if the index case had hemorrhagic smallpox, then the maximum secondary attack rate would be 100%. These relationships are shown in Figure 5. The maximum secondary attack rate for other mixing groups is illustrated on this plot.

Figure 6A shows the first 60 days of one stochastically simulated smallpox epidemic with 500 randomly selected initially infected people from all age groups in the population for surveillance and containment (scenario 3), while Figure 6B shows the same for surveillance and containment plus preemptive hospital worker vaccination at 50%, and reactive school closing and mass vaccination at 80% (scenario 9). Figure 6A and B show that the model reproduces the characteristic epidemic waves of smallpox roughly every two weeks. Although an outbreak is not prevented, it is reduced to a low level.

Table 3 shows the number of cases not counting the initial cases when surveillance and containment, which includes

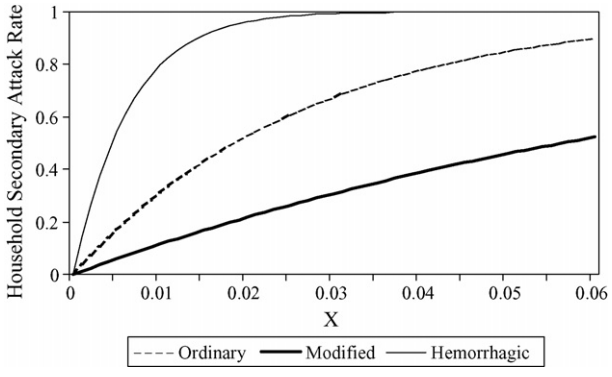


**Figure 5** A plot showing the relationship between the transmission probability $x$ during the second day of fever from an unvaccinated case of smallpox to an exposed unvaccinated person in a mixing group and the maximum household secondary attack (SAR) rate if he circulated in the mixing group for his entire infectious period. This relationship is based on the smallpox natural histories given in Figures 1—3.

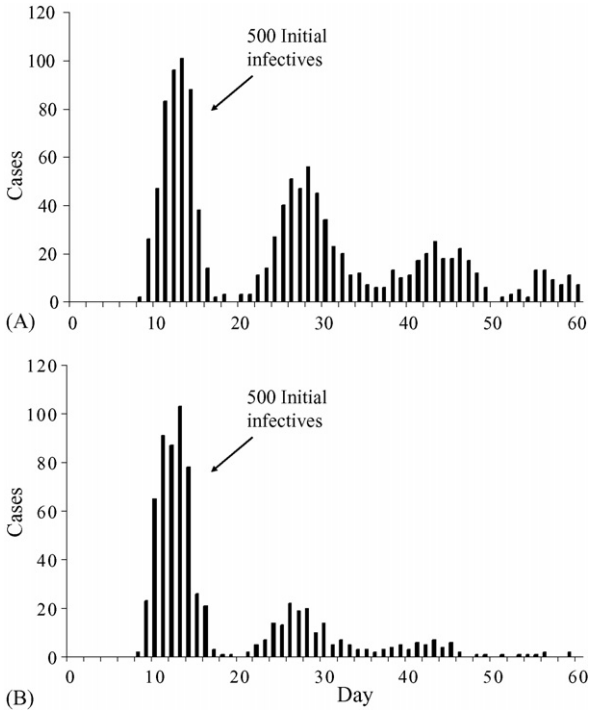


**Figure 6** The first 60 days of one stochastically simulated smallpox epidemic with 500 randomly selected initially infected people from all age groups. (A) Epidemic surveillance and containment (scenario 3). This epidemic had a duration of 196 days, while the average duration of the epidemics under scenario 3 was 194 days. (B) Epidemic with surveillance and containment, 50% preemptive hospital vaccination and 80% reactive mass vaccination with reactive school closure for ten days (scenario 9). This epidemic had a duration of 91 days, while the average duration of epidemics under scenario 9 was 87 days.

