Toward a Containment Strategy for Smallpox Bioterror: An Individual-Based Computational Approach

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I. Introduction

Since the September 11, 2001 terrorist attacks and the subsequent anthrax outbreaks, bioterror concerns have focused on smallpox. Routine smallpox vaccinations in the United States ended in 1972. The level of immunity remaining from these earlier vaccinations is uncertain, but is assumed to be degraded substantially. For present modeling purposes, we assume it to be nil.

As a weapon, smallpox would be far more terrible than anthrax. Anthrax is not a communicable disease. Smallpox is highly communicable. With a case fatality rate of roughly 30 percent (meaning that 30 percent of infected individuals die) it is also very deadly. Many of those who survive the disease, furthermore, are permanently disfigured, their well-being compromised for life.

There is now a heated debate on the appropriate national strategy for smallpox bioterror[1]. The questions include: Who should be vaccinated? Everyone who volunteers? Targeted sub-populations? When should immunization begin? Immediately? Only after a confirmed attack? What is the role of quarantine?

In this monograph, we present a county-level individual-based[2] computational model of a smallpox epidemic. We review and criticize the main vaccination strategies under discussion to date (trace and mass vaccination), and based on the model, we develop a distinct "hybrid" strategy. It differs sharply from both trace and mass vaccination, while combining useful aspects of each. It involves both pre-emptive (i.e., pre-release) and reactive measures. As the basis for a national smallpox containment strategy, we believe it enjoys important advantages over the alternatives.

Models

In gauging the scale of the smallpox bioterror threat, and in designing an effective policy response, it is crucial to have *epidemic models* depicting the spatial spread of the disease in a relevant setting. Without the use of explicit models, there is no systematic way to gauge uncertainty, or to evaluate competing intervention strategies. Building on previous work [4,5,6,8,9]. we have developed an individual-based computational modeling environment for the study of epidemic dynamics in general. (See Appendix 1). It can be applied to an indefinite variety of pathogens and social structures. Here, we develop an individual-based model of smallpox at the county level. (An application to genetically modified smallpox is noted below). For an introduction to the individual-based modeling technique see [8]. For diverse applications of the methodology see [3].

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[1] In the summer of 2001, researchers at the Johns Hopkins Center for Civilian Biodefense Strategies, in collaboration with several other organizations, formulated a policy exercise known as "Dark Winter" [19]. This exercise raised many important policy questions for bioterror attack response.

[2] Individual-based modeling is also called agent- based modeling. To avoid confusion between our agents (individual people) and infectious disease agents, we will use the term individual based modeling predominantly in this paper.

Unlike compartmental epidemic models that assume perfect homogeneous mixing and mass action kinetics [1,14], the agent-based approach explicitly tracks the progression of the disease through *each individual* (thus populations become highly heterogeneous by health status during simulations), and tracks the contacts of each individual with others in the relevant social networks and geographical areas (e.g., family members, co-workers, schoolmates). All rules for individual agent movement (e.g., to and from workplace, school, and hospital) and for contacts with and transmissions to other people (e.g., family members) are explicit, as is stochasticity (e.g., in contacts). No homogeneous mixing assumptions are employed at any level. The prime social units that loom largest in the smallpox data [18], such as hospitals and families, are explicitly represented, and our vaccination (and isolation) strategy is focused on these units of social structure. Calibration of our model to this data, and statistical analysis of core model runs, is discussed below.

Our model differs from the primary (and valuable) competing approaches [11,14], in a number of ways. For example, it differs from [11] in its explicit inclusion of hospitals. Most fundamentally, as a "pure" individual-based model, it (unlike both [14] and [11]) eschews all homogenous mixing assumptions at any level[3].

II. The County Level Model.

The software we have developed permits generalization to multiple levels of social structure. For present purposes, we model a county composed of towns, hospitals, households, schools, and workplaces.

Calibration

The model structure was chosen for comparability to data describing the relationship between cases and the individuals who transmitted the disease to those cases in 49 outbreaks of smallpox in Europe from 1950 to 1971 [18]. This data set reveals the crucial role of hospital transmission and household transmission in smallpox outbreaks. We wished to build the simplest model that captured the heterogeneity of transmission in the different settings of hospitals, families, workplaces, and schools. To ensure the replicability of our results, numerical assumptions and technical details are given in Appendix 1. Selected salient assumptions are noted in the text.

Parameters of the model were chosen by selecting from a biologically plausible range, the parameters which minimized the squared error between simulation results and observations from Mack on both the number of cases resulting from each outbreak and the settings (hospital, home, workplace, etc.) in which transmission occurred [18]. More details of this procedure are included in Appendix 1.

Model Structure

[3] There are further differences, including parametric ones. For useful remarks comparing continuous and discrete individual approaches in the present connection, see [15].

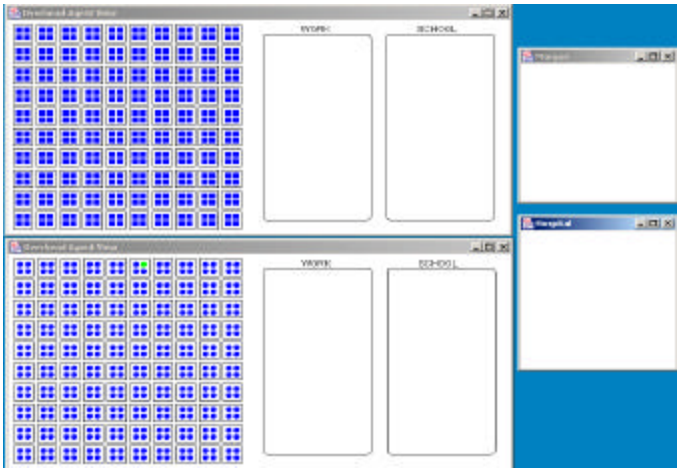
In the present version of the general model, each town is assumed to contain 100 family households, each with two working adults and two school-aged children-- 400 individuals in total. At two towns, the county population is thus 800.

Each town has one school and one workplace. All children attend their own town's school (there is no inter-town bussing). A small fraction of adults, by contrast, do commute to work in the other town. In our base runs, we assume that 10% of adults commute. There is a single county hospital used by both towns. A small number of adults from each town (in the present version, 5 adults from each) work in the common hospital. Finally, there is a single morgue housing individuals who have died.

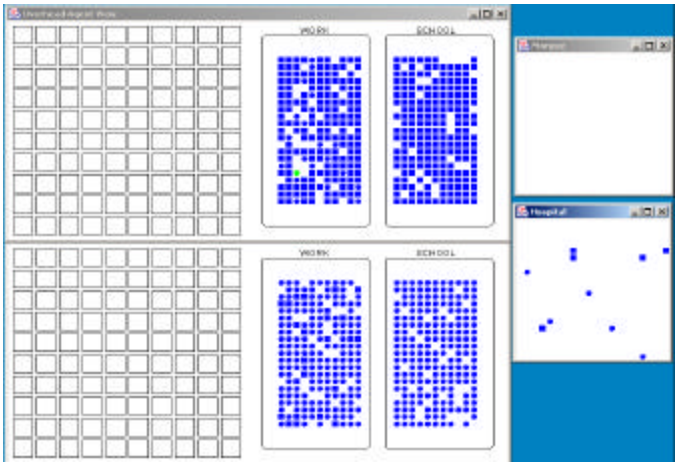
Time and Contacts

Each modeling day is equally divided between a "Daytime," when adults work and children attend school, and a "Nighttime," when family members (exclusively) interact at home. Each of these phases of the day is composed of several rounds in which each individual is processed, or "activated," once. The essential event that occurs when an individual is active is that she is contacted by other individuals. A contact is an event in which another individual is selected at random from the relevant pool (a co-worker, schoolmate, or family member) and that random individual contacts the active individual. Numerical assumptions regarding contacts and transmissions per contact are given in Appendix 1. Note that the per contact probability of contracting the infection depends on what stage of illness the contacting individual is in (see Appendix 1).

Nighttime



Daytime



Graphics

The graphical set-up is depicted in Figure 1 below, which shows two snap-shots of the county, labeled Nighttime and Daytime.

Clearly, there are two towns, Circletown and Squaretown, inhabited respectively by circle individuals and square individuals. The point of circles and squares is simply to make commuting individuals discernable, and to depict the hospital workers' hometowns. As runs progress, individuals return home at night, and go to work and school during day, a process that iterates indefinitely. That summarizes the social contact process. Meanwhile, the epidemic is running its course.

Smallpox Assumptions

Our assumptions about the course of smallpox in the individual are given in Figure 2, which also describes the color-coding used in the model graphics.

Before we release our index case (the first infective individual) into the population, we assume all individuals to be susceptible. That is, we assume no background of immunity (e.g., from previous vaccinations). Susceptible individuals are colored blue. Referring to the timeline, let us assume an individual contracts the infection at day zero. At that point, he is colored green. Although the person is, in fact, infected with smallpox, he is asymptomatic and non-contagious for twelve days. However, unless the infected individual is vaccinated within four days of exposure, the vaccine is ineffective (as shown in Figure 2). As a policy matter, this is a critical point: it will be necessary to vaccinate people *before* they manifest any symptoms. From day 12 to day 15, infected individuals are assumed to be febrile and contagious with smallpox, but do not yet exhibit the smallpox rash. They feel sick, but precise diagnosis is not yet possible.

