
Individual-based Computational Modeling of Smallpox Epidemic Control Strategies

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Abstract

In response to concerns about possible bioterrorism, the authors developed an individual-based (or “agent-based”) computational model of smallpox epidemic transmission and control. The model explicitly represents an “artificial society” of individual human beings, each implemented as a distinct object, or data structure in a computer program. These agents interact locally with one another in code-represented social units such as homes, workplaces, schools, and hospitals. Over many iterations, these microinteractions generate large-scale macroscopic phenomena of fundamental interest such as the course of an epidemic in space and time. Model variables (incubation periods, clinical disease expression, contagiousness, and physical mobility) were assigned following realistic values agreed on by an advisory group of experts on smallpox. Eight response scenarios were evaluated at two epidemic scales, one being an introduction of ten smallpox cases into a 6,000-person town and the other an introduction of 500 smallpox cases into a 50,000-person town. The modeling exercise showed that contact tracing and vaccination of household, workplace, and school contacts, along with prompt reactive vaccination of hospital workers and isolation of diagnosed cases, could contain smallpox at both epidemic scales examined.

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Agent-based modeling is a new scientific approach in the tradition of cellular automata made possible by recent advances in computing. In brief, an agent-based model or “artificial society” includes some population of “agents,” typically individual human beings, each implemented as a distinct object, or data structure in a computer program. These agents interact locally with one another in the computer code. Over many iterations, these microinteractions can generate large-scale macro-

scopic phenomena of fundamental interest, specifically, the course of epidemics in space and time. When calibrated to actual epidemic data, these models become credible bases for policy analysis.

One distinguishing feature of individual-based models is that the individuals in the model (the people) are not aggregated into a few homogeneous pools (e.g., susceptibles, infectives, and removeds).¹ Rather, agent populations are highly heterogeneous; every single individual is explicitly modeled and tracked. A second distinguishing feature of agent models is that events transpire on an explicit space. In the agent approach, people interact only with neighbors in the space, who change as agents move around, for example, coming and going to school or work in the model. Our simulation approach attempts to create a realistic depiction of local social contact dynamics in discrete and explicitly represented social units (the home, the hospital, and so on). In agent models where individual decision making is present, agents have bounded rationality and typically make use of simple rules based on local information.²

All of this action can be depicted graphically in real time, as if looking down on the social space from above, watching agents move to and from the various social units (homes, schools, workplaces), changing colors as they progress through the phases of the disease. It is centrally important to note that, because of their explicit

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inclusion of physical space, local interactions, and individual heterogeneity, the agent models produce fundamentally different spatiotemporal epidemic dynamics than smoothed differential equation models.³ When this highly visual mode of modeling produces a novel hypothesis, all the graphics can be turned off, and the model can be run stochastically for millions of cycles to explore the robustness of the finding. There is no sacrifice of rigor; indeed, we can generate extremely high volumes of clean data and analyze it statistically to yield a very high-fidelity characterization of model behavior and robust calibration to historical data.

The modeling approach taken derives directly from that previously developed by Epstein et al.⁴ This work was undertaken under the auspices of the Smallpox Modeling Working Group of the U.S. Department of Health and Human Services Secretary's Advisory Council on Public Health Preparedness. The charge to members of the working group was to modify their existing smallpox epidemic models to incorporate agreed-on values for the natural history and transmission of the disease and then use the model to analyze epidemic outcomes under a variety of plausible attack and response scenarios.

MODEL

Assumptions and Parameters

This article describes an extended version of our basic agent-based smallpox model, distributed over a range of social architectures, population sizes, and assigned response scenarios.⁴ Throughout this article, we use the detailed biomedical assumptions agreed on by the Smallpox Modeling Working Group (see [Appendix A](#) for a listing of working group members). Values assigned included the distribution of ordinary, modified, and hemorrhagic smallpox to be expected in the U.S. population and, for each form of the disease, the assumed distributions of incubation periods, time to disease recognition, infectiousness, and mobility effects of infection and disease.¹ Other parameters, such as the probability of smallpox transmission per contact at various phases of the disease's natural history, and contact rates per day in various social units (the home, school, workplace, and hospital) were estimated by calibration of the model to real epidemiologic data. A detailed description of all aspects of the model is included in the technical appendix (available as a Data Supplement at <http://www.aemj.org/cgi/content/full/j.aem.2006.07.017/DC1>).