**Table 3** Distribution of cases excluding initial cases for surveillance and containment with vaccination of close contacts (scenario 3)[a]

| Source of cases | Cases | | |
|---|---|---|---|
| | Mean | Q1[b] | Q3[b] |
| Household | 82 | 70 | 93 |
| Neighborhood cluster | 62 | 50 | 72 |
| Daycare | 6 | 3 | 8 |
| Schools | 101 | 78 | 120 |
| Workgroup | 60 | 19 | 87 |
| Hospital (smallpox ward) | 413 | 362 | 463 |
| General neighborhood | 52 | 44 | 60 |
| Community | 54 | 46 | 63 |
| Total[c] | 828 | 694 | 935 |

[a] Based on 100 simulations.
[b] Q1: first quartile; Q3: third quartile.
[c] A small number of people may have been infected from more than one source.

vaccination of close contacts (scenario 3), is instituted. The total number of cases averages 828, with 50% of the cases from the hospital, 18% from the family or other close contacts, 19% from schools or the workplace, and 13% from the neighborhoods and community at large. This latter 13% of infecting contacts would be untraceable. These percentages are quite close to those observed for European smallpox epidemics for 1950–1971 (Table 4).

Table 5 gives the numbers of smallpox cases and deaths for the baseline and for scenarios 3–10. (Results for scenarios 1 and 2 are not in the Table 5, but are given below.) If the only action were the isolation of cases (baseline scenario), then the model predicts an average of 1750 cases and 523 deaths. If we add vaccination and carry out surveillance and containment (scenario 3), then the average number of cases would be reduced to 828 and the number of deaths to 211. Figure 6A indicates that for surveillance and containment there would be a relatively large second wave of cases after the initial wave, and then a much smaller third and fourth wave. Preemptive vaccination of 10% of hospital workers in addition to surveillance and containment (scenario 4) has a small effect on the average number of cases; however, preemptive vaccination of 50% of the hospital workers (scenario 5) has a relatively large effect on reducing the number of cases. Reactive mass vaccination of 40% of the susceptible population (scenarios 6 and 7) has a large additional effect. On average, 80% reactive mass vaccination (scenarios 8 and 9) is the most effective in reducing the outbreak to a minimal number of cases. By comparing scenarios 4 and 10, we see that reactive closing of the schools for ten days is not particularly effective.

**Table 4** Average distribution of the sources of infection for smallpox cases with surveillance and containment (scenario 3), compared to the distribution observed in European epidemics, 1950–1971

| Location | Model | European |
|---|---|---|
| Hospital | 50% | 50% |
| Family or other close contact | 18% | 22% |
| Workplace or school | 19% | 14% |
| Unknown source | 13% | 14% |

Table 6 gives the numbers of fresh smallpox vaccinations for scenarios 3–10. Under surveillance and containment (scenario 3), an average of 7501 fresh doses of vaccine would be used, far fewer than the ~25 500 doses that would be used under 40% reactive mass vaccination plus surveillance and containment and preemptive hospital vaccination (scenarios 6 and 7) or the ~45 000 doses that would be used under 80% reactive mass vaccination plus surveillance and containment and preemptive hospital vaccination (scenarios 8 and 9). The average number of doses used with surveillance and containment decreases with increasing level of preemptive hospital worker vaccination, since the total number of vaccinations due to contact tracing is decreased due to fewer cases. This can be seen by comparing the number of vaccine doses needed for scenarios 3–5.

For orientation purposes, we ran the simulator assuming no prior immunity, no interventions, and that cases do not withdraw to the home or go to the hospital (scenario 1).