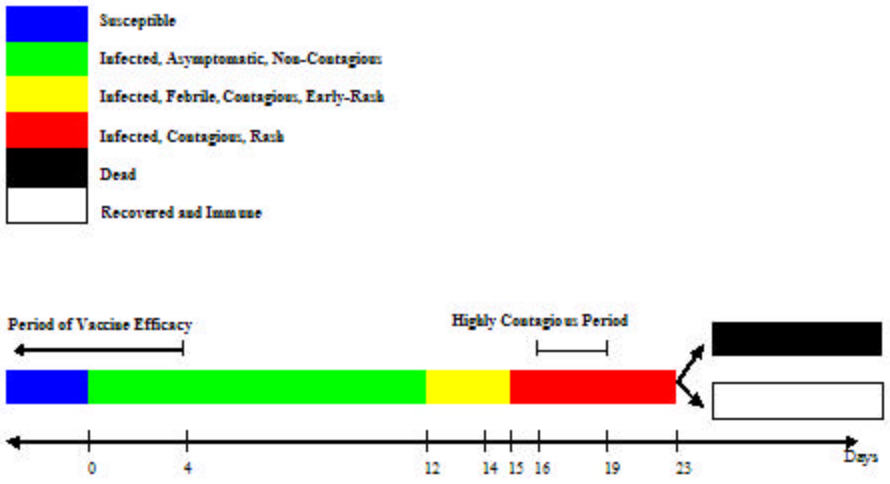


Figure 2. Progression of smallpox. See [10].

Finally, at the end of day 15, smallpox rash is evident. After twelve hours in this state, individuals are assumed to be hospitalized. After eight days (day 23 of illness), during which they have a cumulative 30% probability of mortality, surviving individuals recover and return to circulation permanently immune to further infection. Dead individuals are colored black and placed in the morgue[4]. Immune individuals are colored white. Contagiousness varies in the course of the infection. Individuals are assumed to be 10 times as infectious during days 16 through 19, than during days 12 through 15. In the final phases of the rash, infectivity returns to the day 12 value, as indicated in Figure 2. In the simulated epidemics below, individuals will be colored by their state: healthy (blue), infected (green), contagious early-rash (yellow), rash (red), and dead (black) or immune (white). At any time, the population will be heterogeneous by health status.

III. Simulated Epidemics

We present a number of runs and statistical analyses. All simulations in this paper assume a single initial infective individual (e.g., a bioterrorist or bioterror victim) who is an adult commuter[5].

We will present snapshots from our computer simulation. It is important to note, when presenting a simulated epidemic, that any such realization is but one sample path of a stochastic process. There are run to run differences due to random effects, even when all parameters are fixed across runs. Indeed, as we shall see, these random effects can be dramatic, spelling the difference between large-scale epidemics and abortive ones that never take off. Hence, a statistical treatment will be necessary, and is offered below. To begin, however, it builds intuition to "watch" the base case epidemic unfold in our county over time. Again, we imagine a smallpox bioterrorist initiating the epidemic by infecting (or by being) a commuting adult.

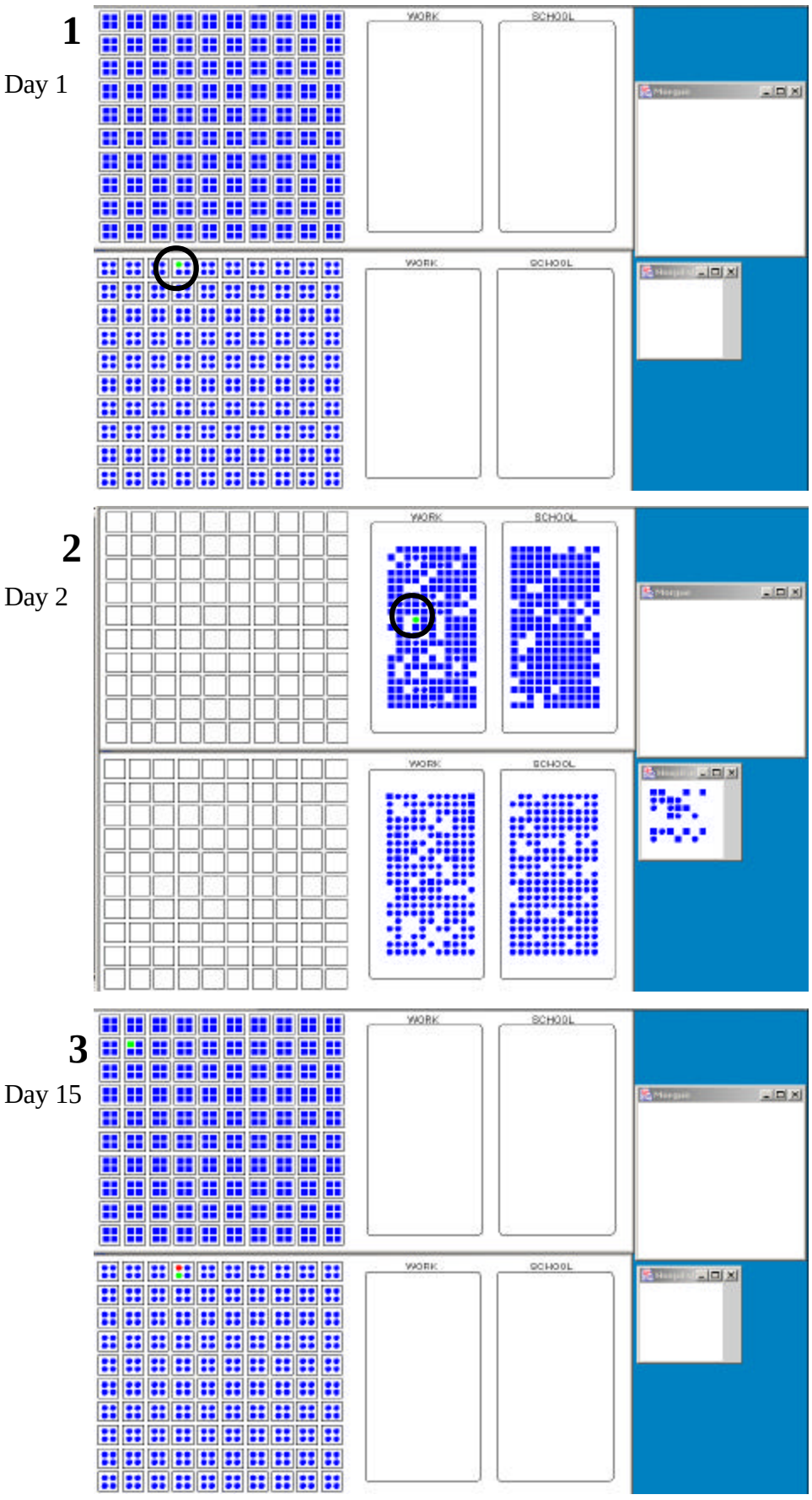
Base Case: No Intervention

The base case scenario is obtained by setting model parameters to values found by calibration to the European data set, and by assuming no preexisting immunity in the population. The epidemic is allowed to simply run its course without any vaccination or isolation strategy. We present nine frames (snapshots) from the full simulation, which can be viewed as a movie at http://www.brookings.edu/es/dynamics/models/default.htm.

[4] The morgue is a closed system so no transmission occurs there.

[5] On reflection, the assumption of a single index case is quite conservative. In a city of twelve million (e.g., Manhattan), 1 initial per 800 would translate into 15,000 initial infectives. Of course, this assumes a *linear* scale-up, which may well be unrealistic. Our point is simply that, scaled in any plausible way, 1 in 800 will translate up to an enormous attack force, in the bioterror interpretation. Although we do not believe we are not artificially simplifying the problem, our software allows for expansion by orders of magnitude, as discussed in the extensions section.

Figure 3 Base Case Run. No Interventions.



