

# Modeling Responses to Anthrax and Smallpox Attacks

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If safeguards against a biological attack fail, the paramount task will be to treat those who have been infected with biological agents. We have investigated requirements for responding to anthrax and smallpox attacks. We have also studied the benefit of an early response made possible by detection methods such as biosensors. We conclude that early medical response can mitigate an anthrax attack, and that the rate of antibiotic distribution is important in reducing casualties. For a smallpox attack, we identify circumstances under which the outbreak can be controlled primarily by a strategy of contact tracing and isolation, and we identify situations that call for supplementing those measures with mass vaccination.



## The anthrax mailings of October 2001

revealed just how real the danger is of terrorist attacks using biological agents. That attack, in which envelopes containing anthrax spores were mailed to various government and media leaders, led to anthrax infections in 22 people—half of them inhalation cases and half cutaneous ones. Five died. In addition to the human cost, the attack led to the need for extensive and expensive decontamination of several postal facilities as well as the Hart Senate office buildings. The perpetrators of this attack have never been identified. But a decade earlier in Japan, a terrorist organization tried to use anthrax as a weapon: at least eight times during the early 1990s, the Japanese cult Aum Shinrikyo released anthrax from a mid-rise building in Tokyo or botulinum toxin from moving vehicles [1]. Police and media in Tokyo reported foul smells, stains on sidewalks and cars, and animal deaths in connection with the anthrax released [2]. Fortunately, the anthrax strain dispersed was similar to the one used for animal vaccination [3], and no one reportedly died in the incidents.

A biological-terrorist attack on an urban, civilian area could infect tens of thousands of people with potentially deadly diseases. A public health response to such an attack would be a massive undertaking. Since the treatments known for the most likely agents are best administered before the onset of symptoms, it is important to detect the attack early, using environmental sensors, and move aggressively to treat those who have been exposed. On the other hand, because a public health response is both expensive and can have negative consequences, such as panic and breeding of antibiotic-resistant pathogens, it is also imperative to avoid

acting on false alarms from environmental sensors. This article addresses requirements and architectures for responding to attacks with two potential bioterror agents: anthrax (which is not contagious) and smallpox (which is contagious).

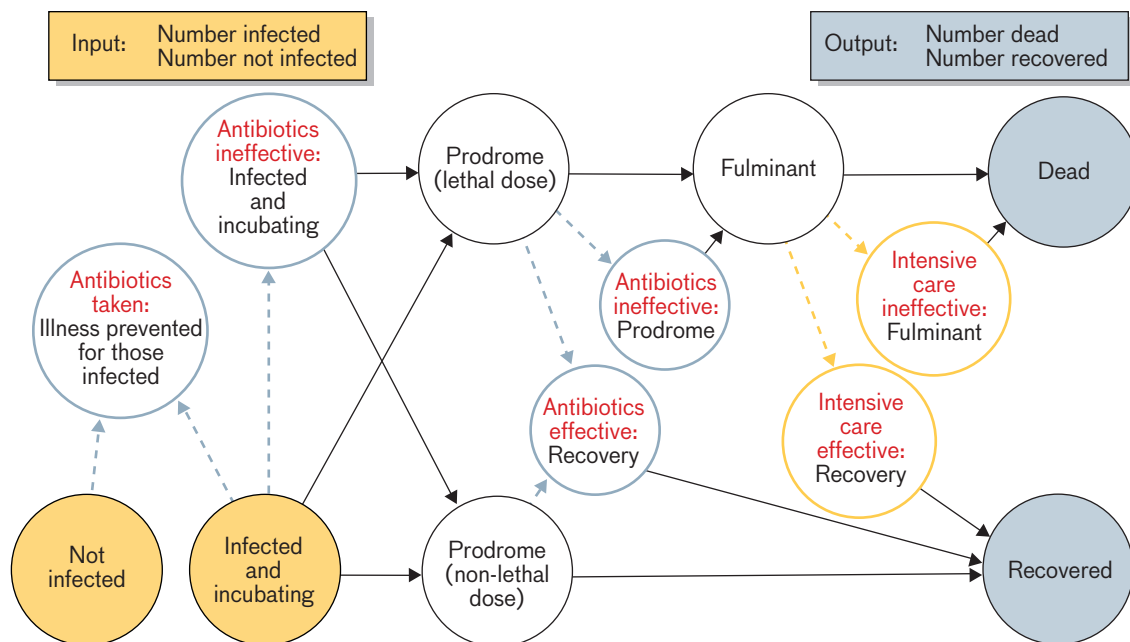
Anthrax is caused by the bacterium *Bacillus anthracis*. This organism is found in nature and can be easily cultured. Because it can form hardy spores that are environmentally persistent, anthrax can remain stable in the soil for decades. This stability makes anthrax a relatively easy agent for terrorists to acquire and prepare. The most severe symptoms result from a toxin that the bacteria secrete. To prevent this toxin from accumulating, antibiotic treatment to kill the bacteria must begin within a few days of exposure. The inhaled form of the disease is highly lethal; historical fatality rates approach 90% [4]. In the most recent large-scale exposure—an accidental release of spores from a military weapons facility in Sverdlovsk, Russia (now called Yekaterinburg)—the fatality rate may have been close to 40% of those reported to have symptoms, despite treatment [5].

Smallpox is caused by the variola virus, which was eradicated from nature by the World Health Organization global eradication campaign. The last natural case occurred in Somalia in 1977 [6]. The only sanctioned samples of the virus now in existence are kept frozen at the Centers for Disease Control (CDC) in Atlanta and at the Vector Institute in Novosibirsk, Russia. Once smallpox was wiped out, all variola samples were reportedly either voluntarily destroyed or else sent to one of the two sanctioned repositories. However, the security of the Vector samples after the collapse of the Soviet Union has been a cause for concern, as is the possibility that stocks have been kept clandestinely in other parts of the world. In addition, because the virus's genome has been published, some researchers are concerned that variola could be synthesized by using techniques of genetic engineering [7]. Smallpox is a highly lethal disease, generally killing one third to one half of those who are infected. In certain cases, death rates were far higher; historians estimate that smallpox introduced by Spanish conquistadors killed as many as three quarters of the inhabitants of the Incan empire, who had no history of exposure or resulting immunity, shortly before the arrival of Pizarro's expedition in the early 1500s [8].

Vaccination was long used to provide immunity but was discontinued in the United States in 1972 because the risk of complications, including death, outweighed the risk of contracting the disease naturally. The same vaccine that provides immunity can also be an effective treatment if administered within the first few days after exposure. A public health response to a smallpox attack would therefore include a combination of measures: vaccination of persons who were exposed (if the attack is identified soon enough), isolation of contagious persons, vaccination and quarantine of those whom the infected people have been in contact with, and mass vaccinations of the public at large. Depending on the nature of the attack, it might also be wise to close transportation networks to slow or halt the spread of the disease.