Simulated Social Structures

The basic social structure represented in the model was the town. Towns were composed of smaller social units representing households, workplaces, schools, and hospitals. The basic model unit of time was the "day," which was parsed into two equal halves, a nighttime when all healthy individuals were at home and a daytime when healthy individuals were at work or school. No genders were assigned. Adults cycled between work and home, whereas children cycled between school and home.

The number of persons per household was distributed according to U.S. census figures.⁵ For the "uniform" towns, all adults in a town went to one workplace and

all children went to one school. For the "hub-and-spoke" and "ring" towns (see following text), the town was divided into districts, each with its own local workplace and local school. Where the town architecture was composed of more than a single uniform district, 10% of workers "commuted" to the workplace of a contiguous district. Children attended school in the town in which they lived. For all towns, there was a single hospital, including 150 adult health care workers who worked at the hospital rather than at the common workplace. During the daytime and nighttime, contacts were made with one of the eight possible physically neighboring individuals on the grid surface, wherever the individual was at that time (household, workplace, and so on). The proportion of contacts that were potential transmitting contacts in each social unit was assigned according to the calibration of the model to historical data.⁶

In this study, we examined models for two sizes of total population: 6,000-person towns and 50,000-person towns. For the 6,000-person towns, we examined three social architectures: a single uniform town of 6,000 persons, a ring town of six districts of 1,000 persons each, and a hub-and-spoke town with a single central district of 2,000 persons surrounded by four districts of 1,000 persons ([Figure 1](#)). In each town there was a single hospital that served all districts but was staffed by persons from one district. Index cases were always seeded into one district, the district containing the hospital. The social architectures for 50,000-person towns were analogous but larger.

Calibration of the Model to Historical Data

The parameters governing the probability of smallpox transmission per contact, and the contact rates in different social settings, were chosen through a calibration of simulated epidemics with historical data. The historical data describe outbreaks resulting from 49 importations of a single case of smallpox into nonendemic Europe during the period from 1950 to 1971.⁶ Two distributions from these real epidemic data were used for the calibration: 1) the distribution of the total number of cases resulting from each of these importations and 2) the distribution of the location where transmissions occurred (in a hospital setting, in a workplace or school setting, or in the home). A parameter sweep was performed in which the per-contact transmission probability and the contact rate in the hospital, the home, and the workplace or school were systematically varied. The resultant distributions of epidemic sizes and transmission locations from 1,000 calibrating simulation runs were compared with the known historical distributions. The model parameter settings for per-contact transmission and contact rates in each social setting were chosen that minimized the sum of squared deviations from the known historical distributions.

Baseline "No Response" Scenarios

We first conducted an evaluation of simulated epidemics in the unrealistic setting of a complete absence of public health response. Two base case "no response" scenarios were examined. These scenarios served as baselines for comparison of intervention strategies. Scenario 1 presupposed only a low level of immunity among adults due to vaccination 30 years ago or more. Scenario 2 was