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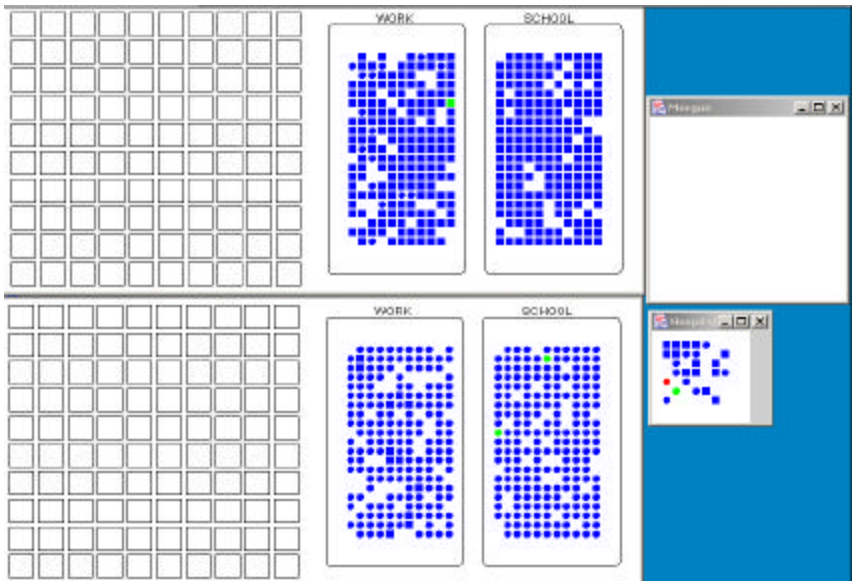
Day 16



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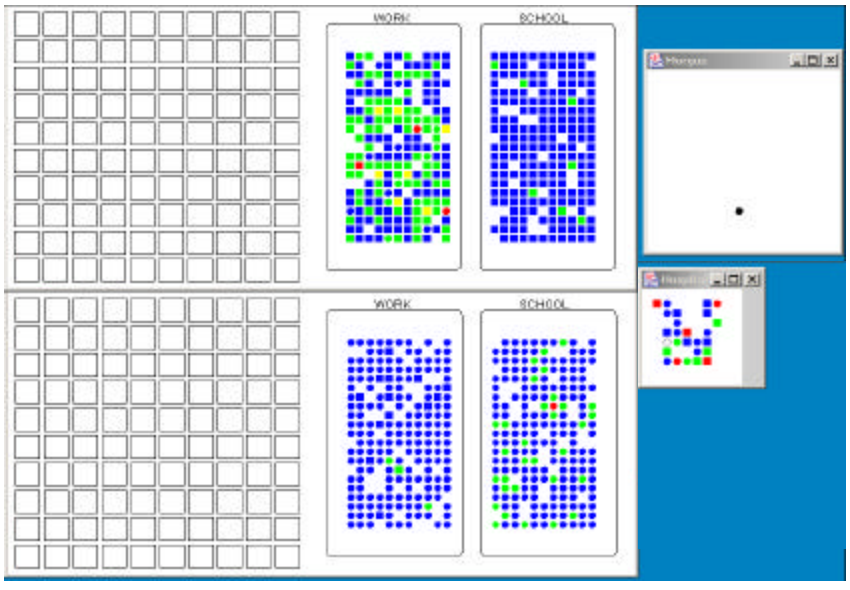
Day 24

6

Day 42



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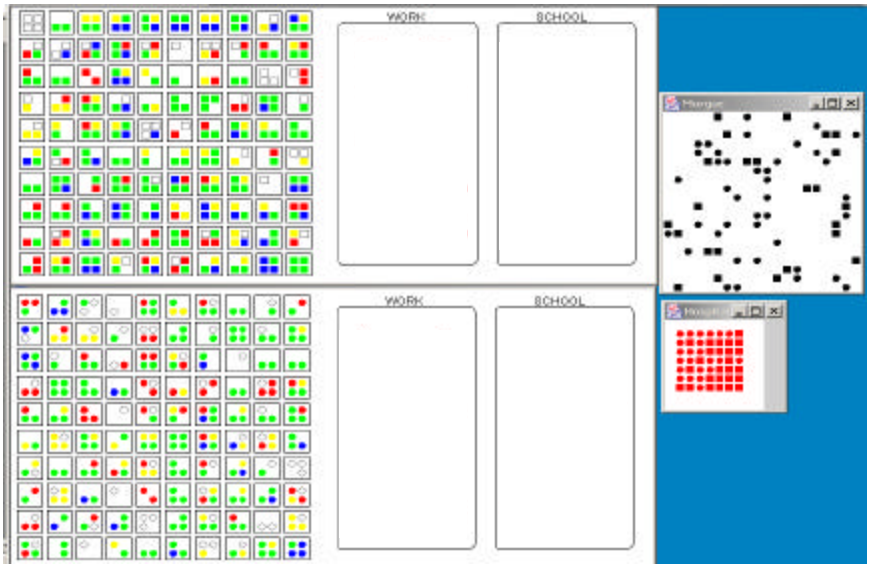
Day 52



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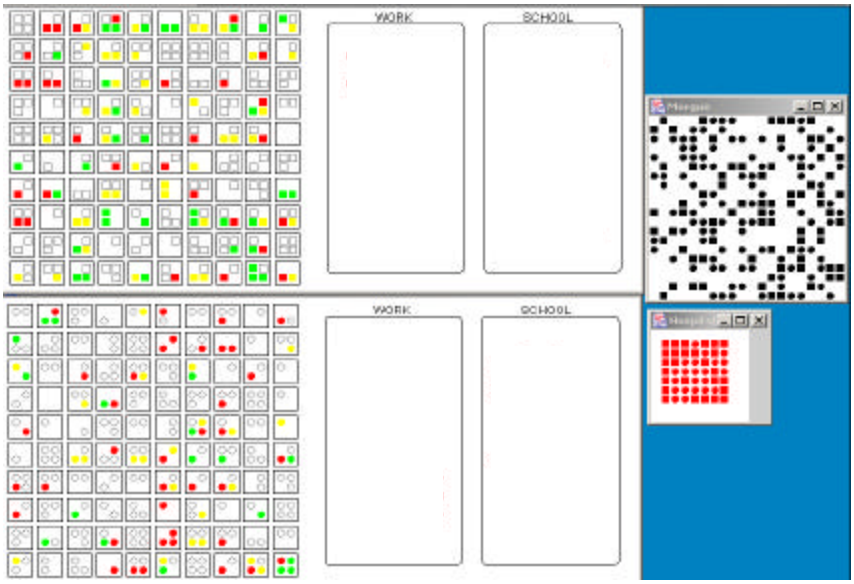
Day 62



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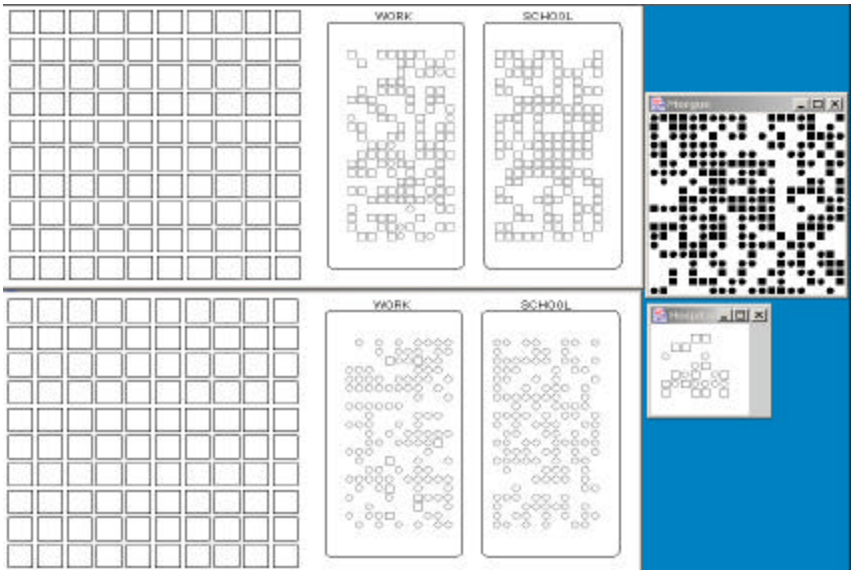
Day 82



Frame 1 simply shows our index case, an adult Circletown commuter at home at night. He is green (and circled), indicating that he is infected but asymptomatic. Frame 2 shows the index case at his Squaretown workplace the next day. Frame 3 depicts the situation on day 15, at which point our index case has developed the full smallpox rash. On day 16 (Frame 4), he reports to the hospital. In this particular run, he dies 8 days later, and is taken to the morgue on day 24, as shown in Frame 5. At this point, he has spread the disease to numerous others (green), but none of them are aware that they are ill. Frame 6 depicts the situation at day 42. Notice that, at this point, the epidemic is far worse in Squaretown than in Circletown, despite the fact that it began in Circletown. So, seemingly sensible strategies like "concentrate vaccination on the town where the outbreak begins" may do poorly. By the time one vaccinates there, the epidemic may well have spread beyond. Frame 7 (day 52) and Frame 8 (day 62) show the hospital filling to capacity and the morgue filling up. They also show that many people recover (colored white). Finally, the epidemic's end state is shown in Frame 9 (day 82). With no intervention[6], everyone in the county eventually contracts smallpox, and roughly 30 percent die of the disease. It is noteworthy that the base case assumes no background of immunity. It may represent well the dynamics when European smallpox was first introduced into virgin indigenous populations.

Typical time series of incidence (top) and number of infected individuals (bottom) are shown in Figure 4 for a representative simulation in which there is no intervention.

This, then, is the problem we wish to address. What is the appropriate policy response? We begin with a review of traditional vaccination strategies and their problems. Next we offer a hybrid vaccination strategy of our own. The substantial role of voluntarism is noted.

IV. Vaccination Strategies

The vaccination strategies that have loomed largest in the policy debate thus far are "trace vaccination" and "mass vaccination". Each strategy has advantages and disadvantages.

