

Emergency response to an anthrax attack

Lawrence M. Wein^{*†}, David L. Craft[‡], and Edward H. Kaplan[§]

^{*}Graduate School of Business, Stanford University, Stanford, CA 94305-5015; [‡]Operations Research Center, Massachusetts Institute of Technology, Cambridge, MA 02139-3407; and [§]Yale School of Management, and Department of Epidemiology and Public Health, Yale School of Medicine, New Haven, CT 06520-8200

Edited by Burton H. Singer, Princeton University, Princeton, NJ, and approved January 28, 2003 (received for review November 11, 2002)

We developed a mathematical model to compare various emergency responses in the event of an airborne anthrax attack. The system consists of an atmospheric dispersion model, an age-dependent dose–response model, a disease progression model, and a set of spatially distributed two-stage queueing systems consisting of antibiotic distribution and hospital care. Our results underscore the need for the extremely aggressive and timely use of oral antibiotics by all asymptomatics in the exposure region, distributed either preattack or by nonprofessionals postattack, and the creation of surge capacity for supportive hospital care via expanded training of nonemergency care workers at the local level and the use of federal and military resources and nationwide medical volunteers. The use of prioritization (based on disease stage and/or age) at both queues, and the development and deployment of modestly rapid and sensitive biosensors, while helpful, produce only second-order improvements.

Despite the fatal delivery of *Bacillus anthracis*, the bacterium that causes anthrax, via the United States mail in 2001 (1) and the dire warnings about an airborne anthrax attack (2–4), detailed guidelines for postexposure prophylaxis in the aftermath of such an attack, specifying who receives treatment and how these people are prioritized, do not appear to be in place (ref. 5, page 2247). To investigate these issues, we formulated a mathematical model to compare several response strategies to a mass-casualty airborne anthrax attack in a large city.

The model (Fig. 1) incorporates a Gaussian plume (6), which is used to compute the number of spores inhaled by a person who is at any given location in the vicinity of an instantaneous point release of anthrax. Although the Gaussian plume model may be too simplistic to monitor and predict the spatiotemporal anthrax concentrations after an actual attack, the remaining “downstream” portion of our model can be used in conjunction with a more sophisticated atmospheric model that captures wind changes and other atmospheric complexities ignored here (7). Indeed, the atmospheric model affects the logistics only via the initial conditions, and hence the insights from our analysis are likely to be robust. Also, although the impact of a release depends on a variety of factors including the time of day of the release and the stability conditions (6), and the form (liquid or dry) of the agent and the method of dissemination (8), the cumulative level of uncertainty in these factors is dwarfed by the uncertainty in the size of the release (see Fig. 4).

An age-dependent dose–response model, together with a population density and an age distribution, generates the fraction of people at each location of each age who are infected. Absent intervention, each infected person progresses through three log-normally distributed disease stages: incubation, prodromal, and fulminant (1). Intervention begins $\tau = 48$ h after the attack. The region ≈ 200 km downwind (the first 30 km downwind is an urban area of 10.8 million people, and further downwind is a rural area occupied by 0.7 million people) and within ≈ 20 km crosswind of the source release is divided into service zones, each containing a two-stage queueing system that distributes oral antibiotics and provides hospital care within the zone. These servers are from local hospitals and neighborhood emergency health centers (hld.sbcom.army.mil/downloads/wbirp/nehc.green.book.pdf). At queue $i = \{A, H\}$ ($A =$ anti-

biotics, $H =$ hospital), there are n_i servers per km^2 and the mean service time is μ_i^{-1} . In addition, m_H mobile hospital care providers, representing federal and military personnel and nationwide medical volunteers, arrive $\tau_m = 18$ h after the attack is detected and serve overflow hospital patients. Combination antibiotics prevent a fraction e_1 of people in the incubation stage from developing symptoms and prevent a fraction e_2 of prodromals from progressing to the fulminant stage. The remaining fraction of prodromals have their prodromal clock reset (according to another log-normal distribution) when they receive antibiotics. Everyone who enters the fulminant stage eventually dies, but those completing their hospital care while still prodromal survive. A time-varying geographic ring dictates which asymptomatics (either uninfected or incubating) enter the antibiotics queue. The ring computes the fraction of people at each location who have developed disease symptoms, a quantity we refer to as observed anthrax burden, and places people at a given location into the antibiotics queue if the observed burden at this location exceeds a specified threshold p . Hence, as the attack plays out and more people exhibit symptoms, the ring enlarges and more people are placed in queue. People who develop symptoms immediately enter the antibiotics queue if their location is not already in the ring. In addition, people enter the hospital queue as soon as they have incurred symptoms and received antibiotics, which can occur in either order. We consider five priority policies (described in Table 1) that differ by how people waiting in the two queues are prioritized for service, based on observable disease (i.e., symptomatic vs. asymptomatic) and age. The mathematical model is a system of integro-partial differential equations (see *Supporting Text*, which is published as supporting information on the PNAS web site, www.pnas.org).

For the base-case values of the model parameters (Table 2), 1.49 million people of 11.5 million (13.1%) are infected in a long thin region (Fig. 2b) downwind of the point of release of 10^{15} spores (≈ 1 kg; ref. 9). At the time intervention begins, 12,700 people are prodromal and 17 are in the fulminant stage. Under the mass service policy in the base case, 123,400, or 8.3% of those infected, die. Relative to the mass service policy, the four other priority policies in Table 1 reduce the total number of deaths by 4.3%, 7.1%, 4.9%, and 7.7%, respectively; i.e., prioritizing symptomatics provides a 4.3% reduction in deaths, prioritizing by age generates a 2.8% reduction, and prioritizing prodromals offers a 0.6% improvement. Note that our model overestimates the benefits of prodromal priority at the hospital queue because care providers will not always be able to observe whose lives can, and cannot, be saved.

A sensitivity analysis of the number of deaths under the five priority policies for six key parameters was performed (Fig. 3). A less aggressive prophylactic strategy (i.e., higher value of the ring parameter p) is extremely costly (Fig. 3a): the death count doubles if p is increased from 0 to 0.07 under all five priority policies, and $\approx 660,000$ people (44% of those infected) perish if only symptomatics receive antibiotics ($p = 1$). Moreover, our

This paper was submitted directly (Track II) to the PNAS office.

[†]To whom correspondence should be addressed. E-mail: lwein@stanford.edu.