In response to the threat of bioterrorism, the U.S. government has created a strategic national stockpile (SNS) of pharmaceuticals and medical supplies. The SNS is configured in units known as push packages, which are strategically located in undisclosed warehouses throughout the United States so that they can be delivered anywhere in the country within 12 hours of the decision to deploy the assets [9]. The stockpile includes enough 60 day regimens of antibiotics to treat approximately 41.5 million people for inhalation anthrax [10] and enough doses of smallpox vaccine for every American. In addition, the CDC and Department of Health and Human Services have developed guidance documents and an education program to aid state and local health authorities on developing their plans for distributing the necessary antibiotics or vaccine.

To investigate response architectures and requirements for responding to anthrax and smallpox attacks, we have constructed an outbreak-and-response model for each disease. These models enable us to predict how the outbreaks will evolve and to quantify the effectiveness of public health responses. We model the disease progression by using a Markov chain model, in which the probability of when an individual will move to the next disease state is defined by a probability function determined by observed case data. When modeling the responses to an anthrax attack, we impose the logistical constraints of limited antibiotic distribution rates and treatment capacity; for responses to a smallpox attack, we impose limits on the rates of contact tracing and mass vaccination.



**FIGURE 1.** In the anthrax outbreak and response model shown schematically here, black arrows indicate the transition is between stages of inhalational anthrax. Blue dashed arrows represent transitions that are constrained by antibiotic distribution rate; orange dashed arrows represent transitions constrained by capacity limits in intensive care units.

### Modeling Anthrax

The initial stage of inhalation anthrax is the incubation period, during which the individual exhibits no external signs of infection. After incubation comes the onset of flu-like symptoms, including low-grade fever, cough, chills, and chest pains. These premonitory symptoms, known as the prodrome, last anywhere from one to five days [11]. The final, fulminant stage of inhalation anthrax is marked by sudden onset of high fever, sweating, and shortness of breath [12].

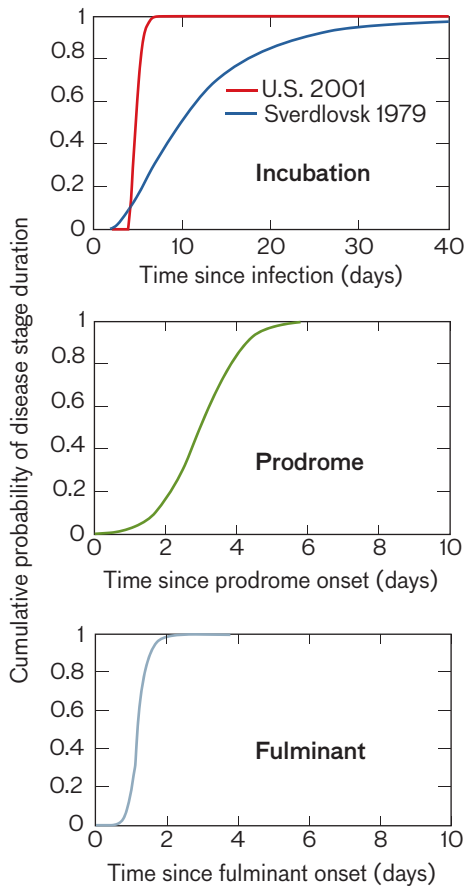
Figure 1 shows our inhalational anthrax outbreak-and-response model, highlighting the transitions between the disease stages and the transitions that simulate a public health response. An individual may take many possible paths in the model. Without treatment, a person who inhales a lethal dose of spores in the attack will travel along the path from incubation to prodrome to fulminant illness and finally death. The probability of when an individual with anthrax leaves one disease stage and moves to the next is formalized by a cumulative distribution function (CDF). These CDFs, shown in Figure 2, define the distributions of the durations of the simulated incubation, prodromal, and fulminant periods.

The primary response to an aerosol anthrax attack will be mass distribution of oral antibiotics—preferably

before people develop symptoms, as the efficacy of antibiotics decreases as time elapses. We assume that taking antibiotics early during the incubation period will prevent the onset of illness 97.5% of the time, corresponding to nearly complete compliance with taking the antibiotic regimen [13], and that antibiotics taken during the prodrome will be 60% effective at bringing about recovery [14]. Once a patient is fulminant, intensive care is required to prevent death.

Our model assumes that anyone who is not suffering from fulminant illness will be in the queue to receive the antibiotics being distributed. Infected individuals waiting for antibiotics who have inhaled a lethal dose during the attack, of course, will become fulminant if they do not receive antibiotics. We assume that infected and non-infected persons are uniformly distributed in the queue and that distribution will continue until everyone who has not succumbed to fulminant illness is given antibiotics. The presence in the queue of anyone not in danger of dying decreases the efficiency of antibiotic distribution to those who have inhaled a lethal dose and thus desperately need the medication.

Upon reaching the final fulminant stage, an individual will seek intensive care and be admitted if room is available, as indicated in Figure 1 by the dashed orange



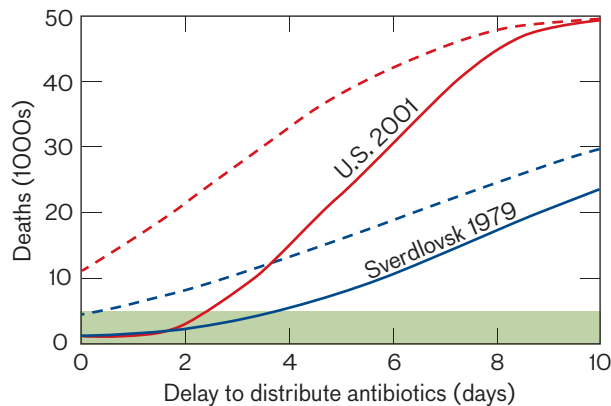
**FIGURE 2.** Cumulative distribution functions (CDFs) show how long people stay in the three stages of inhalational anthrax: incubation [16, 17], prodromal, and fulminant [11]. One incubation model is based on the incubation periods observed after the 2001 U.S. attacks and the other on those of the fatal cases after the 1979 Sverdlovsk release. These models represent uncertainty in the incubation period of inhalation anthrax, which is thought to be dose-dependent. The U.S. model is based on a narrow range of incubation periods (4 to 6 days); the Sverdlovsk model is based on a wider range of incubation periods (2 to 40 days).

arrows. We assume an intensive care capacity limit of 4100 persons, the number of ventilators currently in the SNS [15]. (There are plans to purchase an estimated 6000 additional ventilators in preparation for a pandemic influenza outbreak [18].) A shortage of ventilators does not drive the results, however, given that only 5% of those who receive intensive care at such a late stage in the disease’s progression are assumed to recover. In 2001, four individuals who were afflicted with inhalation anthrax received antibiotics only after they became fulminant; all died [19].