Trace Vaccination

Trace vaccination is an elegant idea. Given a confirmed smallpox case, we trace every contact the individual has had, and we vaccinate that group. The Centers for Disease Control has adopted priority-based trace vaccination in its Smallpox Response Plan and Guidelines [7]. Contacts are technically defined as:

"Persons who had…close proximity contact (<2 meters=6.5 feet) with a confirmed or suspected smallpox patient after the onset of the smallpox patient's fever." [7]

This approach was effectively used in the smallpox eradication effort [10]. However, there is great concern that in advanced industrial settings, one's network of contacts is huge, and will include individuals who rode the same urban metro system, or flew out of the same airport. The

[6] Here, we assume that agents continue to go to work and school, hospitalized individuals are not isolated and that no agents flee the county.

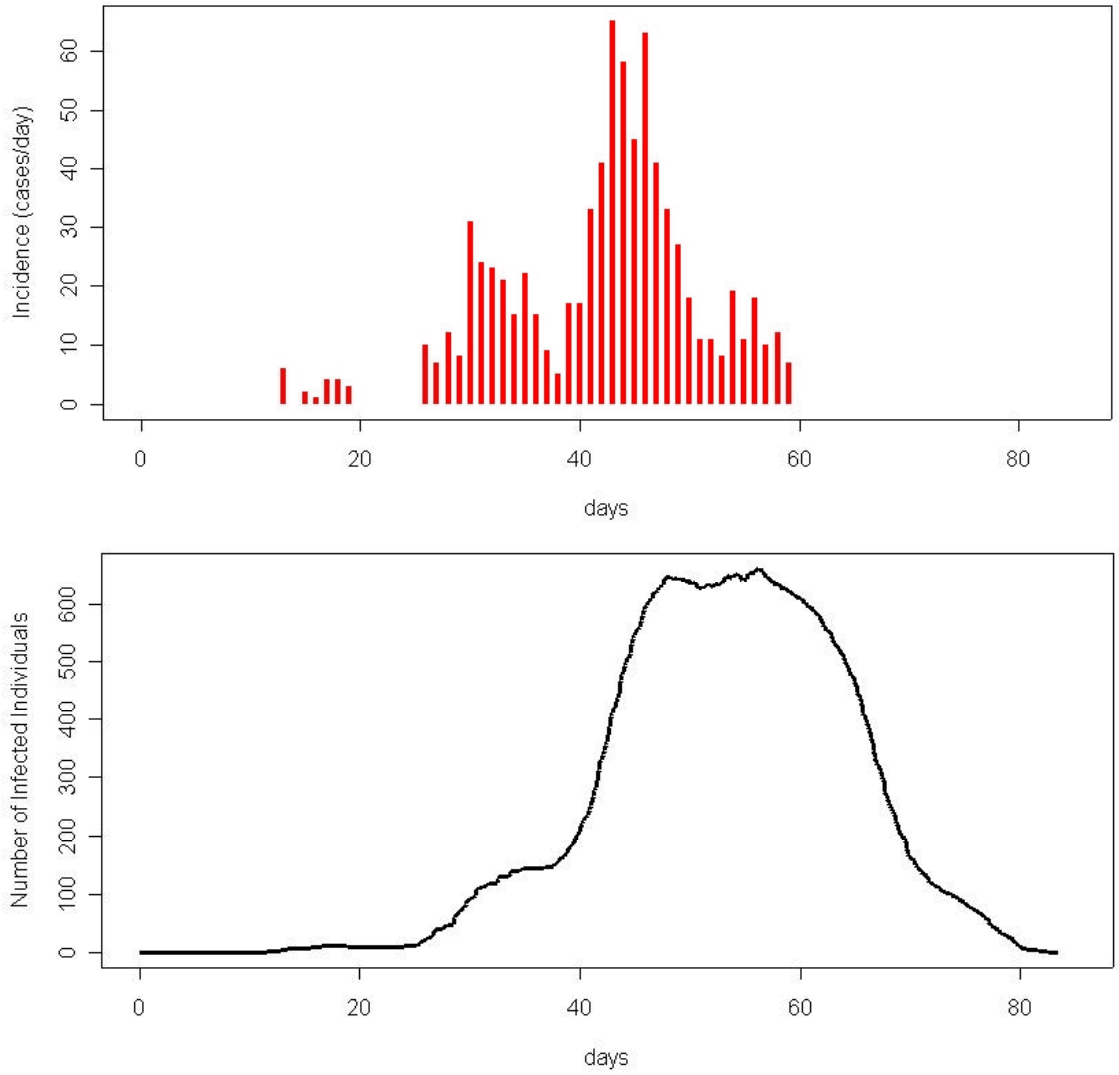


Figure 4. Typical Results for Base Case Run: Incidents per Day and Time Series of Cumulative Infected.

contacts will correspondingly be dispersed all over the city or country. The resource demands for full trace vaccination quickly become daunting. The value of incomplete, or imperfect, trace vaccination remains uncertain. Below, we present a new strategy involving such an approach.

Mass Vaccination

Indiscriminate mass vaccination poses a distinct set of problems. The first is that administration of the smallpox vaccine is not without risk. Complications from the vaccine include postvaccinal encephalitis, progressive vaccinia, eczema vaccinatum, generalized vaccinia, and accidental infection [17]. It is estimated that 40 complications would result from every 1 million doses given [17]. Of these, an estimated 1 in every 1 million persons vaccinated would die from complications [17].

Second, vaccination is not recommended for a significant proportion of the population, groups at special risk of vaccine complications. These groups include: persons with eczema, patients undergoing chemotherapy for leukemia, lymphoma or generalized malignancy, patients with HIV, persons with hereditary immune deficiencies and pregnant women [12]. Vaccination of these persons, or even inadvertent innoculation with the vaccine strain, could lead to serious disease or death.

In summary, while perfect trace vaccination is infeasible from a practical standpoint, mass vaccination carries relatively greater risks of vaccine-related morbidity and mortality.

V. Bifurcations and Epidemic Quenching

Epidemiologists have long known that introductions into populations with some background level of immunity can yield large outbreaks or outbreaks of just a handful of cases, without observing outbreaks of sizes between the very small and the very large. This bifurcation phenomenon is described in the literature by the results of stochastic compartmental models [1,2,23], using the terms stochastic extinction or fade out. We introduce the term *epidemic quenching* to denote dynamics in which the stochastic extinction occurs at the scale of discrete social units. Thus, introductions can be quenched at the level of the family, the workplace, or the town. We believe this approach accurately captures the local stochastic nature of real epidemics. The best vaccination strategies may well be strategies that take advantage of the importance of social structure to real epidemics.

VI. The Policy Challenge

The challenge for government is therefore as follows: *Design a policy that is more feasible than trace vaccination, less risky than mass vaccination, and is highly effective in containing a smallpox epidemic.* In designing such a policy, we will exploit the essential feature of epidemics

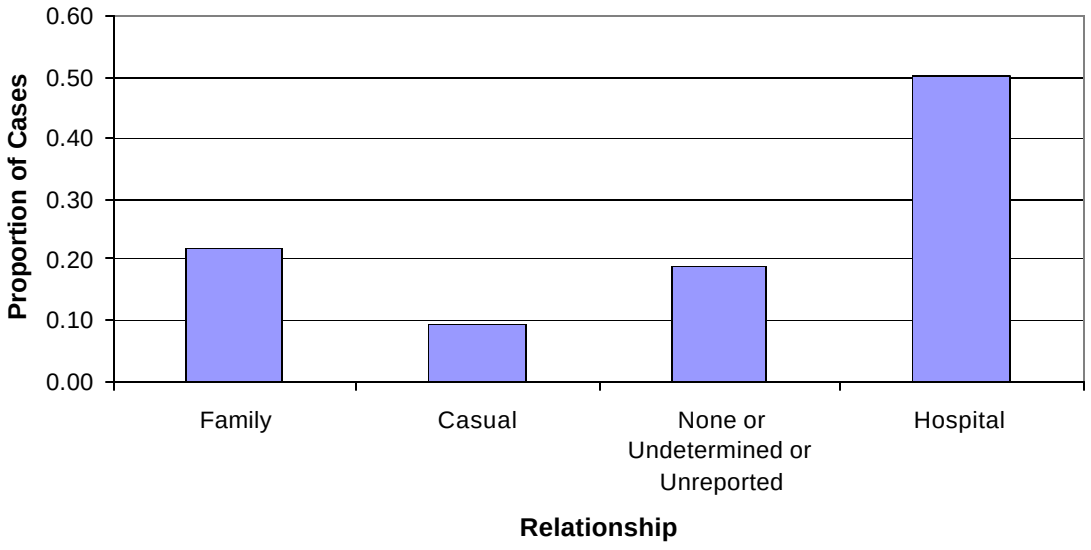


Figure 5. Smallpox Cases by Relationship to Transmitting Case for 680 Cases Occurring in Europe 1950-1971 [18].

as dynamic processes: they are nonlinear stochastic phenomena. What strategies might give the public a reasonable chance that an epidemic will be "quenched"? The actual data on European introductions of smallpox from 1950-1971 is shown in figure 5.