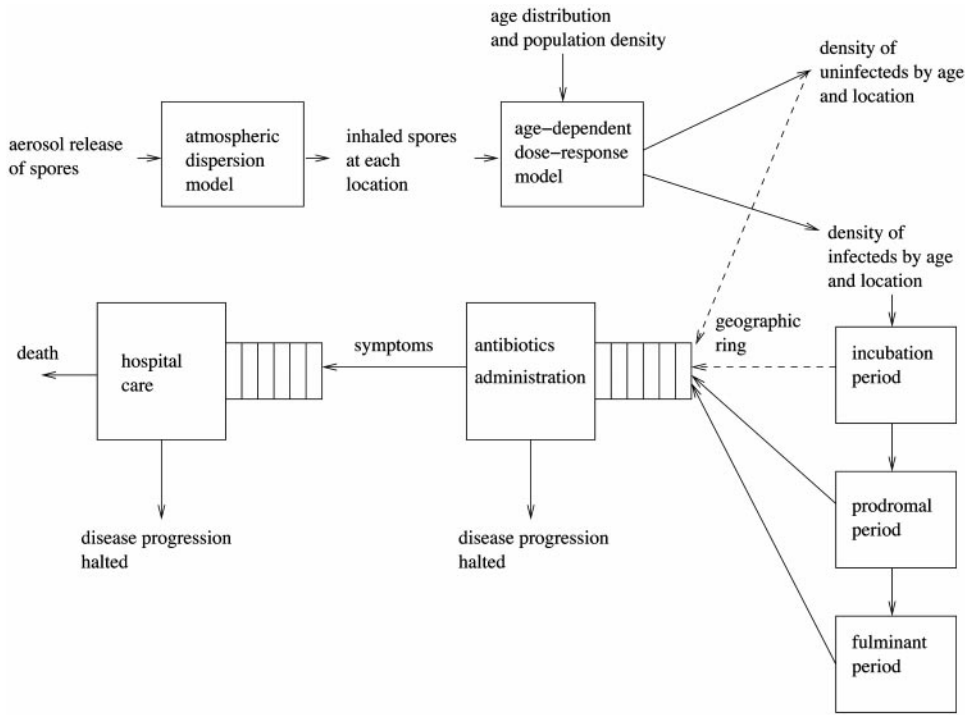


Fig. 1. Graphical depiction of the simulated system, which incorporates an atmospheric dispersion model, a dose-response model, a disease progression model, and an intervention model, which is described by a two-stage queueing system in each service zone. Asymptomatics enter the antibiotics queue according to a geographic ring strategy (dashed line). People in the two queues are prioritized according to the five policies in Table 1.

model underestimates the increase in deaths due to positive p values in Fig. 3a because we ignore the self-reporting delay of symptomatics; this delay averaged 3.5 days in the 2001 attack (1) but would likely be smaller in a subsequent large-scale attack. The death count is sensitive to the number of antibiotic distributors per capita, and the number of deaths can be nearly halved by eliminating queueing (Fig. 3b), which can be achieved by a 7.5-fold increase in the distribution capacity or by preattack distribution. The hospital queue is the system bottleneck (Fig. 3c). If care capacity is increased 75-fold, no one waits for service in the hospital queue, and further capacity increases yield no improvements. At this ideal capacity level, the number of deaths is <300 for all but the mass service policy. In the practically relevant ranges, the number of deaths is approximately linearly decreasing in the antibiotic efficacy (Fig. 3d and e), both as prophylaxis (due primarily to patient adherence) and as treatment in the absence of hospital care (which is a medical

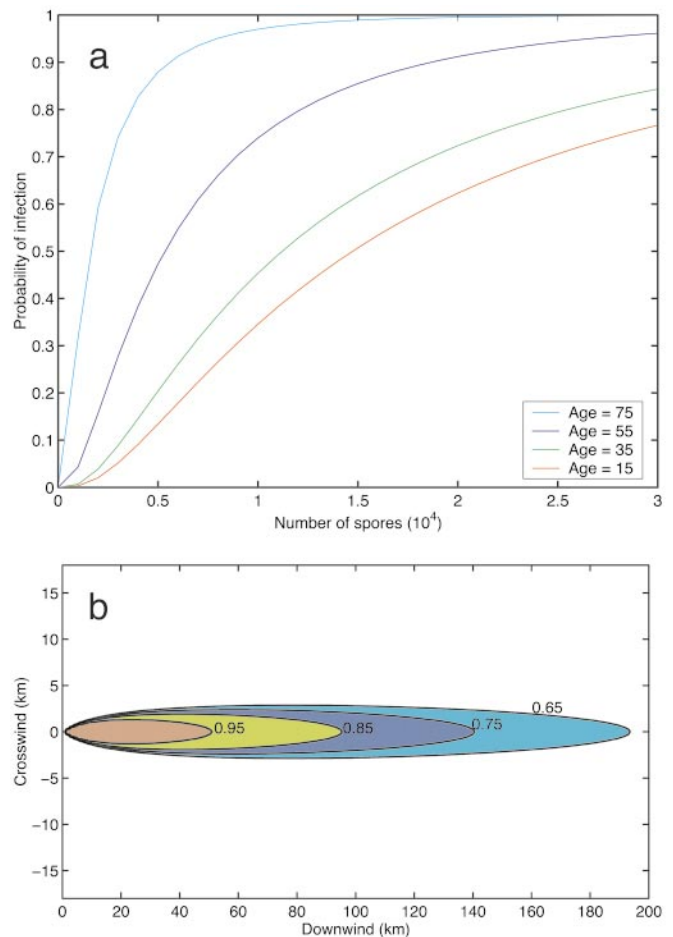


Fig. 2. (a) The age-dependent dose-response model for four ages, based on Eq. 2 of Supporting Text. (b) Age-aggregated spatial probability of infection, showing four contours of constant prevalence.

Table 1. Description of the five priority policies

Priority policy	Priority at antibiotics queue	Priority at hospital queue
Mass service	None	None
Symptomatic	Symptomatics	None
Symptomatic age	High, symptomatics	None
	Medium, asymptomatics over 55	
	Low, asymptomatics under 55	
Symptomatic/prodromal	Symptomatics	Prodromals
Symptomatic age/prodromal	High, symptomatics	Prodromals
	Medium, asymptomatics over 55	
	Low, asymptomatics under 55	

At the antibiotics queue, e.g., the symptomatic policy serves asymptomatics only if there are no symptomatics waiting for service. The third and fourth policies each build on the symptomatic policy in a different way, and the last policy combines these two policies.