**Table 5** Scenario results, excluding the 500 initial cases[a]

| Scenario: action | Cases | | | Deaths | | |
|---|---|---|---|---|---|---|
| | Mean | Q1[b] | Q3[b] | Mean | Q1 | Q3 |
| Baseline | 1750 | 1527 | 1427 | 523 | 455 | 584 |
| 3: SC[c] | 828 | 694 | 935 | 211 | 173 | 239 |
| 4: SC + PHV10% | 768 | 653 | 872 | 197 | 168 | 231 |
| 5: SC + PHV50% | 678 | 595 | 750 | 180 | 156 | 206 |
| 6: SC + PHV10% + RSC + RMV40% | 439 | 390 | 474 | 96 | 84 | 107 |
| 7: SC + PHV50% + RSC + RMV40% | 367 | 341 | 394 | 83 | 73 | 91 |
| 8: SC + PHV10% + RSC + RMV80% | 253 | 218 | 276 | 38 | 32 | 44 |
| 9: SC + PHV50% + RSC + RMV80% | 203 | 185 | 219 | 33 | 29 | 38 |
| 10: SC + PHV10% + RSC | 712 | 152 | 798 | 182 | 152 | 206 |

PHV, pre-emptive hospital vaccination; RSC, reactive school closure; RMV, reactive mass vaccination.
[a] Based on 100 simulations.
[b] Q1: first quartile; Q3: third quartile.
[c] SC, surveillance and containment with vaccination of close contacts.

**Table 6** Number of vaccine doses[a]

| Scenario | Doses | | |
|---|---|---|---|
| | Mean | Q1[b] | Q3[b] |
| 3 | 7501 | 6825 | 7966 |
| 4 | 7221 | 6542 | 7772 |
| 5 | 6725 | 6231 | 7185 |
| 6 | 25 677 | 25 481 | 25 856 |
| 7 | 25 472 | 25 267 | 25 667 |
| 8 | 45 246 | 45 203 | 45 284 |
| 9 | 45 214 | 45 178 | 45 262 |
| 10 | 6888 | 6336 | 7357 |

[a] Based on 100 simulations.
[b] Q1: first quartile; Q3: third quartile.

Nearly the entire population is infected, an average of 49 500 cases. This result is expected since infected people are modeled to circulate in the community over their entire infectious period. The average number of deaths is 16 598 people. The addition of prior immunity (scenario 2) makes a small difference in the number of cases, averaging 46 643 people. Prior immunity makes a larger difference in the number of deaths, an average of 13 681. This decrease is mostly due to the increased number of modified smallpox cases among those people previously vaccinated. In addition, by comparing the baseline average of 1750 cases to the average of 46 643 cases under scenario 2, we see the great effectiveness of people with early smallpox symptoms simply withdrawing to the home and entering hospital isolation.

Table 7 shows the results of a sensitivity analysis where we vary the time it takes to recognize a case and begin isolation of the case and vaccination of close contacts under the surveillance and containment scenario 3 (see case recognition days in Figures 1—3). This further delay could be the result of some cases not being caught quickly, confusion about smallpox symptoms, or some other problem with the medical response. If we delay an additional day, the number of cases and deaths doubles. More than one day further delay would result in a further approximately 50% increase in the number of cases and deaths.

**Table 7** Surveillance and containment for various delays in case recognition, excluding the 500 initial cases[a]

| Additional delay in recognition (days) | Cases | | | Deaths | | |
|---|---|---|---|---|---|---|
| | Mean | Q1[b] | Q3[b] | Mean | Q1 | Q3 |
| Current model[c] (no additional delay) | 828 | 694 | 935 | 211 | 173 | 239 |
| 1 | 1681 | 1509 | 1848 | 416 | 370 | 459 |
| 2 | 2017 | 1879 | 2162 | 503 | 461 | 533 |
| 3 | 2217 | 1995 | 2373 | 578 | 522 | 625 |
| 4 | 2372 | 2081 | 2601 | 658 | 585 | 720 |
| 5 | 2786 | 2574 | 3007 | 780 | 720 | 841 |

[a] Based on 100 simulations.
[b] Q1: first quartile; Q3: third quartile.
[c] Model default: smallpox cases are recognized in the hospital either seven days (ordinary and modified cases) or four days (hemorrhagic cases) after onset of fever.