**Anthrax Results**

The response begins with detection that an anthrax attack has occurred. Ideally, this information will come from an environmental sensor shortly after the release; if that fails, the alert may be raised with the first medical diagnosis. If the attack is detected environmentally, there will have to be some confirmation that a large-scale attack has taken place. Confirmation could come from sampling surfaces or HVAC filters in the neighborhood of the environmental sensor that recorded the positive sample before public health authorities launch a large-scale response. Similarly, public health authorities might wait for multiple confirmed anthrax cases before swinging into action. Once the decision has been made to mount a large-scale response, supplies of antibiotics must be brought to the affected city from the SNS, distribution centers must be set up, and the antibiotics must be distributed. Each of these steps takes time: an estimated 12 to 18 hours for the attack characterization, 12 hours to deliver the push package from the SNS, and perhaps one day to set up the distribution centers. (We expect these steps to be performed sequentially; doing them concurrently could, in principle, save time.) Current plans call for antibiotics to be distributed to the affected population in three days, and even faster goal rates have been suggested.

The starkest conclusion from the model, as summarized in Figure 3, is that time is of the essence. We examined the impact on fatalities due to a delay in treatment in the event of a large-scale anthrax attack—that is, one that would kill 50,000 people if a public health response was not mounted. As the plot shows, reducing the number of potential deaths by 90% requires public health officials to start distributing antibiotics within two to three days after the attack, and to complete distribution to the entire population within three days. That corresponds to a rate of 700,000 people per day out of a total population of 2.1 million (roughly the number of inhabitants within the beltway encircling Washington, D.C.). Achieving such a reduction in deaths would be difficult even if the attack were detected by environmental sensors, giving responders a head start. But that goal would be impossible if the first report of the attack came from medical diagnosis, which would not occur until some four to six days after the attack. The curves labeled “U.S. 2001” were obtained by assuming the distribution of incubation periods similar to that observed in the inhalation anthrax cases of 2001;

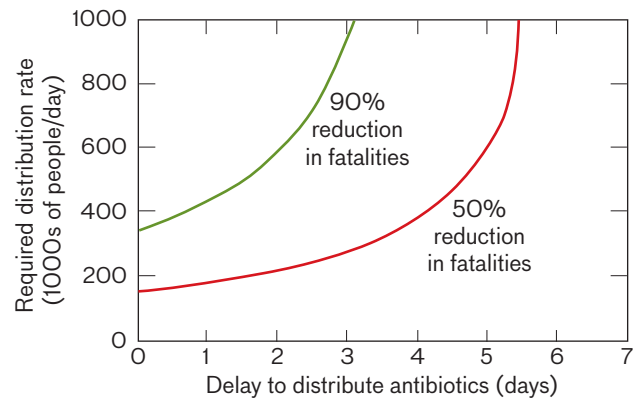


**FIGURE 3.** Delays before starting to distribute antibiotics following an anthrax attack will directly result in more deaths, according to models based on the U.S. attack in 2001 and the Sverdlovsk release in 1979. Shown here is the impact of delays if distribution is complete after three days (solid lines) and eight days (dashed lines).

those labeled “Sverdlovsk 1979” assume the distribution of incubation periods based on the fatal cases resulting from the accidental release in Sverdlovsk.

The three-day distribution plans are aggressive; many public health officials suspect distribution will take much longer to complete. The dashed curves in Figure 3 shows the effect on lethality if it takes eight days to distribute the antibiotics; clearly, the slower pace results in many deaths even if distribution begins immediately. Figure 4 shows the distribution rate required to achieve a 50% or 90% reduction in fatalities. This result enables policy makers to trade off investments that enable distribution to start sooner (prepositioning the antibiotics, for example) against those which might allow more rapid distribution (for example, training additional personnel to determine and distribute the needed antibiotic and dose).

It may prove difficult to distribute antibiotics as rapidly as desired; after all, the speed of delivery depends in part on the public’s cooperation, which can be neither completely tested nor practiced in advance. One way to improve the situation may be to focus the efforts on those most likely to have been exposed. In principle, a map of the anthrax plume could help make this improvement. In practice, however, public health officials do not want to do this. In the first place, they are properly skeptical of the ability to map plumes accurately. In addition, they have concerns that separating the unexposed from the exposed may take more time than dispensing antibiotics; also, the public health culture is opposed to turning away



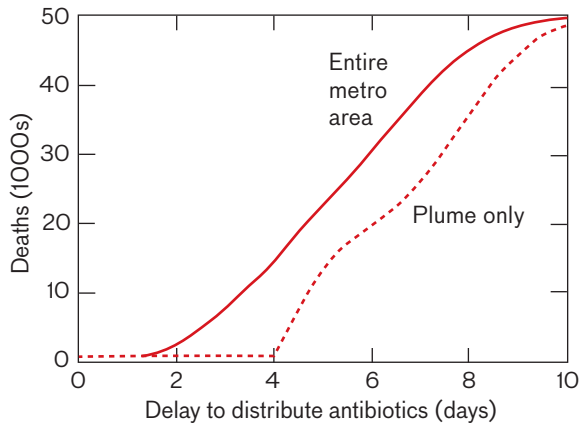
**FIGURE 4.** A delay before starting antibiotic distribution forces public health authorities to dispense medication more rapidly in order to reduce the death rate. These results here and in Figure 5 were produced by assuming the U.S. incubation period model.

individuals seeking treatment. Nor is it possible to know how well plume mapping will help focus treatment on those who need it. But the uncertainty can be bounded between treating everyone in the metropolitan area and treating only those who were exposed to potentially lethal doses (120,000 people in our model attack). Figure 5 compares these two bounds. The plot shows the high value in determining those who were exposed.

### Modeling Smallpox

Because smallpox was once endemic, more information regarding its disease progression is available than there is for inhalation anthrax. Smallpox begins with an incubation period that usually lasts about twelve days, during which the individual exhibits no symptoms. As with inhalation anthrax, the incubation period is followed by a prodrome of flu-like symptoms. This prodrome, marked by onset of a high fever, typically lasts two to four days. Then a rash develops—first as small red spots on the back of the throat and then on the skin. The skin rash evolves into fluid-filled raised bumps, which eventually flatten and form scabs [20]. Smallpox is most contagious during the first seven to ten days of rash onset [21]. Figure 6 shows the CDFs defining the distribution of simulated incubation, prodromal, and contagious periods of smallpox. These CDFs define the probability of when a person will leave a given disease stage.