Table 2. Parameter values for the model in the base case

Parameter	Description	Value	Ref.
Q	Amount released	10^{15} spores	<i>Supporting Text</i>
u	Wind speed	5 m/s	9
h	Release height	100 m	<i>Supporting Text</i>
b	Breathing rate	$0.03 \text{ m}^3/\text{min}$	9
α	Probit intercept	-9.733	<i>Supporting Text</i>
β	Probit dose slope	1.025	<i>Supporting Text</i>
γ	Probit age slope	-0.016 year^{-1}	<i>Supporting Text</i>
δ	Probit age quadratic	0.0006 year^{-2}	<i>Supporting Text</i>
X	Region limit downwind	201 km	This paper
Y	Region limit crosswind	18 km	This paper
θ_u	Urban population density ($x \leq 30$ km)	10^4 people/ km^2	3
θ_r	Rural population density [$x \in (30, 201)$ km]	10^2 people/ km^2	This paper
	Urban zone size	9 km^2	<i>Supporting Text</i>
	Rural zone size	81 km^2	<i>Supporting Text</i>
m_1	Median incubation	10.95 days	10
d_1	Dispersal factor of incubation	2.04	10
e_1	Prophylactic efficacy during incubation	0.9	<i>Supporting Text</i>
m_2	Median of prodromal phase	2.35 days	1, 10
d_2	Dispersal factor of prodromal phase	$\sqrt{2}$	<i>Supporting Text</i>
m_3	Median of fulminant phase	1.41 days	1, 10
d_3	Dispersal factor of fulminant stage	$\sqrt{2}$	<i>Supporting Text</i>
e_2	Prob. of infinite postantibiotic prodromal	0.4	<i>Supporting Text</i>
m_2	Median of finite postantibiotic prodromal	2 days	10
d_2	Disp. factor of finite postantibiotic prodromal	$\sqrt{2}$	<i>Supporting Text</i>
	Fatality rate if febrile	1.0	1, 11
τ	Detection delay	2 days	10
$n_A(x, y)$	Density of antibiotic servers	$1.21 \times 10^{-3} \theta(x, y)$	<i>Supporting Text</i>
μ_A	Service rate for antibiotics	$(7 \text{ min})^{-1}$	<i>Supporting Text</i>
$n_H(x, y)$	Density of hospital servers	$1.41 \times 10^{-4} \theta(x, y)$	<i>Supporting Text</i>
μ_H	Service rate in hospital	$(6 \text{ h})^{-1}$	<i>Supporting Text</i>
m_H	Number of mobile hospital servers	0	This paper
τ_m	Delay for mobile hospital servers	18 h	<i>Supporting Text</i>
p	Ring parameter	0	This paper
t_b	Biosensor time delay	6 h	This paper
l_b	Biosensor detection limit	10^4 spores	This paper
d_b	Biosensor density	$(9 \text{ km}^2)^{-1}$	This paper

unknown). The impact of prophylactic adherence is large: the death toll is $>50\%$ higher if e_1 is reduced from 0.9 to 0.8. Finally, under the symptomatic age/prodromal policy, deploying 2,800 mobile servers cuts the death count in half and 8,500 servers reduces it to one-tenth of the base case (Fig. 3f). Despite the 18-h delay, adding a fixed number of mobile servers has much more impact than adding the same number of local servers because the former are typically busy while the latter may be idle in less congested service zones.

Fig. 4 shows the impact of deploying biosensors with various characteristics (the biosensor parameter values are hypothetical because these data are classified), assuming preattack antibiotic distribution and prodromal priority at the hospital queue. The number of deaths is insensitive to the time delay to obtain biosensor results if this delay is <1 day (data not shown). Fig. 4 shows that a higher biosensor detection limit can be partially compensated for by deploying a higher geographical density of biosensors. The increase in death count by detecting the attack via early symptoms rather than biosensors is modest when the release size is $<10^{14}$ spores (or 100 g); larger releases cause a significant increase in deaths because of hospital congestion. Consequently, little can be gained in this scenario (e.g., preattack antibiotic distribution) by improving the biosensors beyond the base case values in Table 2. Finally, the upper curve in Fig. 4a provides a sensitivity analysis of the number of deaths versus the size of the release, which is the most uncertain quantity in our

model. Even with preattack antibiotic distribution, $\approx 20,000$ people would perish if only 10^{14} spores (100 g) were released. This curve is concave when plotted on a linear scale, and increasing the release size by 3 logs over the base case only doubles the death toll.

Because deterrence and counterproliferation are not highly effective at combating biological warfare, security from such an attack rests primarily on a strong logistical response (12, 13). Secretary of State Colin L. Powell recently presented evidence at the United Nations Security Council (14) that Iraq has produced vast quantities of anthrax, incorporated perfected drying techniques into mobile biological weapons production facilities, tested the jet spraying of 2,000 liters of simulated anthrax, authorized the use of poison gas if the United States attacks it, and is housing the base of an Al Qaeda terrorist cell. These arguments suggest that the likelihood of an attack on the scale of our base-case assumptions has increased to a nonnegligible level.

Consequently, as with the case of smallpox (13, 15) (www.whitehouse.gov/news/releases/2002/12/20021213-7.html), a concomitant increase in preparation to contain the consequences of such an attack is now urgently required. More specifically, our analysis has a number of policy implications, many stemming from the observation that aggressive hospital care for symptomatics is the bottleneck operation in this multistage service process (16). An aggressive prophylactic strategy