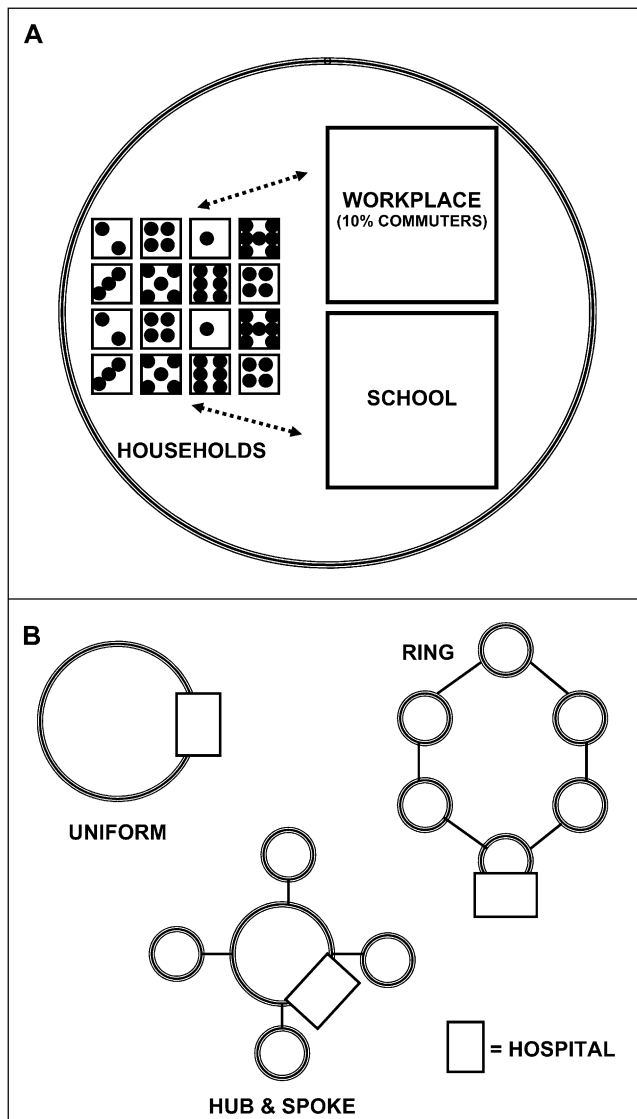


Figure 1. Schematic diagram of the social structures represented in the model. (A) Basic town/district social unit with multiple households, one school, and one workplace. (B) Town social architectures of single uniform, ring, and hub-and-spoke structure.

identical to scenario 1 except that transmission from hospitalized persons was set at zero to determine if the force of infection in the community alone was sufficient to sustain the simulated epidemics.

Evaluation of “Response” Scenarios

We then conducted an analysis of eight response scenarios specified by the working group. These scenarios involved contact tracing and vaccination of family, coworker, and hospital contacts, hospital isolation of all cases, preemptive vaccination of health care workers, school closures, and mass reactive vaccination. The complete spectrum of scenarios is summarized in Figure 2. For each of the three architectures of the 6,000-person town model, each of the eight response scenarios was run 35 different times, with a different random seed each time. Note that the model is stochastic; the use of

a different random seed for each run ensures that particular realizations of the same model produce different random contact patterns in the population. The random seeds also ensure that model parameters drawn from set distributions (see Longini et al.¹ and Figure 1) vary from individual to individual and run to run. For each combination of town architecture and response scenario, we report here the mean and the standard deviation (over the 35 simulated epidemic runs) for the following key epidemic outcome measurements: total number of cases, total number of deaths, total number of vaccinations, and total epidemic duration.

For the 50,000-person town model runs, the analysis format was similar to that for the 6,000-person towns, except that here 500 initial infected individuals were introduced into the population. Because these runs absorb substantially more computational resources than the comparable 6,000-person town simulations, we explored only two architectures: the single uniform large town of 50,000 and a ring of six districts of equal size. Instead of 35 simulated epidemic runs per scenario-architecture pair, we present the statistics for just ten stochastic realizations.

RESULTS

Tabular Results

Cases, deaths, vaccinations, and epidemic durations for simulated epidemics under the two “no response” and the eight response scenarios are shown in Tables 1 and 2 for populations of 6,000 individuals and 50,000 individuals, respectively.

Simulated Epidemics in the Baseline “No Response” Scenarios

Simulations under the highly unrealistic “no response” scenarios 1 and 2 gave rise to large and lengthy epidemics. Each index case, on average, initiated an epidemic chain of transmission that subsequently infected hundreds of other individuals.

Evaluation of Response Scenarios in 6,000-person Towns

Response scenarios 3–10 were all examined in model populations with each of the three (single uniform, ring, and hub and spoke) town architectures, and 35 simulated epidemics were run for each scenario in each architecture. Results are displayed in Table 1. Although there are some minor differences in the impact of the different response scenarios in different town structures, the results for each response scenario show substantial concordance across all three town structures. Results are therefore presented in the text by scenario rather than by town structure.

In striking contrast to the “no response” scenarios 1 and 2, the interventions in scenario 3 alone are sufficient to limit the epidemic to a mean of fewer than 48 cases and a mean duration of less than 77 days. The addition of 10% or even 50% preemptive vaccination of hospital workers (scenarios 4 and 5) does not add appreciably to the protections afforded in scenario 3. Mass reactive vaccination of either 40% or 80% of the total population (scenarios 6–9) does provide some additional protection of the