Our model assumes that the U.S. population is fully susceptible to smallpox infection. Routine vaccinations

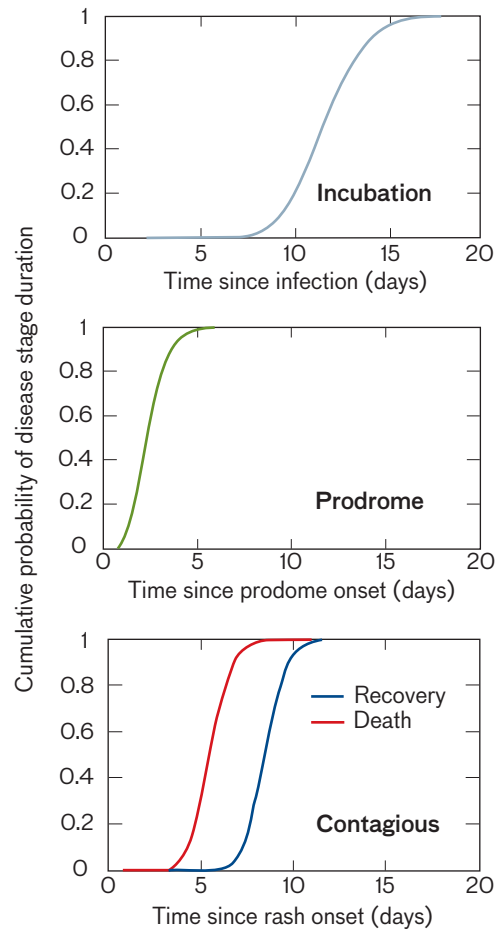


**FIGURE 5.** Fatalities are expressed as a function of delay to distribute antibiotics, assuming distribution to all 2.1 million people in a metropolitan area (solid line) and to only the 120,000 people estimated to be in the anthrax plume (dashed line) at a rate of 700,000 people per day.

ceased 35 years ago, and smallpox vaccinations received more than 20 years prior to infection have been observed to have little effect on the disease course [22]. However, even vaccination decades prior to infection does apparently lower the chances of dying from the disease. The smallpox fatality rate in Europe between 1950 and 1971 was only 11% for people who had been vaccinated more than 20 years prior to exposure; in contrast, 52% of unvaccinated individuals who contracted the disease died [23]. Using estimates of waning immunity [24] (based on the age-dependent fatality rates observed during this period in Europe) and assuming that 95% of children born before 1972 were vaccinated by their first birthday [25], we estimate an overall fatality rate of about 30% for the U.S. population in 2007 [26].

Although there is currently no antiviral treatment for smallpox, administering the smallpox vaccine within four to five days of exposure can prevent illness [27]. Given these post-exposure observations, we assume the vaccine is highly effective when administered within the first three days post-exposure (97.5% effective, the efficacy assumed for those not infected [28]). We further assume that the post-exposure efficacy begins to decrease linearly after three days, becoming completely ineffective by day seven.

Whether a disease has the potential to generate an epidemic depends on a parameter called the basic reproductive number, or  $R_0$ .  $R_0$  is defined as the expected average number of secondary infections that result from



**FIGURE 6.** CDFs for a simulated smallpox outbreak define the durations of the incubation [29], prodromal [30], and contagious periods leading either to recovery [31] or death [32]. Time to death is based on the most severe manifestation of smallpox.

a single contagious person in a fully susceptible population. If  $R_0$  is greater than one and no interventions are imposed to reduce the number of secondary cases, then the outbreak will become an epidemic. Historically, the basic reproductive number for smallpox has been between 3 and 10 [33, 34], which means that in the absence of a response it will spread quickly.

Using  $R_0$ , we define a contact rate ( $\beta$ ), which represents the number of contacts per day per person:

$$\beta = \frac{R_0}{N\phi S_\mu}$$

where  $\phi$  is the fraction of contacts that result in infection (one in five),  $S_\mu$  is the mean contagious period in days (taking fatality rate into consideration), and  $N$  is the population size in the simulation. Because  $\beta$  is constant, the

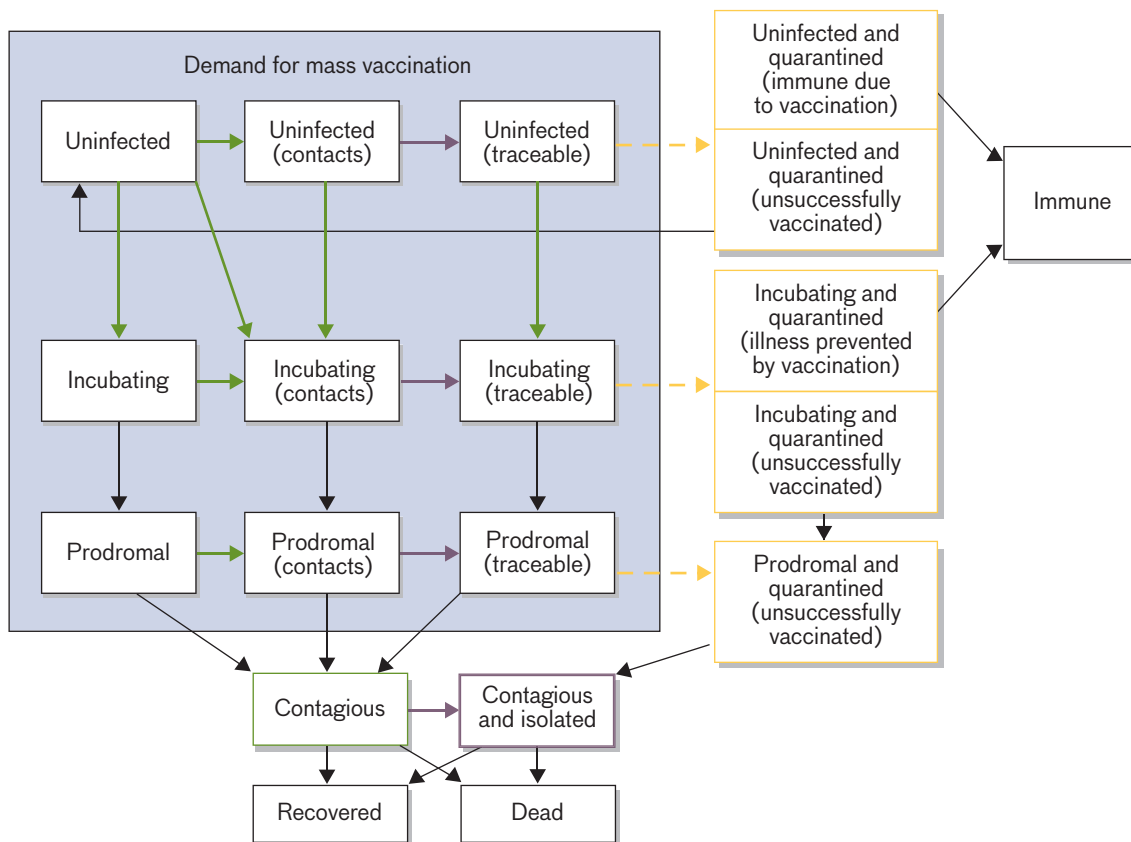
likelihood of smallpox transmission during the contagious period is modeled as being uniform—an approximation to observed data [35]. Although public awareness of an outbreak may reduce the level of social interaction among the population, the amount of decrease pertinent to disease transmission is uncertain; therefore, we model the transmission as fixed. The model assumes homogenous mixing—that is, everyone is equally likely to become infected by a contagious individual. Thus the number of contacts during the time interval  $\Delta t$  is  $\beta UC\Delta t$ , where  $U$  is the number of susceptible people (not yet infected) and  $C$  is the number of contagious people.