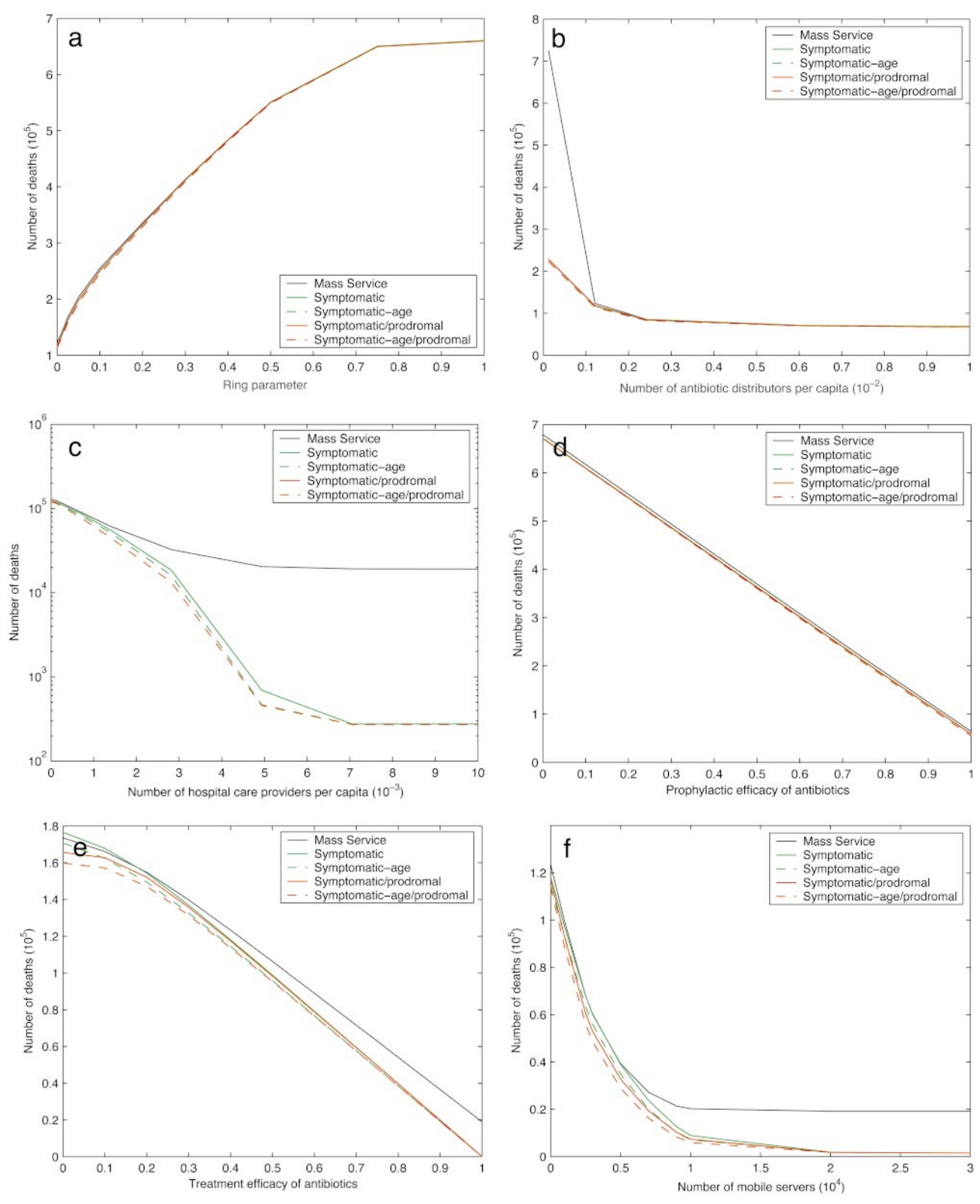


Fig. 3. Sensitivity analysis for various model parameters. For all five policies in Table 1, the number of deaths versus the ring parameter (p) (a), the number of antibiotic distributors per capita [$n_A(x,y)/\theta(x,y)$] (b), the number of hospital care providers per capita [$n_H(x,y)/\theta(x,y)$] (c), the prophylactic efficacy (e_1) (d), the treatment efficacy (e_2) (e), and the number of mobile servers (m_H) (f).

(Fig. 3a) is crucial because it eases the bottleneck by preventing incubating people from progressing to symptoms. Many people declined or discontinued antibiotic prophylaxis during the 2001

outbreak (17, 18), and an effective education program is required to maximize adherence in a subsequent attack. Pre-attack distribution of antibiotics, to be taken only if an attack occurs,

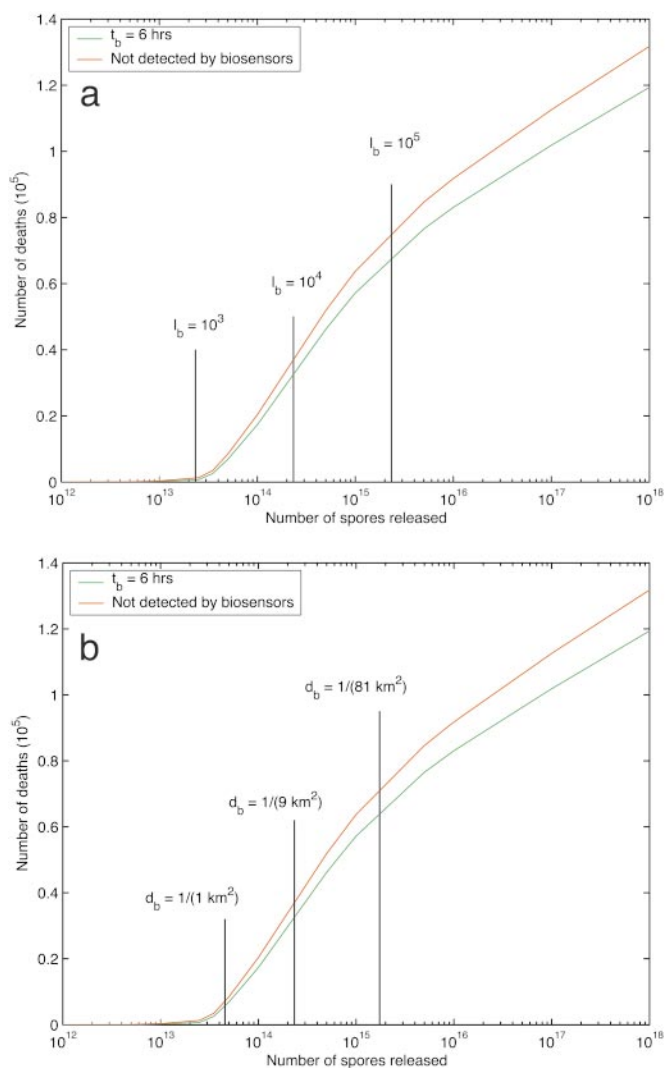


Fig. 4. The impact of biosensors, which are characterized by their time delay ($t_b = 6$ h) to obtain results, detection limit (I_b), and geographical density (d_b). The detection delay τ equals the biosensor delay t_b if the maximum spore count at any biosensor location is greater than the detection limit I_b (i.e., the attack is detected by biosensors), and τ equals 2 days otherwise (i.e., the attack is detected via early symptomatic cases). We assume preattack distribution of antibiotics (i.e., no time is spent in the antibiotics queue), and prodromals are given priority in the hospital queue. All other parameters are set to their base case values. (a) With the geographical density fixed at $1/(9 \text{ km}^2)$, we find the number of deaths as a function of release size for three values of the detection limit. (b) With the detection limit fixed at 10^4 spores, the number of deaths is plotted as a function of release size for three values of the geographical density. In both a and b, the number of deaths is discontinuous in the release size, following the upper death vs. release size curve to the left of the vertical line (there is a vertical line corresponding to each value of the varied parameter), and following the lower curve to the right of the vertical line.

would eliminate the delay in the antibiotics queue and would significantly reduce the number of fatalities (Fig. 3b). If this approach is deemed too risky (Cipro, the brand name for ciprofloxacin, has unpleasant side effects, and the costs and risks of preattack distribution need to be thoroughly investigated; the U.S. government has enough Cipro to treat several million people for the recommended 60 days, <http://usinfo.state.gov/topical/global/hiv/01102415.htm>) then it is imperative, due to the shortage of emergency hospital workers, that nonmedical professionals and volunteers administer antibiotics (J. M. Hauer, Congressional testimony, Senate Health Education, Labor, and