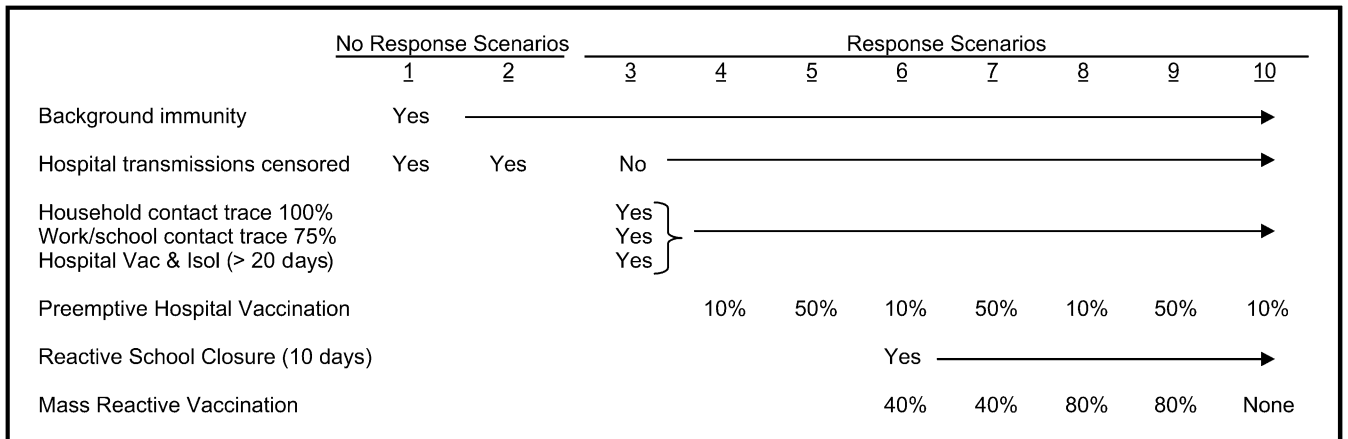


Figure 2. Summary sketch of the interventions and combinations of baseline conditions and interventions studied in “no response” scenarios 1 and 2 and response scenarios 3–10.

population, reduces the mean number of infected persons to fewer than 33, and shortens the mean epidemic duration to less than 60 days. The number of vaccinations given per infected person in scenarios 3, 4, and 5 was relatively low, averaging about 325 vaccinations per epidemic response. While reactive mass vaccination was effective in reducing the number of infections, the number of vaccinations per infected person was substantially greater under these scenarios (scenarios 6–9). School closure for ten days without mass vaccination (compare scenario 10 with scenario

4) appeared to provide little additional protection. The single uniform town tended to generate a higher mean total number of infected persons than did the more structured ring or hub-and-spoke town architectures, but this difference was not consistent across all scenarios.

Evaluation of Response Scenarios in 50,000-person Towns

Response scenarios 3–10 were examined for 50,000-person towns with the single uniform and the ring

Table 1
Summary of Results of Epidemic Simulation Runs Showing the Effects of “No Response” Scenarios 1 and 2 and Response Scenarios 3–10 on Epidemics Initiated by the Introduction of Ten Smallpox Cases into 6,000-person Towns