One strategy for responding to a smallpox outbreak is contact tracing, which entails interviewing smallpox cases to create a list of people they have had contact with who might be infected and then rapidly getting in touch with as many of them as possible. The goal: vaccinate these contacts early during the incubation period,

when vaccination is most likely to prevent smallpox. The model assumes that those infected are uniformly distributed throughout the list of contacts. Figure 7 shows the model states and transitions related to disease progression and contact tracing, if we assume tracing leads to quarantine and vaccination. We verified the model by comparing its predictions to an actual historical outbreak (see the sidebar “Real-World Validation of Smallpox Model” on page 125).

### Smallpox Response Options

A smallpox outbreak would call for some combination of three types of response: contact tracing, isolation of contagious cases, and mass vaccination. The current plan, based on CDC guidelines, is to use contact tracing along with isolation [36]. Mass vaccination would be a last resort, used only if one of the following conditions hold: the number of cases or locations is too large for effective



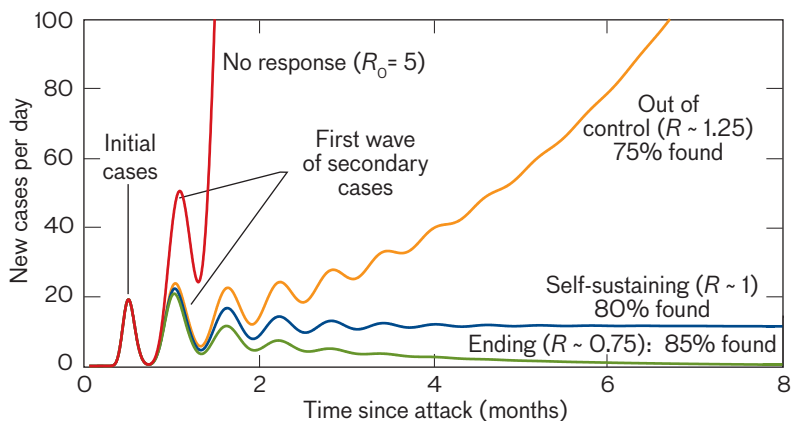
**FIGURE 7.** This schematic of the smallpox model shows the states and transitions related to disease progression and outbreak response, assuming that contact tracing leads to quarantine and vaccination. The black, green, and purple arrows indicate transitions due to disease progression, homogenous mixing, and isolation of contagious cases, respectively. The orange dashed arrows indicate contact tracing that is constrained by a tracing rate. Those states in the blue box represent demand for mass vaccination, if a mass vaccination campaign is occurring.

contact tracing; there is no decline in the number of new cases after two generations; or there is no decline after 30% of the vaccine has been used [37].

Several recent analyses about how to handle a potential smallpox outbreak have fueled the debate about appropriate responses; see Reference 38 for a review. Attempting to identify a single optimal control strategy, however, is not realistic [39]. What policy makers need is an indication of when a given response is most appropriate, taking into consideration a number of constraints and considerations such as the achievable rates of contact tracing and mass vaccination, the potential for adverse medical reactions to vaccination, and, of course, cost. The questions at hand include the following: What is the impact of limited rates of contact tracing and of mass vaccination? Under what circumstances should contact tracing be supplemented with mass vaccination? What is the effect of a mass vaccination campaign that is limited in coverage because of contraindications against vaccination? How much can contact tracing mitigate a partial-coverage mass vaccination campaign?

The contact tracing strategy evolved out of the global eradication campaign, which initially focused on mass vaccination of 80% of the world population [40]. As the eradication campaign intensified, however, the surveillance and containment strategy of case detection, isolation, and contact tracing was adopted and proved to effectively control the subsequent natural outbreaks. However, this approach may not be effective for a bioterror attack. In the latter case, there may not be sufficient public health resources to interview all the cases and then trace, vaccinate, and monitor their contacts for signs of smallpox so that they can be quickly isolated if vaccination does not prevent illness. Rapid case detection and isolation will of course decrease the number of contacts that must be traced.

As a backup to the contact tracing strategy, CDC guidelines call for mass vaccination. A major difference between contact tracing and mass vaccination is that contact tracing necessarily evolves as the outbreak evolves, while mass vaccination can be implemented even before the first case is identified. The goal of mass vaccination is to rapidly confer immunity to the general population and



**FIGURE 8.** Plot of the number of new cases per day following an attack shows the impact of contact tracing on the spread of the disease. ( $R$  is the average number of new infections per case after the response is initiated.)

thereby rapidly end an outbreak and potentially limit its geographic spread. However, there are immense logistical challenges to administering vaccine to a metropolitan population of a million or more people. In addition, an estimated 15% of the population may be excluded from such a campaign because of medical conditions that would make voluntarily vaccination unwise [41] and thus make it highly unlikely that such a campaign will result in complete population coverage.

### Contact Tracing

The goal of contact tracing is to vaccinate contacts early during the incubation period, when vaccination has the highest likelihood of preventing smallpox. Given the mobile nature of our society, it may not be an easy task to quickly track down all potentially infected contacts. Historically, however, most instances of smallpox transmission occurred among close, sustained contacts [42, 43]—typically by inhalation of infected droplets of saliva or by direct contact with the infected person's body or bedclothes [44]. Coughing, which can facilitate disease transmission, was rarely observed [45]. Most importantly, by the time a smallpox case was most contagious—that is, after rash onset—he or she was typically bedridden [46]. The CDC defines a primary contact (to be traced) as someone who has been within two meters of the infected person for three or more hours [47].

A common measure of the efficacy of a control strategy is the average number of new infections per case after



the response is initiated—a value we denote as  $R$ . If  $R$  is less than one, then the outbreak will die out. In the context of contact tracing,  $R$  can be approximated by the number of infected contacts who are not traced before infecting other people. In terms of the basic reproductive number,  $R_0$ ,

$$R \approx (1 - f_t)R_0,$$

where  $f_t$  is the fraction of contacts traced before they infect others. Using contact tracing alone to end an outbreak requires that at least 67% to 90% of contacts must be traced, if  $R_0$  has a value between 3 and 10. Figure 8 shows the impact of identifying various percentages of contacts if  $R_0 = 5$  and if there are no limits on the tracing rate.