Pensions Committee, March 25, 1999). Increasing the number of hospital care providers is the most obvious remedy for easing the bottleneck, which could be achieved by expanded training for inhalational anthrax to nonemergency health-care workers (e.g., other doctors and nurses, respiratory therapists, emergency medical technicians with advanced life support training). Pre-attack training and organization of federal and military resources, the m_H mobile servers in our model, harnessed from, e.g., the Department of Defense, Veterans Administration hospitals, the Public Health Service's Disaster Medical Assistance Teams, the National Guard, the National Disaster Medical System, and the American Red Cross (J. M. Hauer, Congressional testimony, Senate Health Education, Labor, and Pensions Committee, March 25, 1999), can also significantly lower the death count from an attack (Fig. 3f); special emphasis should be given to the federal resources that are local [e.g., the National Guard (19)], which would reduce the delay τ_M in our model and further decrease the number of fatalities (data not shown). The number of mobile servers can also be increased via a government-sponsored program that encourages pulmonary specialists to travel to afflicted regions to treat patients. Perhaps such a program could be incorporated into the Medical Reserve Corps, which was recently established to enable health professionals to volunteer in their communities in the event of a large-scale emergency. Preattack vaccination of first responders is needed to prevent a depletion of intervention personnel. Also, secondary bottlenecks must be avoided: antibiotics and ventilators need to be stockpiled or rapidly obtained, and supplementary modes of transportation must be secured to transport symptomatics to hospitals. As is done in many service operations, prioritizing people in queue is a relatively easy way to achieve further service improvements, in this case fatality reductions ($\approx 10,000$ lives saved in the base case). Although the symptomatic-age policy at the antibiotics queue should not impose a logistical challenge, the prodromal policy at the hospital queue may require training from military doctors. Our base case optimistically assumes that the detection delay is only 48 h, thereby assuming that the first symptomatic cases (10) are successfully diagnosed and mobilization is rapid. Although a longer delay is extremely costly (in our base case, the death count doubles if the detection delay increases from 2 to 4.8 days), hypothetical rapid and accurate biosensors without preattack antibiotic distribution and ample hospital care resources would provide a false sense of security: even if the detection delay was reduced to 6 h, $\approx 70,000$ deaths would be incurred in our base case. Although the results in Fig. 4 are based on a simplistic atmospheric model, they do suggest that improving biosensor technology beyond the base case values in Table 2 offers less reduction in the death count than getting people through both queues as quickly as possible.

Although many of these proposals raise legal, ethical, and institutional issues, their cumulative impact would be enormous in the face of a large-scale attack. In addition, given (i) the relative ease of obtaining anthrax, (ii) the irreducible uncertainty in the model parameters (e.g., the release size, the efficacy of antibiotics in the febrile stage, and the possibility of a dose-dependent incubation period), and hence the potentially huge death toll, (iii) the possibility of panic, flight, communications breakdown, economic disruption, and general societal dysfunction in the aftermath of an attack, (iv) the possibility of attacks in multiple cities, and (v) the difficulty and cost of mounting an effective emergency response strategy, serious consideration should be given to preattack mass vaccination should the probability of an attack loom sufficiently large. Because the necessary supply of anthrax vaccine will not be available for at least several years [although the current vaccine is safe and reliable (5), it requires a series of shots over 18 months and annual boosters to reach and maintain effectiveness, and its only producer, BioPort, has a

2-year contract to produce 10 million doses for the U.S. military, www.wral.com/wtc/1216247/detail.html], planning for an effective emergency response must continue in earnest.

E.H.K. was supported in part by the Center for Interdisciplinary Research on AIDS at Yale University, via Grant MH/DA56826 from the National Institutes of Mental Health and Drug Abuse.

1. Jernigan, J. A., Stephens, D. S., Ashford, D. A., Omenaca, C., Topiel, M. S., Galbraith, M., Tapper, M., Fisk, T. L., Zaki, S., Popovic, T., *et al.* (2001) *Emerging Infect. Dis.* **7**, 933–944.
2. World Health Organization (1970) *Health Aspects of Chemical and Biological Weapons* (W.H.O., Geneva).
3. Office of Technology Assessment, U.S. Congress (1993) *Proliferation of Weapons of Mass Destruction*, U.S. Government Printing Office Publication OTA-ISC-559 (U.S. Government Printing Office, Washington, DC).
4. Henderson, D. A. (1999) *Science* **283**, 1279–1282.
5. Inglesby, T. V., O'Toole, T., Henderson, D. A., Bartlett, J. G., Ascher, M. S., Eitzen, E., Friedlander, A. M., Gerberding, J., Hauer, J., Hughes, J., *et al.* (2002) *J. Am. Med. Assoc.* **287**, 2236–2252.
6. Hanna, S. R., Briggs, G. A. & Hosker, R. P. (1982) *Handbook on Atmospheric Diffusion*, U.S. Department of Energy Report No. DOE/TIC-11223 (U.S. Department of Energy, Washington, DC).
7. Committee on Research and Development Needs for Improving Civilian Medical Response to Chemical and Biological Terrorism Incidents (1999) *Chemical and Biological Terrorism* (Natl. Acad. Press, Washington, DC), pp. 179–181.
8. Patrick, W. C., III (1996) *Politics Life Sci.* **15**, 208–210.
9. Meselson, M., Guillemin, J., Hugh-Jones, M., Langmuir, A., Popova, I., Shelokov, A. & Yampolskaya, O. (1994) *Science* **266**, 1202–1208.
10. Brookmeyer, R., Blades, N., Hugh-Jones, M. & Henderson, D. A. (2001) *Biostatistics* **2**, 233–247.
11. Advisory Committee on Immunization Practices (2001) *Clin. Toxicol.* **39**, 85–100.
12. Chyba, C. F. (2002) *Foreign Affairs* **81**, 122–136.
13. Kaplan, E. H., Craft, D. L. & Wein, L. M. (2002) *Proc. Natl. Acad. Sci. USA* **99**, 10935–10940.
14. Powell, C. L. (February 6, 2003) *N.Y. Times*, Section A, p. 18.
15. Centers for Disease Control and Prevention (2002) *Smallpox Vaccination Clinic Guide* (Centers for Disease Control and Prevention, Atlanta).
16. Goldratt, E. M. & Cox, J. (1984) *The Goal* (North River Press, Croton-on-Hudson, NY).
17. Williams, J. L., Noviello, S. S., Griffith, K. S., Wurtzel, H., Hamborsky, J., Perz, J. F., Williams, I. T., Hadler, J. L., Swerdlow, D. L. & Ridzon, R. (2002) *Emerging Infect. Dis.* **8**, 1133–1137.
18. Jefferds, M. D., Laserson, K., Fry, A. M., Roy, S., Hayslett, J., Grummer-Strawn, L. & Kettel-Khan, L. (2002) *Emerging Infect. Dis.* **8**, 1138–1144.
19. Carter, A. B. & Perry, W. J. (1999) *Preventive Defense: A New Security Strategy for America* (Brookings Institute Press, Washington, DC).