This data set is focused on the question, where did infected individuals contract smallpox? Importantly, 50% contracted it at the hospital; 22 % contracted it from family; 14 % contracted the disease as a result of contact at the workplace or school. The remaining transmissions resulted from either fomite transmission (2 %), unidentified contact (6 %) or were unreported and unknown (4 %). Our model was built with these units of social structure in mind, and includes hospitals, families, work, and other venues precisely to allow calibration to these data. We have succeeded in fitting the model to those data. A strength of the agent-based approach is that it facilitates a focus on heterogeneous social units with distinctive internal dynamics, as opposed to models with homogeneous compartments.

This European smallpox epidemic data clearly suggests that vaccinating hospital workers preemptively (before any attack) and vaccinating family contacts reactively (as soon as possible after) would be a powerful defense. Is it? Yes, as Figure 6 indicates.

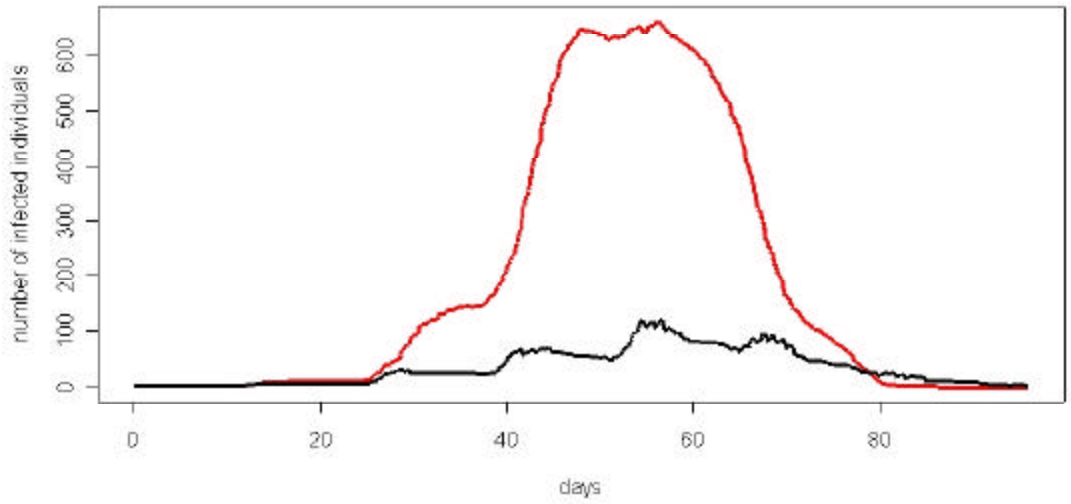


Figure 6. Results of Interventions. The black time series shows a typical run that implements our suggested intervention. The red time series is the original curve from Figure 4 which shows the no intervention case.

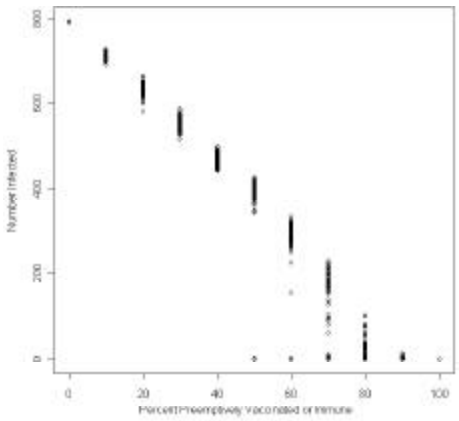
The red curve is the time series for a typical run with no interventions. The black curve is for the vaccination strategy just stated: preemptive hospital vaccination, isolation of cases in the hospital and reactive contact tracing of household members of cases. Notice that neither of these involves elaborate contact tracing. If, to these measures, we begin to add moderate levels of mass pre-emptive vaccination, a significant fraction of epidemics are quenched in our model.

Quenching Through Combined Vaccination Efforts

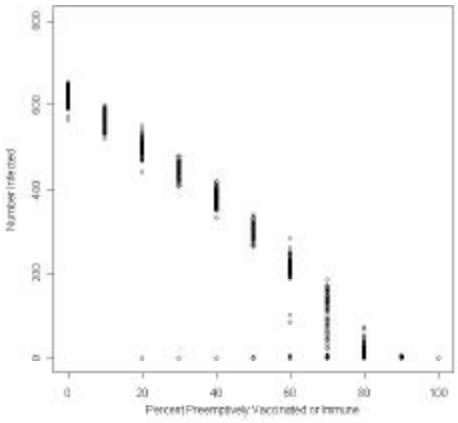
Combining vaccination efforts -- pre-emptive mass vaccination, pre-emptive vaccination of hospital workers, and reactive household trace vaccination -- has dramatic effects on both quenching (confinement of the disease to discrete social units) and the extent of the epidemic

(absolute number of cases). Since epidemics are stochastic, single runs can be misleading. Hence, we conducted a statistical analysis. We assume all hospital workers in the model to be vaccinated preemptively. Then, for 5 distinct levels of reactive family trace vaccination (0%, 25%, 50%, 75%, 100%) we study how the course of the epidemic varies as we increase the level of preemptive mass vaccination. At each level of mass vaccination the model was run 100 times with a different random seed each run. The entire analysis is shown in Figure 7. The main observation is that with increasing levels of family contact tracing, the distribution of the number infected in each epidemic shifts downward at every level of preemptive mass vaccination.

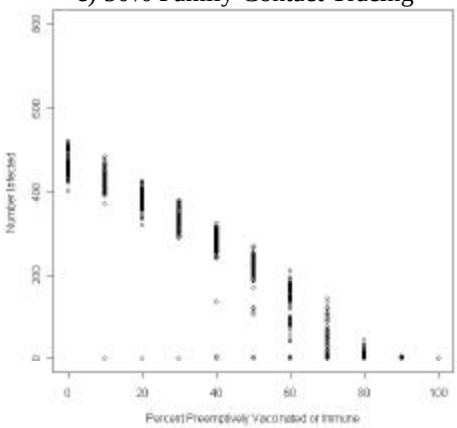
a) 0% Family Contact Tracing



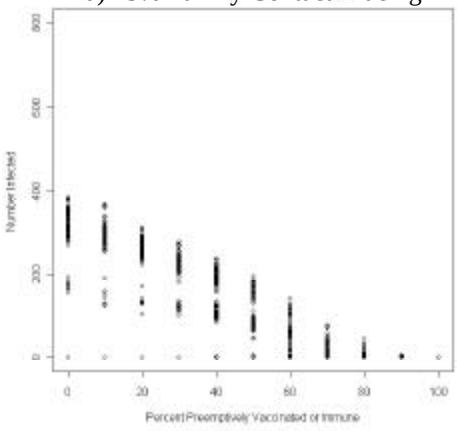
b) 25% Family Contact Tracing



c) 50% Family Contact Tracing



d) 75% Family Contact Tracing



e) 100% Family Contact Tracing

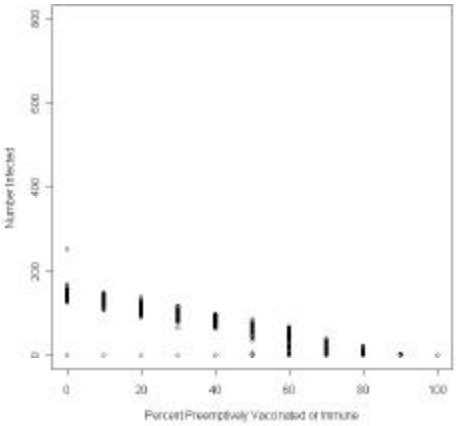


Figure 7. Number Infected versus Percent Preemptively Vaccinated for 5 Levels of Family Contact Tracing.

While the best policy results are obtained at 100% family contact tracing (Fig. 7e), the most illuminating scientific results are evident in the graph that displays 75% family contact tracing (Fig. 7d). Here we see clear bifurcations: Particularly at lower levels of preemptive mass vaccination (50% or less) the addition of reactive family contact tracing produces a trimodal distribution of epidemics.

We examine this 75% family contact tracing case in much greater detail in Figure 8. This offers a higher resolution version of graph 7d, with the frequency explicitly plotted above each point.

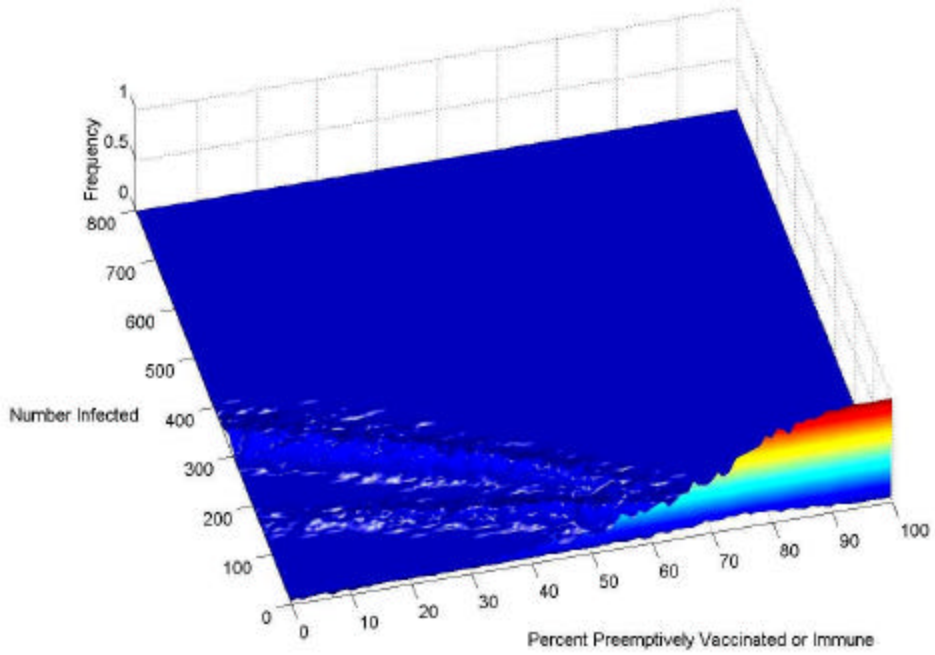


Figure 8. Probability Surface of the 75% Family Contact Tracing Case.