Scenario	Single Uniform Town				Four Hub-and-spoke Towns				Ring of Six Towns			
	Cases	Deaths	New Vaccinations	Duration (days)	Cases	Deaths	New Vaccinations	Duration (days)	Cases	Deaths	New Vaccinations	Duration (days)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
No response												
1	5,231.6 (46.5)	1,650.4 (34.7)	NA (NA)	649.7 (124.4)	5,226.9 (58.3)	1,638.9 (40.0)	NA (NA)	643.1 (146.1)	5,240.2 (47.5)	1,638.7 (30.6)	NA (NA)	629.1 (115.0)
2	2,981.3 (623.2)	935.0 (198.3)	NA (NA)	394.9 (82.2)	2,521.2 (583.0)	788.1 (181.5)	NA (NA)	470.9 (125.5)	2,167.9 (996.3)	676.4 (313.0)	NA (NA)	416.2 (125.3)
Response												
3	47.2 (16.5)	11.3 (5.1)	355.7 (88.2)	76.9 (17.7)	35.5 (14.4)	9.5 (4.9)	295.0 (78.4)	69.2 (15.1)	43.6 (14.8)	11.4 (4.9)	332.9 (68.6)	75.6 (16.5)
4	45.9 (21.9)	11.4 (5.8)	351.6 (99.2)	73.0 (16.0)	39.9 (16.6)	9.3 (4.2)	309.7 (69.5)	70.5 (16.5)	34.8 (12.4)	8.9 (4.2)	306.8 (64.6)	68.5 (16.1)
5	35.9 (12.7)	9.8 (4.2)	316.2 (62.0)	66.9 (12.6)	41.2 (11.8)	11.0 (3.7)	324.6 (60.2)	71.4 (13.2)	38.5 (17.7)	10.3 (5.0)	314.9 (75.9)	65.6 (10.4)
6	32.2 (13.6)	8.4 (4.5)	2,373.1 (46.1)	59.7 (12.7)	28.9 (10.4)	7.0 (3.1)	2,359.8 (45.3)	57.9 (11.1)	24.2 (6.7)	6.8 (3.0)	2,357.9 (44.5)	54.8 (10.6)
7	25.1 (8.6)	7.0 (3.5)	2,364.6 (49.7)	58.3 (13.8)	29.4 (8.9)	7.5 (2.6)	2,373.9 (42.4)	60.0 (9.9)	28.2 (10.7)	7.8 (3.4)	2,363.0 (51.9)	58.3 (15.9)
8	22.2 (10.1)	5.8 (2.9)	4,502.7 (28.9)	46.9 (6.4)	19.8 (7.2)	4.7 (2.6)	4,492.5 (31.3)	46.7 (10.2)	17.5 (4.0)	4.9 (1.9)	4,505.0 (29.5)	43.3 (7.4)
9	17.3 (4.7)	4.3 (2.0)	4,505.7 (38.4)	45.2 (8.0)	19.9 (5.6)	5.9 (2.1)	4,501.8 (38.0)	46.7 (8.1)	18.6 (5.8)	5.1 (2.6)	4,504.1 (29.8)	45.2 (5.8)
10	44.2 (21.1)	11.2 (5.5)	334.9 (94.0)	70.2 (18.3)	42.5 (17.9)	10.9 (5.3)	323.5 (82.4)	75.5 (19.5)	32.5 (10.2)	8.2 (3.9)	282.9 (46.5)	66.1 (10.0)

Data from single uniform town, ring town, and hub-and-spoke town architectures are shown. For each scenario, the number of infected persons, number of deaths, number of vaccinations administered, and duration of the epidemic are shown. Totals include index generation (G₀) cases along with subsequent cases.

Table 2

Summary of Results of Epidemic Simulation Runs Showing the Effects of “No Response” Scenarios 1 and 2 and Response Scenarios 3–10 on Epidemics Initiated by the Introduction of 500 Smallpox Cases into 50,000-person Towns

Scenario	Single Uniform Town				Ring of Six Towns			
	Cases	Deaths	New Vaccinations	Duration (days)	Cases	Deaths	New Vaccinations	Duration (days)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
No response								
1	46,474.6 (109.3)	14,641.7 (117.9)	NA (NA)	1,280.8 (159.6)	46,463.7 (100.0)	14,623.4 (66.2)	NA (NA)	1,204.5 (139.3)
2	26,915.2 (819.4)	8,435.3 (288.6)	NA (NA)	453.2 (30.4)	27,103.0 (784.3)	8,476.0 (220.6)	NA (NA)	531.7 (77.2)
Response								
3	1,609.5 (90.2)	415.6 (29.6)	8,780.7 (445.2)	104.3 (13.1)	1,563.6 (95.4)	406.8 (28.9)	8,325.4 (407.7)	105.1 (16.6)
4	1,635.9 (133.5)	429.9 (35.0)	8,945.1 (592.5)	109.2 (18.6)	1,500.2 (59.2)	400.5 (16.1)	8,114.5 (445.6)	107.3 (10.1)
5	1,657.3 (88.0)	429.6 (22.5)	8,988.3 (371.2)	112.5 (9.7)	1,472.6 (126.7)	392.1 (37.1)	7,993.1 (618.2)	101.9 (11.8)
6	1,146.9 (69.3)	305.1 (21.1)	22,023.1 (149.3)	87.1 (6.5)	1,101.2 (55.8)	299.4 (13.7)	21,723.2 (202.6)	81.4 (6.3)
7	1,160.2 (52.5)	310.6 (20.6)	22,041.2 (206.0)	86.8 (6.2)	1,088.2 (43.2)	295.1 (15.3)	21,784.2 (205.8)	90.5 (11.5)
8	772.5 (45.7)	216.4 (14.0)	37,516.7 (84.8)	66.0 (8.9)	775.0 (17.4)	219.9 (11.6)	37,529.3 (115.3)	65.6 (10.3)
9	780.5 (25.6)	211.7 (12.1)	37,560.0 (59.6)	63.6 (7.4)	756.8 (32.1)	214.8 (10.5)	37,569.0 (117.8)	60.3 (5.0)
10	1,634.8 (79.3)	428.2 (21.6)	8,928.2 (336.2)	116.0 (14.9)	1,512.6 (50.1)	398.3 (20.2)	8,018.1 (248.3)	104.5 (11.1)