Supporting Text

Our model estimates the mean number of deaths from an airborne anthrax attack under five different response strategies. The values of the model parameters are listed in Table 2. We use a Gaussian plume model (1) adapted for an instantaneous point release. The model is identical to the one used by Meselson *et al.* (2) for the Sverdlovsk outbreak, except for the values of the height h and size Q of the release, and hence assumes dispersion parameters given by Briggs (1) for neutral stability in open country, and ignores infectivity decay, deposition, protection from buildings, secondary aerosolization, and limits on vertical mixing. The number of spores inhaled by a person x meters directly downstream of the release point, and y meters crosswind is

$$s(x, y) = \frac{bQ}{\pi u \sigma_y \sigma_z} e^{-\frac{y^2}{2\sigma_y^2} - \frac{h^2}{2\sigma_z^2}} \quad [1]$$

where $\sigma_y = 0.08x/\sqrt{1 + 0.0001x}$, $\sigma_z = 0.06x/\sqrt{1 + 0.0015x}$, u is the wind speed, and b is the breathing rate. The height (100 m) can represent a release from the top of a tall building or from a low-flying aircraft. The release amount corresponds to ≈ 1 kg of anthrax (2).

In our numerical computations, we consider the region up to $X = 201$ km downwind and $\pm Y = 18$ km crosswind. Note that with a wind speed of $u = 5$ m/s and an early evening release, airborne anthrax spores would travel ≈ 200 km before being inactivated by ultraviolet rays from the sun; extending X from 201 to 1,001 km only increases the number of people infected in the base case by 4.0%. Although our model is formulated by using a continuous state space, in the computations we discretize (x, y) space by using a grid of 1 km to calculate the inhaled spore count. This region is divided into an urban area that is within

30 km downwind of the point of release and an outlying rural area. The population density $\theta(x, y)$ is taken to be $\theta_u = 10^4$ people per km² (3) in the urban region and $\theta_r = 10^2$ people per km² in the rural area, which generates 10.8 million urban residents and 0.7 million rural residents in our study region. The probability density function (pdf) of the population's age is $f(a)$, which is assumed to be uniformly distributed (with maximum age 85) within each of the following four age classes: 33.4% 0 – 24, 31.5% 25-44, 22.4% 45-64, and 12.7% 65-85 (4). People do not change location or age in our model.

Because of the strong age dependence in the dose-response relationship of inhalation anthrax (2, 5, 6), we incorporate age into the probit model used by Glassman (7), so that

$$P(s, a) = \Phi(\alpha + \beta \log s + \gamma a + \delta a^2) \quad [2]$$

is the likelihood that a person of age a gets infected from inhaling s spores (8), where $\Phi(\cdot)$ is the standard normal cumulative distribution function (cdf). The four parameters in Eq. 2 were estimated by a least-squares analysis using the ID₅₀ and ID₁₀ values, together with ages 15, 35, 55, and 75, in table 3 of ref. 9; see Fig. 2a.

Let $I_j(x, y, a, t)$ denote the density of people in disease stage j at location (x, y) , age a , and time t , where $j = 0, \dots, 4$, denotes uninfected, incubation, prodromal, fulminant, and death, respectively. Even though monkey studies reveal that the incubation period is inversely related to dose (10-12), we performed a statistical analysis of the data in ref. 2 and were unable to detect a statistically significant relationship between incubation period and either dose or age; a dose-dependent incubation period would increase the death toll in our model by exacerbating congestion at the hospital queues in the urban service zones. The duration of disease stages $j = 1, 2, 3$ have cdf $F_j(t)$, pdf $f_j(t)$, survival function $\bar{F}_j(t)$,

and hazard rate function $h_j(t) = f_j(t)/\bar{F}_j(t)$. These disease durations are taken to be log normal, where the log durations have mean r_j (i.e., the median disease period duration is $m_j = e^{r_j}$) and variance σ_j^2 . The parameters m_1 and σ_1^2 are taken from an analysis of the Sverdlovsk release (13). For $j = 2, 3$, the parameter σ_j^2 was chosen so that the dispersion factor $d_j = e^{\sigma_j^2} = \sqrt{2}$, and hence 95% of the disease period durations fall within half of the median and twice the median (13). The parameter r_j was chosen to coincide with a mean prodromal period of 2.5 days (in the absence of treatment) and a mean fulminant period of 1.5 days (5, 13).

The attack occurs at time 0, and intervention begins at time $\tau = 48$ h. At time τ , the aerosol would be fully dispersed (14). At the time of the attack, we have $I_1(x, y, a, 0) = \theta(x, y)f(a)P(s(x, y), a)$, and $I_0(x, y, a, 0) = \theta(x, y) - I_1(x, y, a, 0)$, and until intervention begins (i.e., for $t \in [0, \tau]$), the system state is given by

$$I_0(x, y, a, t) = I_0(x, y, a, 0), \quad [3]$$

$$I_1(x, y, a, t) = I_1(x, y, a, 0)\bar{F}_1(t), \quad [4]$$

$$I_2(x, y, a, t) = I_1(x, y, a, 0)[F_1(t) - \int_0^t f_1(u)F_2(t-u)du], \quad [5]$$

$$I_3(x, y, a, t) = I_1(x, y, a, 0)[\int_0^t f_1(u)F_2(t-u)du - \int_0^t \int_0^u f_1(v)f_2(u-v)dv F_3(t-u)du], \quad [6]$$

$$I_4(x, y, a, t) = I_1(x, y, a, 0)[\int_0^t \int_0^u f_1(v)f_2(u-v)dv F_3(t-u)du]. \quad [7]$$

To model intervention, we divide the 201×36 -km region into square service zones covering a 9-km² urban area of 9×10^4 people or an 81-km² rural area of 8,100 people. In New York City, a point of distribution for antibiotics serves ≈ 33 K people, and a “911” hospital serves ≈ 127 K people (Hauer, J. M., Congressional Testimony, Senate Health, Education,

Labor and Pensions Committee, March 25, 1999); our choice of 90 K people in an urban zone is between these two values. A two-stage (antibiotics and hospital) queueing system is located in each zone and provides service only to people in that zone. As discussed later, the local servers at these queues are assisted by a set of mobile hospital servers. Individuals continue their disease progression while waiting in queue.