We believe that the bifurcations seen in figures 7 and 8 are clear evidence of "quenching" at the level of structural social units, and we are studying this phenomenon in greater depth.

VII. A Balanced Policy

As noted earlier, the best *policy* results are obtained at 100% reactive family contact tracing, shown in figure 7e. Figure 9 shows the cumulative distribution of infection for the 60% preemptive mass vaccination level in figure 7e. We cite this level of preemptive vaccination because it is obtainable at minimum risk, by re-vaccinating those individuals successfully vaccinated in the past [22]. This group is highly unlikely to suffer any of the side effects emphasized above.

The vertical axis is the frequency of simulated outbreaks (for n=100) that result in fewer than the number of infections indicted on the x-axis. So, for example, 100 percent of the simulation runs result in fewer than 70 infections (23 deaths).

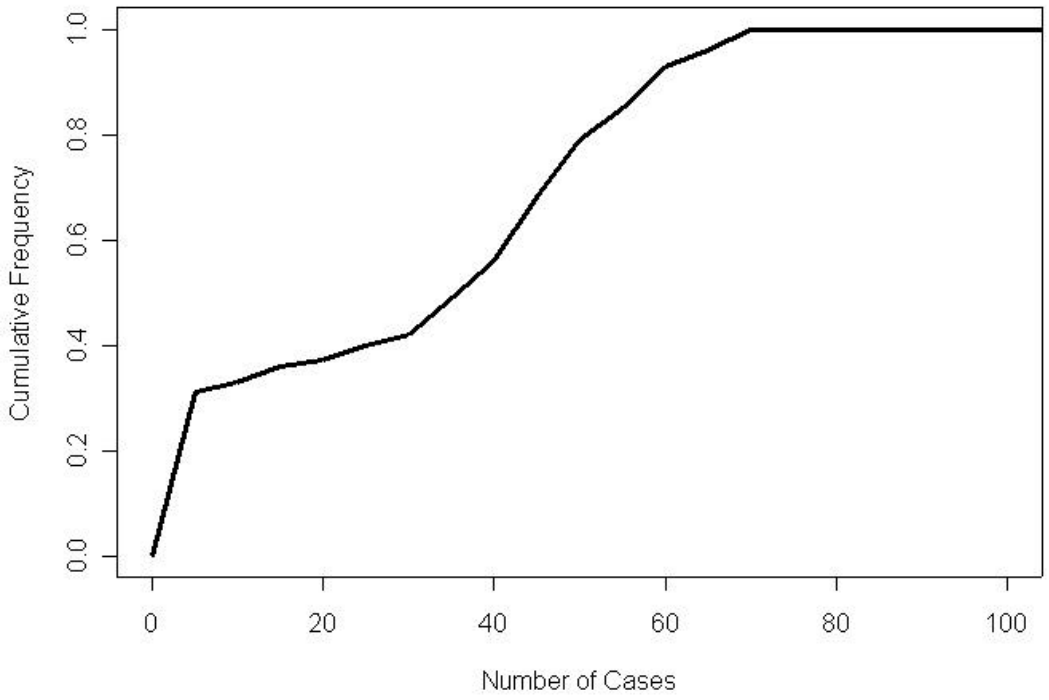


Figure 9. Cumulative Distribution of Outcomes for the Case of 100% Family Contact Tracing, 100% Preemptive Hospital Vaccination, and 60% Preemptive Mass Vaccination.

Now, what one sees reported in the media is, in a sense, the easy part of the policy problem. Of course, if there is a confirmed bioterror release of smallpox, the US government must provide vaccine. Politically, there is no alternative. Hence the US government is stockpiling 286 million doses [14]. But the deeper and politically tougher question is what to do *before* any release to contain the epidemic and ease the burden of further vaccination if necessary (and the attendant risks of indiscriminant immunizations).

In our two-town county model, the following mix of pre-emptive and reactive policy measures achieves these goals:

Pre-emptive Measures

[1] Vaccination of 100% hospital workers
[2] Voluntary revaccination of healthy vaccinees (individuals successfully vaccinated in the past)

Reactive Measures

[3] Isolation of confirmed cases in the hospital
[4] Vaccination of household members of confirmed cases

Referring to figure 9, under this package, 100% of the simulated outbreaks result in less than 70 cases (21 deaths); 75% of outbreaks yield less than 45 cases (14 deaths); and 50% of outbreaks

yield in less than 35 cases (11 deaths). This certainly qualifies as *containment*, compared to the no intervention base case in which the entire population of 800 individuals became infected and roughly 240 die in virtually all runs.

In our model, this package of measures offers the public an excellent chance that a bioterror smallpox attack will be quenched and limited in its severity and sharply reduces the logistical burden and public health risk of further vaccination if necessary. In particular, it minimizes the risks of indiscriminant mass vaccination and, unlike complete trace vaccination, is entirely feasible. Given a credible bioterrorist threat[7], this combination of measures can serve as the basis for a smallpox containment strategy.

VIII. Planned Extensions

We plan to deepen our analysis of smallpox proper, extend our study of interventions, and study a number of further topics.

Addressing Scale

Regarding smallpox proper, further sensitivity analyses will be worthwhile. First among them, perhaps, is the question of scale-up. Do fundamental results change when we expand the model from 800 individuals to populations orders of magnitude larger? Other worthwhile sensitivity analyses would vary the number of initial cases, the number of commuters, and introduce more refined distributions of transmissibility, for example.

Vaccinating Contacts of Contacts

Current modeling efforts (including ours) assess trace vaccination efforts assuming that these entail only the identification and vaccination of contacts of confirmed infected individuals. They have not assessed the effects of vaccinating contacts of contacts of confirmed infected individuals. The Centers for Disease Control Smallpox Response and Guidelines and the smallpox eradication effort both cite the importance of vaccinating contacts of contacts in containing smallpox outbreaks [7, 10]. Our modeling effort has built the capability to quantitatively assess the impact of such an approach and this will be the subject of further inquiry.

Seasonality

Smallpox epidemic dynamics are known to vary with the seasons. Spread efficiency increases in winter relative to summer. These seasonal variations could effect the appropriate mix of intervention strategies. Seasonality, then, is one promising area of further research.

[7] The credibility of this threat at this time is a topic that lies outside the bounds of this research.

Family Isolation

Beyond vaccination, there is another policy: isolation. One can imagine "trace isolation," in which the dendrite of a confirmed smallpox carrier's contacts is traced and isolated. But this is as intractable as trace vaccination. One can also imagine broad isolation strategies like closing all schools and workplaces, or banning cross-town traffic (essentially quarantine of entire towns). More discriminating than quarantine, but less demanding than trace isolation, is the following strategy:

Family Isolation: If any member of a household is diagnosed (presumably at the hospital) to have smallpox, all other household members stay home.

This is surprisingly effective on its own. Indeed, with no vaccination or other additional interventions, this strategy is roughly as effective as random vaccination of half the population, as suggested in figure 10.