## Discussion

This work suggests that the current federal government policy of post-release surveillance and containment, if effectively implemented, could be sufficient to contain either a small or large intentional release of smallpox. We have shown that reactive mass vaccination in addition to surveillance and containment during an attack results in fewer cases and deaths than surveillance and containment alone. However, many more people would need to be vaccinated for reactive mass vaccination than for surveillance and containment. Since the risk of vaccine-related illness is about $10^{-4}$ and vaccine related death is about $10^{-6}$,[2] one would expect an average of 2.5—4.5 vaccine-related illnesses and a small probability that one person would die due to vaccination for the reactive mass vaccination strategies considered here. If logistically possible, implementation of reactive mass vaccination would make sense. Prevaccination of hospital workers results in somewhat smaller outbreaks in the event of an attack. However, since it is not known when or where an attack may occur, prevaccination strategies would require that large numbers of people be vaccinated throughout the entire country. This is true of any prevaccination program before an attack. Such programs either for hospital workers and first responders or for the general population may not be necessary given the effectiveness of surveillance and containment that could be carried out at the location of an attack. The benefits of such prevaccination need to be weighed against the potential harm that would ensue due to vaccine-related injury. The quantitative validity of the above statements depends on the assumptions, parameter values, and model structure that we have used here. However, our general conclusions should be robust to this uncertainty.

Children under one year of age do not receive smallpox vaccine. However, in the absence of maternal antibodies, young children are at very high risk of serious disease and death if they contract smallpox. This makes the surveillance and containment policy very important for these children since the rapid vaccination of family members of index cases and of school children affords very young child indirect protection.

To assess the robustness of our conclusions about the effectiveness of control strategies modeled, we carried out a number of sensitivity analyses not given in the results. The total number of smallpox cases was found to be sensitive to variation in the transmission probabilities $x$ in the different mixing groups. However, the relative effectiveness of the control strategies was not affected across the range from small to larger values of $x$. The most sensitive factor was timing of withdrawal to the home and isolation of cases. A delay in recognition of cases by one or more days beyond the hypothesized control strategy outlined in Figures 1—3 was found to result in poorly contained simulated epidemics (Table 7). The sensitivity analysis also reflects uncertainty about the exact onset of infectiousness relative to symptoms, since earlier than hypothesized onset of infectiousness would be equivalent to a delay in isolation. This result is consistent with a previous modeling exercise that showed logistical delays in fully implementing surveillance and containment could lead to a large outbreak.[5]

We created a 50 000 person model population based on the US census 2000 information and our conception of how a typical American population is connected in terms of potential smallpox transmission. To assess whether we have the approximate connectivity of a typical US population, we compared our person-to-person graph to the graph that was constructed from individual level daily travel and location visited survey data from Portland, Oregon, with a population of 1.6 million people.[6] The average clustering coefficient for both graphs is 0.48. This indicates that the degree to which the two populations are clustered into close mixing groups such as households, schools, and workplaces is similar. The mean shortest path for the Portland population was six, while it is four for our population. Thus, the links between clusters for our population are somewhat shorter than those in Portland. Both our graph and the one for Portland are small world with similar characteristics. Although our population is smaller than the Portland population, the connectivity of any person with others in the population is roughly similar for the two populations. Thus, we believe that our simulation population of 50 000 people is large enough to investigate the effectiveness of the various containment strategies against a large attack.

Our previous modeling work has shown that surveillance and containment would be effective in containing and sometimes preventing a smallpox outbreak for a small number of initial cases.[3] In this work, using a model with different epidemiologic parameter values, we show that surveillance and containment could be effective in containing an outbreak with a large number of initial cases. This suggests that further prevaccination of the population of the USA would be counter-productive. However, a rapid and well-organized response to a smallpox bioterrorist attack would be needed to make containment efficient.