Combination antibiotics have two effects in our model. First, they are assumed to be 90% effective ($e_1 = 0.9$) at preventing symptomatic disease when administered during the incubation period. While the antibiotics themselves are extremely effective (15), the 10% ineffectiveness is assumed to be primarily due to nonadherence of patients. Although full adherence was $< 50\%$ among postal workers in 2001 (16,17), adherence would likely be higher in a subsequent large-scale attack. Also, prodromal individuals who have received antibiotics do not progress to the fulminant stage with probability $e_2 = 0.4$. It has been claimed that 45-80% of severely symptomatic inhalational anthrax patients die if they do not receive immediate aggressive treatment in a state-of-the-art hospital (www.anthrax.mil). The efficacy of combination antibiotics administered during the febrile stage, coupled with aggressive supportive care (e.g., intravenous antibiotics, draining of pleural effusions), was unexpectedly high in the fall of 2001 (5). It is not clear whether this was due to the care or to the particular anthrax strain (10). With probability $1 - e_2$, these individuals have a prodrome duration (their prodromal clock is restarted if they receive antibiotics while in the prodromal stage) that is log normal with median $m_2 = 2$ days, dispersion factor $d_2 = \sqrt{2}$, and hazard rate function $h_2(t)$. People who complete their hospital care while in the prodromal stage survive with probability 1, but neither antibiotics nor hospital care are capable of preventing

death once someone enters disease stage 3 (5, 18). Note that while Sverdlovsk victims who had late onset also had a higher survival rate (2), this may be due to delayed administration of antibiotics and vaccines after the release.

In the five response policies in Table 1, a geographical ring, which grows over time, is used to specify which asymptomatics get in the antibiotics queue and at what time. All people who are symptomatic at time τ enter the antibiotics queue at time τ (the time intervention begins), and anyone who becomes symptomatic after time τ is placed in the queue at this later time if he did not previously join the queue (via the ring). A person enters the hospital queue as soon as he both develops symptoms and receives antibiotics, which can occur in either order. While antibiotics are administered only by local servers, hospital care is administered by both local servers and mobile servers, the former representing workers in a specific service zone, and the latter representing state and federal employees who can be dynamically allocated across the entire region. The density of local servers at queue i (where $i = A$ is the antibiotic queue and $i = H$ is the hospital queue) is $n_i(x, y)$, which we assume is proportional to the population density at each location. The density of antibiotic servers $n_A(x, y)$ was chosen so that, given the service rate μ_i (see below), antibiotics can be distributed to the entire population in 4 days. The number of emergency nurses in the United States in June 2001 was 89,300 and the number of emergency physicians in 2000 in the United States was 32,020 (www.aaem.org). Summing these two quantities, dividing by 286 million people and dividing by three shifts of workers per day gives the density n_H shown in Table 2. In addition, there are m_H mobile hospital servers who are used to handle the overflow of patients who cannot be served locally in a timely fashion; these servers are

available $\tau_m = 18$ h after the attack is detected (Hauer, J. M., Congressional Testimony, Senate Health, Education, Labor and Pensions Committee, March 25, 1999). We assume that each server at queue i is capable of serving patients at rate μ_i . Our mean service time for antibiotic distribution of 7 min in Table 2 is close to the implied mean service time of about 5.7 min if three shifts are used, and 8.5 min if two shifts are used (Hauer, J. M., Congressional Testimony, Senate Health, Education, Labor and Pensions Committee, March 25, 1999). The mean hospital care time of 6 h in Table 2 is intended to include several hours to stabilize a patient (e.g. provide intravenous antibiotics, monitor metabolites and electrolytes) and several additional hours to provide reactive care (e.g., rehydration, thoracentesis, chest tube placement) (5).

For notational purposes, we need to distinguish between the prodromal patients in the hospital queue who may (with probability $1 - e_2$), or may not, progress to the fulminant disease stage. To this end, we define disease stages $\tilde{2}$ and $\hat{2}$ for people in the hospital queue who have finite and infinite prodromal durations, respectively. For $i = A$, $j = 0, 1, 2, 3$, and for $i = H$, $j = \tilde{2}, \hat{2}, 3$, define $Q_j^i(x, y, a, w, t)$ to be the density of people in queue i at time t who are in disease stage j at location (x, y) and have been in this disease stage for exactly w time units. Let $Q_j^i(x, y, a, t) = \int_0^t Q_j^i(x, y, a, w, t) dw$ be the density of people in queue i at time t of age a and in disease stage j at location (x, y) . Note that for $j = 0, 1, \hat{2}$, we need not keep track of people's "disease age" because people in stages 0 and $\hat{2}$ do not progress and the disease age of individuals in stage 1 equals t , since they were infected at time 0. In addition, let $U_1(x, y, a, t)$ be the density of people of age a in disease stage 1 at location (x, y) who have unsuccessfully received antibiotics and will progress to symptoms.

In the equations below, $A_j(x, y, a, t)$, $j = 0, 1$ are the arrival rates of asymptomatics to the antibiotics queue due to the ring strategy, and $S_j^i(x, y, a, t)$ are the service rates from queue i ; both are described in detail later. All transitions are due to these arrivals and services, or to disease progression. By our earlier discussion, the system state at time τ is $Q_2^A(x, y, a, w, \tau) = I_1(x, y, a, 0)f_1(\tau-w)\bar{F}_2(w)$, $Q_3^A(x, y, a, w, \tau) = I_1(x, y, a, 0)\int_0^{\tau-w} f_1(u)f_2(\tau-w-u) du \bar{F}_3(w)$, and $U_1(x, y, a, \tau) = Q_0^A(x, y, a, \tau) = Q_1^A(x, y, a, \tau) = Q_j^H(x, y, a, w, t) = 0$. In addition, $I_j(x, y, a, t) = 0$ for $j = 2, 3$, $t > \tau$. The dynamics for $t \geq \tau$ are given by

$$\frac{dI_0(x, y, a, t)}{dt} = -A_0(x, y, a, t), \quad [8]$$

$$\frac{dQ_0^A(x, y, a, t)}{dt} = A_0(x, y, a, t) - S_0^A(x, y, a, t)Q_0^A(x, y, a, t), \quad [9]$$

$$\frac{dI_1(x, y, a, t)}{dt} = -A_1(x, y, a, t) - h_1(t)I_1(x, y, a, t), \quad [10]$$

$$\frac{dQ_1^A(x, y, a, t)}{dt} = A_1(x, y, a, t) - [h_1(t) + S_1^A(x, y, a, t)]Q_1^A(x, y, a, t), \quad [11]$$

$$\frac{dU_1(x, y, a, t)}{dt} = (1 - e_1)S_1^A(x, y, a, t)Q_1^A(x, y, a, t) - h_1(t)U_1(x, y, a, t), \quad [12]$$