As mentioned, these contacts must be found quickly so that they can either be vaccinated early in the incubation period (when vaccination is most effective) or quarantined before they infect anyone. Figure 9 shows the minimum tracing rates required to end an outbreak as a function of the number of initial cases; this analysis serves to identify an approximate threshold number of initial cases for which the contact tracing strategy should be supplemented with mass vaccination. For tracing rates lower than those indicated by the solid lines, the outbreak will quickly get out of control. Let's suppose that our public health system is able to reach the maximum tracing rate achieved during the contact tracing campaign in Hong Kong following the outbreak of SARS (severe acute respiratory syndrome)—815 people traced per day [48], among a population of six million. At that pace, contact tracing would end an outbreak due to an attack infecting 200 to 500 people, depending on the observed value of the basic reproductive number  $R_0$ . This outcome requires a tracing efficiency of at least 92% for  $R_0 = 10$  and at least 85% for  $R_0 = 5$ . In addition, we may be able to handle even larger attacks if environmental sensing and attack characterization are used to identify and vaccinate those exposed to the attack, thereby reducing the number of initial cases to a number that contact tracing could handle. The potentially large number of people exposed in the bioterror release is an important difference between a biological attack and a natural outbreak; thus strategies that have proven effective in outbreaks, such as contact tracing, may not be a sufficient response to an attack.

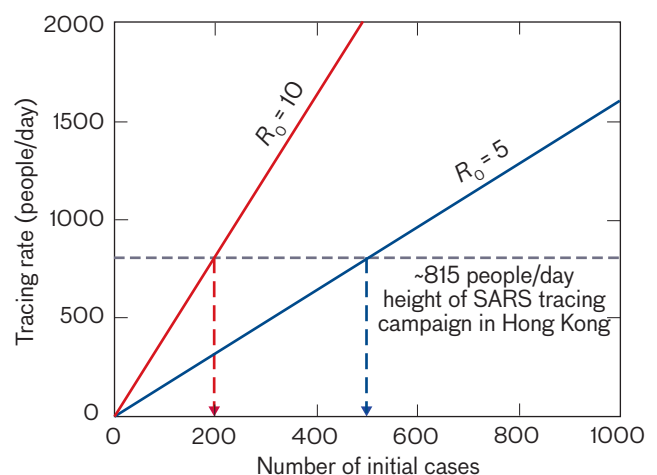
Not surprisingly, the model predicts that increasing the rate and efficiency of contact tracing will limit the

spread and duration of the outbreak. As Figure 10 shows, the number of new cases per day that would result from an attack that produced 100 initial cases would depend on the contact tracing rate. The maximum tracing rate required can be estimated by assuming that all contacts can be identified and determining the minimum rate that results in only a single wave of the initial cases becoming symptomatic and contagious. Any tracing rate above this minimum will limit illness to only these initial cases, and an epidemic will be averted.

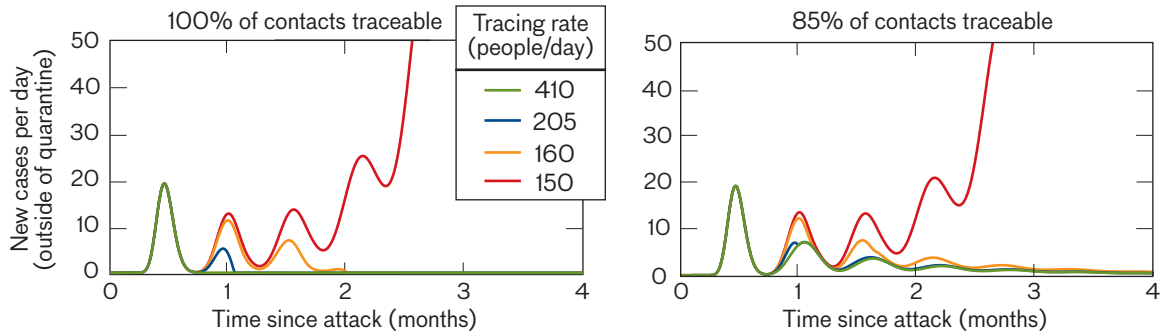
In this analysis, we assume that contagious cases are isolated seven days after onset of symptoms—a delay that might be expected at the start of an outbreak partly because of diagnostic ambiguity (during the first two to three days of the smallpox rash, it is all but impossible to distinguish smallpox from chickenpox [49]). Of course, a key to controlling any contagious disease is rapid case identification and isolation; the sooner a case is isolated the more secondary cases are prevented. Once physicians and the public become familiar with the symptoms of smallpox, it is possible that isolation may occur as early as a few days after symptom onset.

### Mass Vaccination

If the number of cases or outbreak locations is too large for effective contact tracing, then public health officials will initiate mass vaccination. Because this response is



**FIGURE 9.** The contact tracing rate required to end an outbreak depends on the number of people infected during an attack and on the basic reproductive number,  $R_0$ . These requirements are based on the assumption that for an  $R_0$  of 5 at least 85% of contacts are traceable and for an  $R_0$  of 10 at least 92% are traceable.

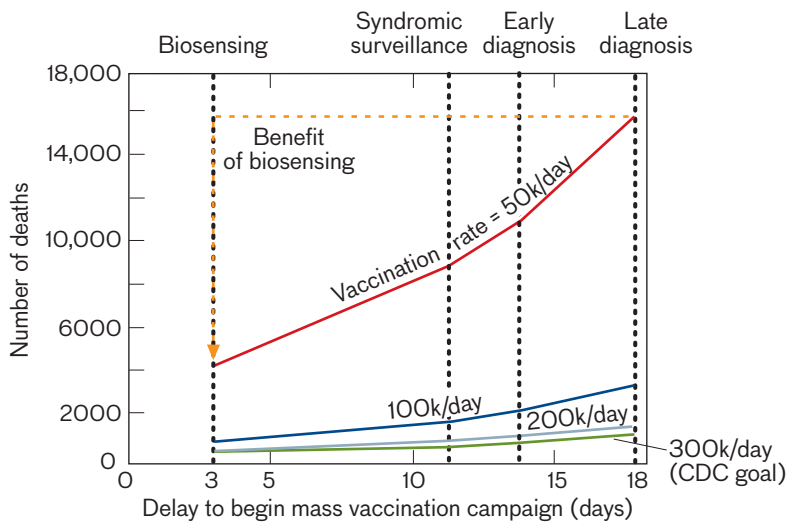


**FIGURE 10.** The higher the contact tracing rate, the more quickly a smallpox outbreak can be extinguished. These plots show the number of new cases per day as a function of tracing rate if all contacts can be found (left) and if 85% of contacts can be found (right). Both assume 100 initial cases and  $R_0 = 5$ .

not dependent on interviewing smallpox cases, mass vaccination could in theory begin after an environmental detection and before the first case ever appears. However, given the high adverse reaction rate for smallpox vaccination, including one to two deaths per million people vaccinated, such a large-scale effort should begin only after the confirmation of an attack.