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## References

1. Cohen J, Enserink M. Public health. Rough-and-tumble behind Bush's smallpox policy. *Science* 2002;**298**:2312–6.
2. Henderson DA, Inglesby TV, Bartlett JG, Ascher MS, Eitzen E, Jahrling PB, et al. Smallpox as a biological weapon: medical and public health management. *JAMA* 1999;**281**:2127–37.
3. Halloran ME, Longini IM, Nizam A, Yang Y. Containing bioterrorist smallpox. *Science* 2002;**298**:1428–32.
4. Eichner M. Case isolation and contact tracing can prevent the spread of smallpox. *Am J Epidemiol* 2003;**158**:118–28.
5. Kaplan EH, Craft DL, Wein LM. Emergency response to a smallpox attack: the case for mass vaccination. *Proc Natl Acad Sci USA* 2002;**99**:10935–40.
6. Eubank S, Guclu H, Kumar VS, Marathe MV, Srinivasan A, Toroczkai Z, et al. Modelling disease outbreaks in realistic urban social networks. *Nature* 2004;**429**:180–4.
7. Bozzette SA, Boer R, Bhatnagar V, Brower JL, Keeler EB, Morton SC, et al. A model for a smallpox-vaccination policy. *N Engl J Med* 2003;**348**:416–25.
8. United States Census Bureau. Census 2000. Age distribution was retrieved from www.census.gov/census2000/states/us.html, and household sizes were retrieved from http://factfinder.census.gov/servlet/DatasetMainPageServlet?_lang=en (see Census 2000 Summary File 1). These Web sites were accessed on 29 October 2002.
9. Enserink M. Infectious diseases. Smallpox vaccination campaign in the doldrums. *Science* 2003;**300**:880–1.
10. Centers for Disease Control. Smallpox vaccination program status by state, 2005. http://www.cdc.gov/od/oc/media/spvaccin.htm. Accessed on January 23, 2005.
11. Hammarlund E, Lewis MW, Hansen SG, Strelow LI, Nelson JA, Sexton GJ, et al. Duration of antiviral immunity after smallpox vaccination. *Nat Med* 2003;**9**:1131–7.
12. Eichner M. Analysis of historical data suggests long-lasting protective effects of smallpox vaccination. *Am J Epidemiol* 2003;**158**:717–23.
13. Smallpox modeling working group, Secretary's Advisory Council on Public Health Preparedness, United States Department of Health and Human Services. The working group was headed by J. Chin (UC Berkeley), and also consisted of L. Anderson (CDC), L. Borio (DHHS), J. Breman (NIH/FIC), G. Curlin (NIH/NIAID), J. Donlon (DHHS), E. Eitzen (DHHS), D.S. Burke (JHSPH), J.M. Epstein (Brookings Institution), J.W. Glasser (CDC), M.E. Halloran (Emory U), D.A. Henderson (DHHS), I.M. Longini (Emory U), E. McKenzie (NIH/FIC), M. Miller (NIH/FIC), F. Murphy (UC Davis).
14. Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID. *Smallpox and its eradication*. Geneva: World Health Organization; 1988.
15. Eichner M, Dietz K. Transmission potential of smallpox: estimates based on detailed data from an outbreak. *Am J Epidemiol* 2003;**158**:110–7.
16. Halloran ME, Longini IM, Cowart DM, Nizam A. Community trials of vaccination and the epidemic prevention potential. *Vaccine* 2002;**20**:3254–62.
17. Watts D, Strogatz S. Collective dynamics of 'small-world' networks. *Nature* 1998;**393**:440–2.
18. Watts DJ. *Small worlds: The dynamics of networks between order and randomness*. Princeton, NJ: Princeton University Press; 1999.
19. Halloran ME, Struchiner CJ, Longini IM. Study designs for different efficacy and effectiveness aspects of vaccination. *Am J Epidemiol* 1997;**146**:789–803.
20. Centers for Disease Control. Smallpox response plan and guidelines (version 3.0), 2002. http://www.bt.cdc.gov/agent/smallpox/response-plan/index.asp.
21. Thomas DB, Arita I, McCormack WM, Khan MM, Islam S, Mack TM. Endemic smallpox in rural East Pakistan. II. Intravillage transmission and infectiousness. *Am J Epidemiol* 1971;**93**:373–83.
22. Mack TM. Smallpox in Europe, 1950–1971. *J Infect Dis* 1972;**125**:161–9.