Data from simulations on the single uniform town and ring town architectures are shown (simulations on the hub-and-spoke town architecture were not performed for the 50,000-person town).

architectures (but not the hub-and-spoke architecture); ten simulation runs were performed for each scenario for each town structure. Results of the epidemic simulations from the 50,000-person town are generally in close agreement with the results from the 6,000-person town presented previously. Specifically, under “no response” scenario 1, the epidemics run to near saturation with a large proportion of the population becoming infected. Epidemics under scenario 2 infect roughly half the population in both town sizes. The interventions in scenario 3 alone are sufficient to limit the epidemic to less than 10% of the population. Addition of 10% or 50% preemptive vaccination of hospital workers does not confer any appreciable additional protection. Mass reactive vaccination of either 40% or 80% of the population (scenarios 6–9) in the 50,000-person town model does provide some additional protection of the population, but the effect is less pronounced than in the 6,000-person town; this may reflect a higher proportion of persons initially infected in the 50,000-person town model (500, or 1% vs. 10, or 0.16%). School closure had no additional appreciable epidemic impact in the 50,000-person town model (scenario 10 vs. scenario 4).

Mass Vaccination

Four of the response scenarios examined in this project involved reactive mass vaccination, with population vaccine coverage of 40% (scenarios 6 and 7) or 80% (scenarios 8 and 9). Although these scenarios yielded smaller and shorter epidemics than response scenarios based

on isolation, contact tracing, and targeted vaccination alone, the largest difference attributable to mass vaccination in the 6,000-person town was a reduction from 45.9 to 17.3 cases (scenario 4 [no mass vaccination] vs. scenario 9 [80% vaccine coverage]). By graphing the total epidemic size versus the number of vaccinations in each scenario, we calculate that the marginal “vaccine cost” to prevent one additional case is 172–213 vaccinations in the 6,000-person town/ten case attack model and 33–39 vaccinations in the 50,000-person town/500 case attack model.

Unique Features of the Model

To appreciate the unique features of this intrinsically stochastic agent-based modeling approach, a detailed analysis of data output from one scenario (scenario 3) in one population size (6,000-person town) with one town architecture (ring) is presented. Thirty-five epidemic simulation runs of this particular configuration were examined.

Epidemic Size and Duration. The size of epidemics ranged from a minimum of 12 cases (in addition to the ten attack cases) to a maximum of 83 cases, and epidemic durations ranged from a minimum of one epidemic generation beyond the attack (G_0) cases to a maximum of six epidemic generations. The mean (\pm SD) simulated epidemic duration was 3.9 (\pm 1.2) epidemic generations after the initial generation (G_0) of ten attack cases. On average, the ten attack G_0 cases represented 23% of the epidemic case total. The first generation (G_1) wave of secondary

cases alone accounted for 43% of the epidemic case totals; incidence thereafter declined rapidly with deployment of intervention strategies.

Epidemic Reproductive Rates. The epidemic reproductive rate (R) for each generation of cases ($RG_{i \rightarrow i+1}$) in each epidemic simulation run was calculated as the number of cases in each generation divided by the number of cases in the preceding generation (e.g., $RG_{0 \rightarrow 1}$ = cases G_1 /cases G_0). This measure is not the same as a true R_0 because in the scenarios evaluated here, multiple cases were introduced into the population and epidemic control strategies were activated on diagnosis of the first attack (G_0) case, thus minimizing transmission by G_0 attack cases that clinically progressed more slowly and transmitted later. The mean measured for $RG_{0 \rightarrow 1}$ (across 35 simulated epidemics) was 1.88. Subsequent mean generational reproductive rates, while epidemic control interventions were deployed in the model, were measured as $RG_{1 \rightarrow 2} = G_2/G_1 = 0.46$, $RG_{2 \rightarrow 3} = 0.43$, $RG_{3 \rightarrow 4} = 0.42$, $RG_{4 \rightarrow 5} = 0.36$, and $RG_{5 \rightarrow 6} = 0.35$; none of the 35 simulated epidemics in the 6,000-person ring town scenario 3 lasted longer than six generations after the attack generation.