The CDC goal is to vaccinate 100,000 people per day per million people in a given area, completing the campaign in 10 days. The CDC estimates that achieving this rate would require 20 vaccination clinics operating 16 hours per day with a staff of 4680 people (800 of them for security) per million people to be vaccinated [50]. One historical precedent gives some idea as to how feasible

this is. The last time a mass vaccination campaign occurred in the United States was 60 years ago in New York City, after a man with undiagnosed hemorrhagic smallpox infected 12 others [51]. Between April 4 and May 2, 1947, an estimated 6.35 million people were vaccinated [52]. The CDC goal rate that would have applied for the total city population of 7.8 million—780,000 people a day—was achieved two weeks after the campaign began [53]. We should keep in mind that this event occurred shortly after World War II, when public faith in government institutions of all kinds was high. Moreover, there was no suspicion at the time that the outbreak was an act of terrorism. News reports indicate a highly cooperative populace. Times have changed, and it is unclear if we can achieve the CDC goal vaccination rate in the event of a bioterrorism incident, given the potential for panic and civil unrest in addition to the massive logistical requirements.



**FIGURE 11.** The fatality rate from a smallpox outbreak depends on both the delay to begin a mass vaccination campaign and the rate at which vaccinations are administered. In this scenario, there are 1000 initial cases,  $R_0 = 5$ , and the entire population is vaccinated.

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Figure 11 shows an estimate of number of deaths as a function of mass vaccination rate and delay to begin the campaign in one scenario:  $R_0 = 5$ , the number of initial cases is 1000, and everyone in the population is vaccinated. While the last condition is unlikely to hold true, it provides a lower bound on the number of deaths to be expected. We modeled this outbreak in a population representative of the Boston area, assuming four different delays to begin mass vaccination. Each delay corresponds to one of the possible means of detecting an attack: biosensing (three-day delay); syndromic surveillance (12 days); and traditional medical

# Real-World Validation of Smallpox Model

Data from the Kosovo outbreak in 1972 align with predictions.

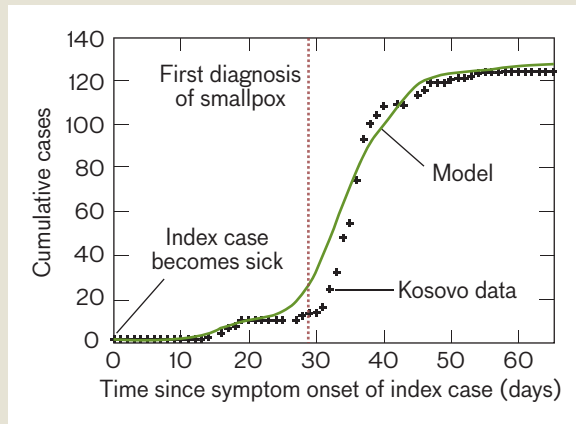
## To validate the model,

we compare its prediction of smallpox cases to the historical record from the 1972 outbreak in Yugoslavia—the last naturally occurring outbreak in Europe and the largest to occur in Europe after 1959 [a]. Three generations of cases resulted from this outbreak, a total of 176 cases and 35 deaths.

The first, or index, case infected 11 friends and relatives, who in turn infected 100 others. Just under half (48%) of these cases involved people infected in a hospital setting before the first diagnosis occurred.

One reason the outbreak was so large was that the first diagnosis of smallpox did not occur until 29 days after the index case became sick. The second generation of cases nearly went unrecognized. The diagnosis was delayed in part because physicians in Yugoslavia had not diagnosed a case of smallpox in more than 40 years [b]

diagnosis (14 to 18 days). Added to these detection delays is the estimated lag before a response can be mounted, which includes 12 hours for the CDC to ship the vaccine and one day to set up the vaccination clinics. Given that there are three million people in the Boston metropolitan area (an estimate of the population within the Interstate 495 beltway [54]), the CDC goal rate is 300,000 people vaccinated per day. As shown, vaccinating the population at this pace effectively suppresses the difference in expected fatalities due to an early response based



**FIGURE A.** Predicted number of cases compared to reported cases.

and in part because the index case apparently had a mild, atypical presentation of smallpox [c]. Two days after the first diagnosis, contact tracing and quarantines began in the province of Kosovo, the origin of the outbreak. Mass vaccination was also initiated. About 2 million people in Kosovo were vaccinated in 45 days (95% coverage), and an estimated 18 million people throughout Yugoslavia were vaccinated in about three weeks (87% coverage) [d].

on biosensing versus a later response based on medical diagnosis. If vaccinations are, for any number of reasons, administered at a slower rate, the impact on resulting deaths becomes significant.

## Combined Strategies

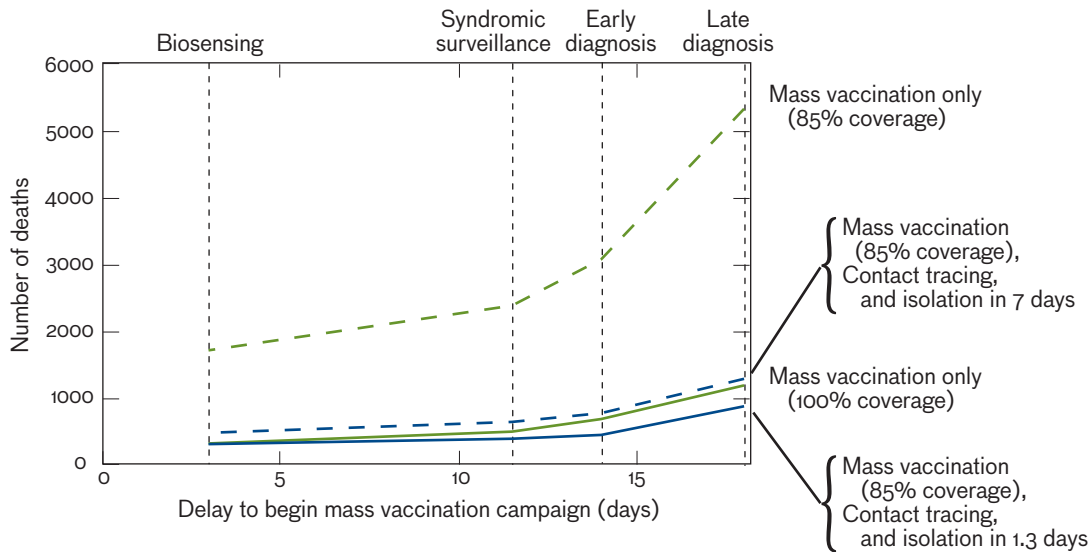
Vaccination of the entire population is extremely unlikely. For an estimated 15% of the U.S. population, the smallpox vaccine is medically ill-advised [55]. This group includes everyone who has ever had eczema or is immunocompro-

Using the reported response delays and mass vaccination rates, and assuming 97.5% of contacts were traced and a six-day delay to isolate cases, we see good agreement between the predicted and recorded cases (Figure A). If fewer contacts were traced but cases were isolated sooner, then the

model makes a similar prediction. There is a trade-off between the fraction of contacts traced and how quickly cases are isolated.