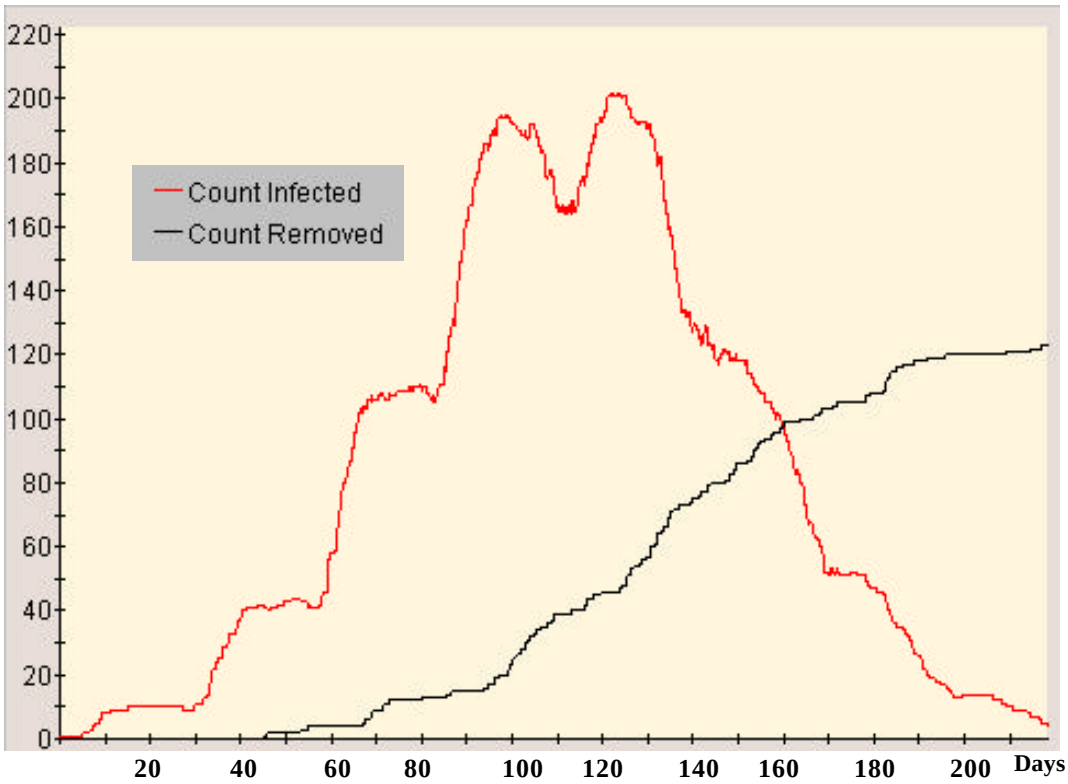


Figure 10. Typical Time Series for Household Isolation Only. 398 Infected, 119 dead.

This makes the important methodological point that epidemics involve two dynamics; the first is the course of the disease in the individual, and is biomedical. The second is the spatial contact process among individuals, and is social. Our family isolation policy operates only on the social contact process, but would be a surprisingly powerful adjunct to the vaccination strategies articulated earlier. Further voluntary measures worthy of analysis are the use of masks, gloves,

and other individual protective options. Among topics beyond smallpox, the threat of novel pathogens looms large.

IL-4 Smallpox

In the wake of the recent Australian mousepox incident [13], there has been concern that incorporation of the interleukin-4 gene into smallpox would produce a more deadly pathogen, that we have termed IL-4 Smallpox. Precisely how IL-4 Smallpox would behave in human hosts is uncertain, but it is known that "interleukin-4 mediates downregulation of antiviral cytokine expression and cytotoxic T-lymphocyte responses and exacerbates vaccinia virus infection in vivo." [20]. As a consequence, it is plausible that the pathogenicity (unvaccinated fatality rate) of IL-4 smallpox would substantially exceed that of unadulterated smallpox, that the smallpox vaccine would be considerably less effective against IL-4 smallpox than against smallpox, and that the transmissibilities of IL-4 and unmodified smallpox would be comparable. We have begun to explore how IL-4 smallpox would spread in our county-level model on plausible, albeit uncertain, numerical assumptions (e.g., that IL-4 smallpox pathogenicity=2 × smallpox; smallpox vaccine effectiveness vs. IL-4 smallpox = ½ smallpox; IL-4 smallpox transmissibility=smallpox). On these assumptions, containment of IL-4 smallpox is far more demanding than smallpox containment. Further research on IL-4 smallpox, and on the problem of novel pathogens in general, is planned.

It should be noted that the problem of engineered pathogens quickly raises a host of policy issues regarding the governance of scientific research in both academia and the private sector. This is an important topic as well (see [21]).

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X. References

1. Anderson, Roy M. and Robert M. May. *Infectious Diseases of Humans: Dynamics and Control.* New York: Oxford University Press, 1991.

2. Bailey, N.T.J. The total size of a stochastic epidemic. *Biometrika* 40:177, 1953.

3. Brian J.L. Berry, L. Douglas Kiel, Euell Elliott (Eds.) Adaptive Agents, Intelligence, and Emergent Human organization: Capturing Complexity through Agent-Based Modeling. Arthur Sackler Colloquia of the National Academy of Sciences. *Proceedings of the National Academy of Sciences*, May 14,2002. vol 99. suppl 3.

4. Donald S. Burke. "Evolvability of Emerging Viruses" in A.M. Nelson, C.R. Horsburgh, Jr (Eds.) *Pathology of Emerging Infections 2.* pp 1-12. Washington, D.C.; ASM Press. 1998.

5. John J. Grefenstette, Donald S. Burke, Kenneth A. De Jong, Connie L. Ramsey, and Annie S. Wu (1997) "An evolutionary computation model of emerging virus diseases", NCARAI Technical Report: AIC-97-030. 1997.

6. Donald S. Burke, Kenneth A. De Jong, John J. Grefenstette, Connie Loggia Ramsey, Annie Wu, Putting More Genetics into Genetic Algorithms. *Evolutionary Computation* 6(4) 387-410.

7. US Centers for Disease Control. Smallpox Response Plan and Guidelines (Version 3.0). www.bt.cdc.gov/agents/smallpox/response-plan/. Accessed 12/05/02.

8. Joshua M. Epstein, and Robert Axtell. *Growing Artificial Societies: Social Science From the Bottom Up* Cambridge, MA: M.I.T. Press, 1996.

9. Joshua M. Epstein. *Nonlinear Dynamics, Mathematical Biology, and Social Science.* Reading MA: Addison-Wesley, 1997.

10. F. Fenner et al, *Smallpox and its Eradication*. World Health Organization, Geneva, 1988.

11. M.E. Halloran, I.M. Longini, A, Nizam, Y.Yang, Containing Bioterrorist Smallpox. *Science* 15 November 2002. Vol **298** pp 1428-1432.

12. D.A. Henderson, T.V. Inglesby, J.G. Bartlett, M.S. Ascher, E. Eitzen, P.B. Jahrling, J. Hauer, M. Layton, J. McDade, M.T. Osterholm, T. O'Toole, G. Parker, T. Perl, P.K. Russell, K. Tonat. Smallpox as a biological weapon. *Journal of the American Medical Association*. **281**,2127 (1999).

13. Ronald J. Jackson et al., Expression of Mouse Interleukin-4 by a Recombinant Ectromelia Virus Suppresses Cytolytic Lymphocyte Responses and Overcomes Genetic Resistance to Mousepox. *Journal of Virology*, February 2001, pp. 1205-1210.

14. E.H. Kaplan, D.L.Craft, L.M. Wein, Emergency response to a smallpox attack: the case for mass vaccination. *Proceedings of the National Academy of Sciences*, U.S.A. **99**, 10935 (2002).

15. Jim Koopman, Controlling Smallpox. *Science* **298.** 1342-1344.

16. J.S. Koopman, S.E.Chick, C.P.Simon, C.S. Riolo, G. Jacquez, Stochastic effects on endemic infection levels of disseminating versus local contacts. *Math Biosci.* **180**, 49 (2002).

17. Lane, JM, Ruben, FL, Neff, JM, Millar, JD. Complications of smallpox vaccination, 1968: national surveillance in the United States. *New England Journal of Medicine* **281**,1201(1969).

18. T.M.Mack, Smallpox in Europe, 1950-1971. *J. Infectious Diseases* **125**,161(1972).

19. O'Toole, T, M. Mair, T.V. Inglesby. 2002. Shining light on "dark winter". *Clinical Infectious Diseases*. 34;972-83.

20. Sharma, D.P., et al. Interleukin-4 Mediates Downregulation of Antiviral Cytokine Expression and Cytotoxic T-lymphocyte Responses and Exacerbates Vaccinia Virus Infection in Vivo. *Journal of Virology*, 70 (10), 1996. Pp. 7103-7107.

21. John Steinbruner, Elisa D. Harris, Nancy Gallagher, Stacy Gunther, *Controlling Dangerous Pathogens: A Prototype Protective Oversight System.* Manuscript, University of Maryland, September 2002.

22. United States Census. Census 2000 Summary File. www.census.gov/census2000/states/us.html. Accessed 12/05/02

23. Whittle, P. The outcome of a stochastic epidemic—A note on Bailey's Paper. *Biometrika* **42**,116(1955).

Appendix 1. Technical discussion

The model was written in Java using the Ascape modeling framework (see http://www.brookings.edu/es/dynamics/models/ascape/). In Ascape, models consist of a variable sized population of agents (objects) who coexist on a landscape of variable size and shape. In the case of this model, the landscape chosen was a 2-dimensional grid resembling an overhead map. The use of an object oriented *class* to implement Ascape agents allows for a large degree of heterogeneity among agents. Each agent object contains and updates a range of information (such as the agent's infection status, her location on the grid, etc.). The agent decides on her own actions (go to work, go to the hospital, interact with another agent, etc.). Agents can be coded to have variable actions, behaviors, and data simply by creating subclasses of the basic agent type. The Ascape library of classes also provides a wide range of methods to develop inter-agent (and agent-landscape) interactions. In this case, the landscape was discretized into spaces corresponding to our model's major social units: homes, schools, workplaces, hospital, and morgue. Each agent has memory of where she lives, who her family members are, and where she works. The model also keeps track of all those agents with whom she has interacted over a variable length of time, which allows us to model interventions such as contact tracing.