Clinical Disease Expression and Transmission. In accordance with the values proposed by the working group expert advisors, cases were assigned one of three different clinical disease expressions: ordinary smallpox, modified smallpox, or hemorrhagic smallpox. Among all of the smallpox cases that occurred in these 35 simulated epidemic runs, 57% were ordinary, 40% were modified, and 3% were hemorrhagic cases. However, these proportions varied according to the epidemic generation (Figure 3A). In G_0 , the proportions were 76% ordinary, 20% modified, and 5% hemorrhagic. In G_1 and subsequent generations, the proportions were 46% ordinary, 51% modified, and 3% hemorrhagic. These changes in clinical disease expression by epidemic generation reflect the effects of postexposure vaccination of contacts, which rendered a number of cases to become modified that would otherwise have been ordinary cases.⁷ We also calculated the epidemic reproductive rate for each clinical disease type for each epidemic generation. The initial disease-type epidemic reproductive rates, or $RG(\text{ordinary})_{0 \rightarrow 1}$, $RG(\text{modified})_{0 \rightarrow 1}$, and $RG(\text{hemorrhagic})_{0 \rightarrow 1}$, were respectively measured to be 1.70, 1.57, and 6.19. The overall initial epidemic reproductive rate $RG(\text{all cases})_{0 \rightarrow 1}$ value of 1.88 is a composite of these values. Subsequent epidemic generational values of R for ordinary, modified, and hemorrhagic smallpox were also calculated and are displayed in Figure 3B. After G_0 , epidemic generational values of RG for modified smallpox were consistently higher than for other types of smallpox at the same generation of the epidemic.

Sensitivity of Results to Day of Withdrawal. We examined the sensitivity of our results to a number of our model assumptions. Most notably, we found that our results were very sensitive to the assumption of the period of time that infected individuals who did not go to the hospital or withdraw to their home on the second day of fever would circulate in the community. These individuals were a small proportion of cases that were not ill

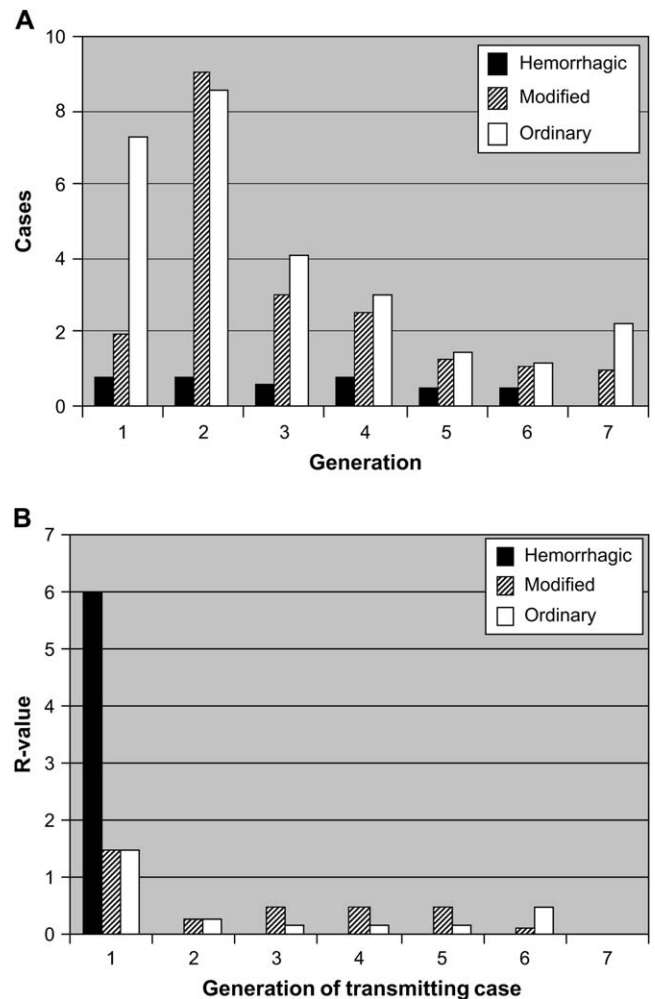


Figure 3. Number of cases of each clinical disease expression type and epidemic reproductive rate attributable to each of these clinical disease types for each epidemic generation. Values shown are averages from 35 epidemic simulations for the 6,000-person ring town under response scenario 3. Generation 0 = index (attack) cases. Ordinary (open bars), modified (striped bars), and hemorrhagic (closed bars) smallpox cases are shown. (A) Cases of each clinical disease type by epidemic generation. (B) Epidemic reproductive rate for each clinical disease type at each epidemic generation.