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- c. Fenner.
- d. *Ibid.*



**FIGURE 12.** The impact of delay on smallpox deaths depends on the control strategy used: mass vaccination (green curves) and combined strategies (blue curves); 1.3 days was the delay to isolate eventually achieved during the SARS outbreak [57].

mised. An additional 10% of the population might also be excluded if they live with people who fall into one of those categories. Theoretically, the required fraction of the population that must be vaccinated to eradicate a disease is  $1 - (1/R_0)$  [56]. An  $R_0$  of 5, for example, means that at least 80% of the population must be vaccinated.

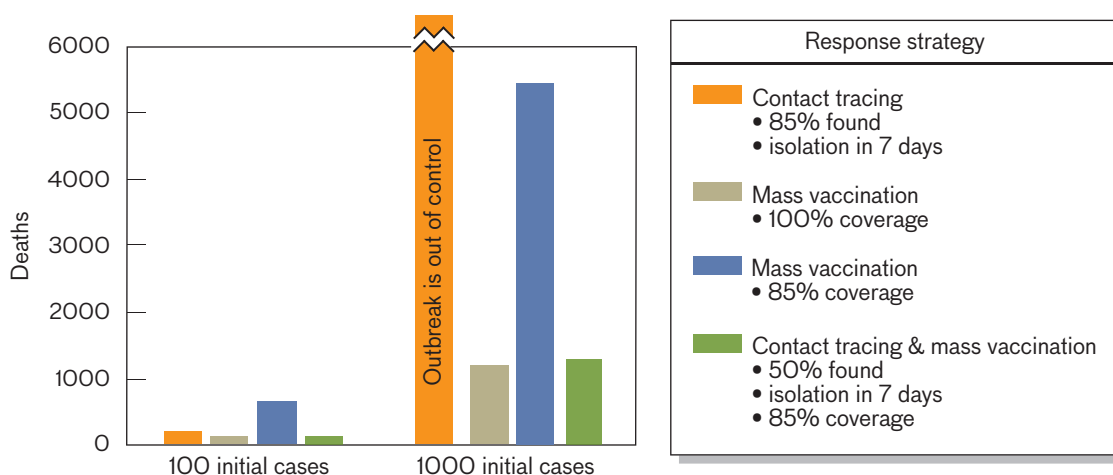
Assuming the CDC goal vaccination rate can be achieved, the dashed green curve in Figure 12 shows the approximate number of fatalities that would result if only 85% of the population is vaccinated and no other actions are taken to control the outbreak. In this case, again, there is a benefit to early detection and early response. Moreover, as one would suspect, this benefit becomes more pronounced as vaccination rates decrease from the aggressive CDC goal rate. Our model shows, however, that mass vaccination alone is not the optimal strategy. If partial population coverage is anticipated, then public health should be prepared to simultaneously mount a contact tracing campaign. Implementation of both mass vaccination and contact tracing will result in nearly the same effect as 100% mass vaccination.

What, then, is the best strategy for controlling a smallpox outbreak after a bioterror attack? As shown in Figure 13, that would depend on the scale of the attack. For an attack that results in only 100 initial cases, contact tracing in which public health officials trace 815 people per day would result in fewer deaths than a partial mass

vaccination campaign alone. Implementing a combined strategy—that is, both mass vaccination and contact tracing—would yield a modest reduction in deaths. Of course, a mass vaccination campaign may be more costly in terms of staffing and other logistical requirements, as well as caring for those who experience adverse reactions to vaccination. For an attack resulting in 1000 initial cases, however, the results would change. In this larger attack, contact tracing at a rate of 815 people per day would not control the outbreak, as we showed earlier in Figure 9. The most effective strategy would instead be to undertake both contact tracing and mass vaccination at the same time; our model shows that this combined approach would result in about 4000 fewer deaths than would a response relying on mass vaccination alone.

**A Tall Order**

By quantifying the outcome of a bioterror attack as a function of how quickly the medical response starts and how quickly it is executed, we have made a first step toward providing policy makers with a valuable tool to guide response architectures and requirements. In the case of a possible anthrax attack, the performance curves that our models produce should help evaluate the mix of investments among technologies that allow an earlier start to antibiotic distribution versus investments that allow faster distribution. Even with an early start



**FIGURE 13.** Choice of a response strategy would have a significant impact on the number of people who die; the difference is accentuated for an attack that infects 1000 people as opposed to 100. For both outbreaks, the expected number of deaths as a result of a complete coverage mass vaccination campaign is shown for reference only; we emphasize this is an unlikely outcome.

in response to a large-scale attack, required distribution rates may still be very high. We have shown that it would be advantageous to focus distribution on those exposed; there is some question, however, whether public health officials could ever have sufficient confidence in attack characterization methods to turn away people who they believe have not been exposed in order to focus resources on those most likely to be infected. Because the nature of the response to a smallpox attack can depend on the size of the attack, public health agencies must plan for a range of attack sizes.

Once the strategic national stockpile (SNS) of medical supplies has been flown in, state and municipal authorities are responsible for distributing the antibiotics. The aftermath of Hurricane Katrina highlighted how quickly state and municipal response systems can be overwhelmed and just how vulnerable the nation may be. Since 2004, the Cities Readiness Initiative program, a program coordinated by the Department of Homeland Security and the Department of Health and Human Services, has been improving the readiness of cities and large metropolitan areas to distribute the SNS assets. Although the pilot program has grown from 21 cities in 2004 to 72 cities in 2007, only 16 states and two cities have met the CDC's highest standard for preparedness [58].

In addition, in order to quickly respond to an attack yet avoid mounting an unnecessary and costly large-scale response, public health must be able to quickly determine

whether alerts from environmental sensors are the result of a wide-scale attack and whether the biological agent released was capable of infecting the public. Terrorists have released apparently harmless organisms, like the Sterne strain of anthrax, in the past. Moreover, current biological-sensor technology focuses on detection of DNA via polymerase chain reaction, a technique that identifies an organism but does not indicate whether it is capable of infecting a person. These issues may be addressed by attack characterization that would nominally involve confirmation of the attack, estimations of geographic extent of the attack, and the infectivity and antibiotic resistance of the organisms. We are investigating, with funding from the Department of Homeland Security, the requirements to characterize the incidents to the level needed for public health action.

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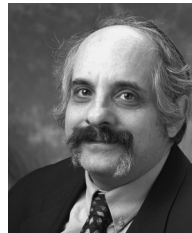
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