When a run of the model begins, all agents are at home, and one agent (a commuter) has already been infected with smallpox. The model is started on day 10 of that initial agent's infection. The model proceeds in rounds: each round consists of one iteration through the entire agent population. The call order is randomized each round and agents are processed, or activated, serially (asynchronously). On each round, when an agent is activated, she randomly selects one of her immediate neighbors (she has up to 8 so-called Moore neighbors depending on her location on the landscape) for interaction. That interaction may, depending on a second random number draw, result in a *contact*. In turn, that contact results in a transmission of the infection from the contacted agent to the active agent with probability zero (if the contacted agent is not infectious) or a positive probability (see Table) that varies according to the contacted agent's disease progress. Both agents record the contact in their memories, regardless of whether it resulted in a transmission (since, in reality, neither would in fact know if transmission had occurred). In the event the active agent contracts the disease, she turns green and her own internal clock of disease progression begins. After 12 days, she will turn yellow and begin infecting others.

This construction of agent interactions allows for enormous flexibility in modeling. How many rounds each agent spends at work or school, how many interactions per round each agent has, how often an interaction results in a contact, how often a contact results in transmission, all are variable in our model and subject to sensitivity analysis. For the runs presented in this paper: each day consists of 20 rounds, divided equally between work and home. Thus, a child spends ten rounds at home (night) and 10 rounds at school during the day. On each round, each agent has one interaction, that is, they select only one neighboring agent with whom to interact. For this formulation, there is therefore a maximum of 10 contacts per day at work and 10 contacts per day at home. Note that the agent's neighbors are fixed at home (they are the same each day) while they are variable at work (the agent lands at the same workplace, but in a different random location at work each day). We further make the number of contacts stochastic. Fewer contacts are assumed to occur at the workplace or school than at the home or hospital. This reflects the observation that transmission usually occurs as the result of direct contact between individuals, contact which is more likely to occur at home (Fenner, 1988).The likelihood of an interaction resulting in a contact at home is 1.0 (resulting in there being 10 contacts each day per agent at home, spread uniformly over her 3 family members) and 0.3 at work (resulting in an expected 3 contacts per day at work). The model records an agent's contacts during the last three days before she turns red. To summarize, a day consists of 10 rounds at home followed by 10 rounds at work or school. On each round, each agent has precisely one interaction which may or may not result in her contracting the virus. The model tracks each individual agent's disease progression (on a daily basis) as well as all agents she has contacted in the last three days before diagnosis.

Stochasticity plays an important role in the model. Our model employs the pseudorandom number generator from the Java 2 platform. The generator uses a 48-bit seed, which is modified using a linear congruential formula. (See Donald Knuth, *The Art of Computer Programming, Volume 2*, Section 3.2.1.) By recording the random seed used in each run, we can faithfully reproduce any run generated by the model. All random events occur at the agent level. That is, the agent draws a random number from a uniform distribution, and depending on the parameter value for the event in question, the agent's state changes. The following elements of the model depend on a random draw:

- Which agent is the index case
- The order in which agents are activated
- The agent's workplace (home town, other town, hospital)

- The agent's daily location in her work place
- Whether or not an agent is traced and/or vaccinated
- Vaccine efficacy
- Whether or not a given interaction results in a contact
- Whether or not a given contact results in a transmission

There are also various aspects of epidemics that involve delays and lags. While we have not fully explored these areas in our model, we plan to introduce a stochastic delay in trace vaccination. The current version assumes a fixed delay of 2 days between the time an agent is diagnosed and when her contacts are vaccinated. In future work, this delay will be drawn from a Poisson distributed clock.

The following table summarizes the model's numerical parameters. For each parameter we have listed the range of possible (and plausible) values and the value assigned in the runs presented. Parameter values were chosen based on a coarse combinatorial search over the entire parameter space. We varied the value of each parameter over its possible range and selected the set of values that produced simulated epidemics most closely matching those found in [18]. Departures from these parameter settings are noted in the text.

Parameter	Chosen value	Possible range
Transmission Rate per Contact during Regular Transmission Period	0.05	0.0-1.0
Transmission Rate during High Transmission Period	0.5	0.0-1.0
Length of Non-Contagious Period (days)	12	0-25
Length of Early Rash Contagious Period (days)	3	0-25
Start of High Transmission Period (days)	16	12-25
End of High Transmission Period (days)	19	12-25
Pathogenicity	0.2	0.2 – 0.4 (for IL-4)
Percent Initially Vaccinated	0	0-100
Percent Hospital Workers Initially Vaccinated	0	0-100
Vaccine Efficacy	1.0	0.5-1.0
Number of Agents Initially infected	1	1-800
Number of Adults who Work in Hospital	10	0-50
Hospital Size	10x10	10x10 - 30x30
Allow Hospital Visitors (Boolean)	True	True, False
Percent Adults who Commute	10	0-100
Family Stays Home When First Family Member Infected (Boolean)	False	False, True
Family Contact Tracing Percent	100	0-100
Work Contact Tracing Percent	0	0-100
Family Contacts of Contacts Percent	0	0-100
Work Contacts of Contacts Percent	0	0-100
Number of Days of Accumulated Contacts to Trace	3	0-15
Number of Interactions per Day per Agent	10	10,80
Rounds per Day	10	1-50
Probability of a Neighbor Agent Being Chosen for Interaction from n Neighbors	1/n	1/n, 1.0
Probability of Contact per Home Interaction	1.0	0.0-100
Probability of Contact per Work/School Interaction	0.3	0.0-100
Probability of Contact per Hospital Interaction	1.0	0.0-100
Contact Tracing Maximum Delay (days)	2	0-10

Appendix 2. Smallpox Policy

Before the United States ceased smallpox vaccination in 1972, all individuals over the age of one year-old required immunization. Nevertheless, the US determined to discontinue routine vaccination because the risk of serious adverse events outweighed the rather low risk of infection due to high vaccine coverage with minimal exposure to smallpox. In addition, practices such as ring vaccination, extremely successful in the eradication efforts, further encouraged the cessation of routine smallpox vaccination.

However, bioterrorism threats have renewed interest in the creation of a substantial smallpox vaccination policy. Therefore, the Center for Disease Control have updated the response plans previously used in the 1970s. The current plan, Smallpox Response Plan and Guidelines, employs many of the methodologies to successfully control outbreaks more than 30 years ago. The main concept in the policy is control of a smallpox epidemic using ring vaccination. The policy further states that the size of the ring of individuals may be modified according to the size of the outbreak, resources, and the effectiveness of the method. Thus, health officials would isolate suspected and confirmed smallpox cases. Subsequently, they would trace and vaccinate contacts of the isolated cases, as well as vaccinate the household contacts of the contacts. Nevertheless, the CDC guidelines (available at: http://www.bt.cdc.gov/agent/smallpox/response-plan/index.asp; accessed 10 December 2002) address a policy prioritizing the following groups for immunization as presented in the response plan:

1. Face-to-face close contacts (= 6.5 feet or 2 meters) or household contacts to smallpox patients after the onset of the smallpox patient's fever.
2. Persons exposed to the initial release of the virus (if the release was discovered during the first generation of cases and vaccination may still provide benefit).
3. Household members (without contraindications to vaccination) of contacts to smallpox patients (to protect household contacts should smallpox case contacts develop disease while under fever surveillance at home).
4. Persons involved in the direct medical care, public health evaluation, or transportation of confirmed or suspected smallpox patients.
5. Laboratory personnel involved in the collection and/or processing of clinical specimens from suspected or confirmed smallpox patients.
6. Other persons who have a high likelihood of exposure to infectious materials (e.g., personnel responsible for hospital waste disposal and disinfection).
7. Personnel involved in contact tracing and vaccination, or quarantine/isolation or enforcement, or law-enforcement interviews of suspected smallpox patients.
8. Persons permitted to enter any facilities designated for the evaluation, treatment, or isolation of confirmed or suspected smallpox patients (only essential personnel should be allowed to enter such facilities).
9. Persons present in a facility or conveyance with a smallpox case if fine-particle aerosol transmission was likely during the time the case was present (e.g. hemorrhagic smallpox case and/or case with active coughing).

In addition, those personnel in direct contact with smallpox cases (i.e. direct medical care, laboratory, law enforcement involved with quarantine and interview of suspected, etc.) are high risk groups prioritized for vaccination. Moreover, additional groups with indirect contact exist and would be considered for voluntary vaccination (i.e. public health personnel involved in surveillance, resource management, fire personnel involved in fire rescue operations, etc.) by the director of the CDC. These secondary groups included for voluntary vaccination according to the response plan is as follows:

1. Public health personnel in the area involved in surveillance and epidemiological data analysis and reporting whose support of these public health activities must remain unhindered;
2. Logistics/resource/emergency management personnel whose continued support of response activities must remain unhindered;
3. Law enforcement, fire, and other personnel involved in other nondirect patient care response support activities, such as crowd control, security, law enforcement, and firefighting/rescue operations.

Of important note is that the Smallpox Response Plan and Guidelines is a draft document that the CDC acknowledges will require updates due to changes in resources. Furthermore, the immunological landscape of citizens in the United States has changed since the 1970s.