enough to withdraw from the community until later in their course of illness. The base model assumes that all individuals will have withdrawn from the community (to the hospital) on day 4 of fever. In our sensitivity analysis, we varied this day from the day fever begins to day 5 of fever. This model change is roughly equivalent to varying the proportion of transmission that occurs before and after symptoms begin, a factor that other investigators have suggested is very important for the controllability of an infectious disease.⁸ The number of cases that resulted in our model of 6,000 persons under scenario 2 varied dramatically as a function of this parameter from a mean of 2,981 cases in our base model assumptions to a mean of 174 cases if these individuals withdrew from the community on the day their fever began.

DISCUSSION

The objective of this modeling exercise was to evaluate the potential effectiveness of epidemic control strategies that might be deployed in response to a bioterrorist attack. Our main finding is that contact tracing and vaccination of household, workplace, and school contacts, along with effective isolation of diagnosed cases, can control epidemics of smallpox. In our 6,000-person town model, we found that in scenario 3 (the combination of interventions most closely parallel to current U.S. governmental policies) the expected total number of smallpox cases that would ensue from ten simultaneous introductions would be 25–40 additional cases.⁹ Our findings in the 50,000-person town model were consistent with these estimates; under scenario 3, 500 introductions into a population of 50,000 would give rise to approximately 1,100 new cases of smallpox. In both size versions of the model, reactive mass vaccination at the town level had additional value in bringing an epidemic under control. We estimate the number of reactive mass vaccinations required to incrementally reduce the epidemic by one case to be about 190 vaccinations in the 6,000-person town/10 attack case model versions and about 35 vaccinations in the more intense 50,000-person town/500 attack case model version.

Although a good deal of variation in the size and other characteristics of the modeled epidemics is expected in a highly stochastic epidemic model, we were nonetheless surprised by some of our observations.^{10,11} In our epidemic simulation runs, 1) epidemics ranged dramatically in size and duration based on chance alone, 2) the epidemic impact of individual index (attack) cases ranged from no transmissions whatsoever to large and lengthy transmission chains, and 3) the epidemic reproductive rate varied substantially by clinical disease type and by epidemic generation and was dependent on the underlying social network configuration. These results suggest that the heterogeneity of our microscale, agent-based model has significantly impacted the resultant epidemics.

LIMITATIONS

It is possible that some important parameters may not have been considered in the development of this model. For example, age-specific differences in the pathogenicity and transmissibility of smallpox were not considered, other than as they relate to age older than 32 years and prior vaccination status as well as social contact processes (schools for children vs. workplace for adults). We did not explicitly include risks of smallpox vaccination as a source of adverse outcome in our model. The number of vaccinations used in each modeled response is given in the Results section and can be used to estimate adverse outcomes. Another potentially important biological variable unexamined in this exercise is the effect of seasonality on transmission of smallpox.⁷ Perhaps the most important model parameters incompletely considered in this work are the social networks and contact processes that dictate disease transmission patterns. Clearly, there is a trade-off between the inclusion of a large degree of detail and heterogeneity in the social

structure in a model and the complexity of the resultant model.¹² We have included the level of social detail that we believed necessary to capture the transmission dynamics of smallpox. Although we explicitly modeled person-to-person contacts in hospitals, households, schools, and workplaces, our representations of these social units were admittedly crude. Although we addressed a range of model parameterizations and model structures, a larger sensitivity analysis may reveal surprising results. In future work, we will continue to examine the sensitivity of our results to specific model parameters.

Another limitation of this work is not the model itself but its proper interpretation and use. We caution that the numbers of cases generated in various scenarios should not be taken as quantitative predictions, but instead as a basis for comparing and evaluating different intervention strategies. We also note that in this exercise we modeled only a single geographically confined attack on a relatively small discrete social unit (6,000- or 50,000-person town). In the event of a real smallpox attack, response strategies would have to consider larger social networks and possible repeated introductions over a wide geographic area.

CONCLUSIONS

Our simulation exercise revealed that contact tracing and vaccination of household, workplace, and school contacts, along with prompt reactive vaccination of hospital workers and isolation of diagnosed cases, could contain smallpox at both epidemic scales examined. Individual-based simulations of smallpox epidemics provide a valuable tool in crafting policy regarding outbreak response.

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APPENDIX A

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