$$Q_2^A(x, y, a, 0, t) = h_1(t)I_1(x, y, a, t) + h_1(t)Q_1^A(x, y, a, t), \quad [13]$$

$$\frac{\partial Q_2^A(x, y, a, w, t)}{\partial w} + \frac{\partial Q_2^A(x, y, a, w, t)}{\partial t} = -[h_2(w) + S_2^A(x, y, a, t)]Q_2^A(x, y, a, w, t), \quad [14]$$

$$Q_3^A(x, y, a, 0, t) = \int_0^t h_2(w)Q_2^A(x, y, a, w, t) dw, \quad [15]$$

$$\frac{\partial Q_3^A(x, y, a, w, t)}{\partial w} + \frac{\partial Q_3^A(x, y, a, w, t)}{\partial t} = -[h_3(w) + S_3^A(x, y, a, t)]Q_3^A(x, y, a, w, t), \quad [16]$$

$$Q_2^H(x, y, a, 0, t) = (1 - e_2) \left[h_1(t)U_1(x, y, a, t) + \int_0^t S_2^A(x, y, a, t)Q_2^A(x, y, a, w, t) dw \right], \quad [17]$$

$$\frac{\partial Q_2^H(x, y, a, w, t)}{\partial w} + \frac{\partial Q_2^H(x, y, a, w, t)}{\partial t} = -[h_2(w) + S_2^H(x, y, a, t)]Q_2^H(x, y, a, w, t), \quad [18]$$

$$\begin{aligned} \frac{dQ_2^H(x, y, a, t)}{dt} = e_2 \left[h_1(t)U_1(x, y, a, t) + \int_0^t S_2^A(x, y, a, t)Q_2^A(x, y, a, w, t) dw \right] \\ - S_2^H(x, y, a, t)Q_2^H(x, y, a, t), \end{aligned} \quad [19]$$

$$Q_3^H(x, y, a, 0, t) = \int_0^t h_2(w)Q_2^H(x, y, a, w, t) dw, \quad [20]$$

$$\begin{aligned} \frac{\partial Q_3^H(x, y, a, w, t)}{\partial w} + \frac{\partial Q_3^H(x, y, a, w, t)}{\partial t} = S_3^A(x, y, a, t)Q_3^A(x, y, a, w, t) \\ - [h_3(w) + S_3^H(x, y, a, t)]Q_3^H(x, y, a, w, t), \end{aligned} \quad [21]$$

$$\frac{dI_4(x, y, a, t)}{dt} = \int_0^t \left[h_3(w) \left(Q_3^A(x, y, a, w, t) + Q_3^H(x, y, a, w, t) \right) + S_3^H(x, y, a, t)Q_3^H(x, y, a, w, t) \right] dw, \quad [22]$$

and the total dead is $\int_0^\infty \int_0^X \int_{-Y}^Y I_4(x, y, a, \infty) dy dx da$.

It remains to specify the rates $A_j(x, y, a, t)$ and $S_j^i(x, y, a, t)$ appearing in the above equations for the various policies. The ring-based strategy behind $A_j(x, y, a, t)$ tracks the cumulative number of symptomatic anthrax cases per capita at location (x, y) by time t , assuming that this location has not entered the ring by time t . This quantity, which we call the observed anthrax burden, is $\int_0^\infty I_1(x, y, a, 0) da F_1(t)/\theta(x, y)$. The ring at time t consists of all locations that have burdens at least as large as the threshold p . Hence, location (x, y) enters the ring at time

$$t^*(x, y) = F_1^{-1} \left(\frac{p\theta(x, y)}{\int_0^\infty I_1(x, y, a, 0) da} \right) \quad \text{if} \quad \int_0^\infty I_1(x, y, a, 0) da > p\theta(x, y), \quad [23]$$

and $t^*(x, y) = \infty$ otherwise, where $F_1^{-1}(\cdot)$ denotes the inverse cdf of the incubation period. Because intervention does not begin until time τ , if we let $I_{\{x\}}$ denote the indicator function of the event x , then

$$A_0(x, y, a, \tau) = I_0(x, y, a, 0) I_{\{\tau \geq t^*(x, y)\}}, \quad [24]$$

$$A_1(x, y, a, \tau) = I_1(x, y, a, 0) \bar{F}_1(\tau) I_{\{\tau \geq t^*(x, y)\}}, \quad [25]$$

and, for $t > \tau$,

$$A_0(x, y, a, t) = I_0(x, y, a, 0) I_{\{t=t^*(x, y)\}}, \quad [26]$$

$$A_1(x, y, a, t) = I_1(x, y, a, 0) \bar{F}_1(t^*(x, y)) I_{\{t=t^*(x, y)\}}. \quad [27]$$

Finally, we specify the service rate terms $S_j^i(x, y, a, t)$. Define $Q_j^i(x, y, t) = \int_0^\infty Q_j^i(x, y, a, t) da$ to be the total density of people in disease stage j at location (x, y) in queue i at time t , $Q_2^H(x, y, t) = \sum_{j=\{\hat{2}, \hat{2}\}} Q_j^H(x, y, t)$ to be the total density of prodromals at the hospital queue at location (x, y) at time t , and $Q^i(x, y, t) = \sum_{j=0}^3 Q_j^i(x, y, t)$ to be the total density of people at location (x, y) in queue i at time t . The mass service policy is defined by

$$\begin{aligned} S_j^i(x, y, a, t) &= \mu_i \min\left(1, \frac{n_i(x, y)}{Q^i(x, y, t)}\right) \\ &+ \frac{\mu_i}{Q^i(x, y, t)} (Q^i(x, y, t) - n_i(x, y))^+ \min\left(1, \frac{m_i}{\int_0^X \int_{-Y}^Y (Q^i(x, y, t) - n_i(x, y))^+ dy dx}\right) I_{\{t \geq \tau + \tau_m\}} \end{aligned} \quad [28]$$

for $i = A$, $j = 0, \dots, 3$ and for $i = H$, $j = \tilde{2}, \hat{2}, 3$, where, for ease of presentation, we define $m_A = 0$. The first term on the right side of Eq. 28 represents service by the local servers. Note that the maximum departure rate per capita is $n_i(x, y)\mu_i$ and if there are more people in queue than servers, the departure rates are proportional to the relative densities of people in queue. The second term (for $i = H$) in Eq. 28 depicts the m_H mobile servers processing overflow people [i.e., leftover people in regions (x, y) where $Q^i(x, y, t) > n_i(x, y)$] in proportion to their overflow densities in queue. The symptomatic priority policy, where asymptomatic people in the antibiotics queue are only served if the number of servers exceeds

the number of symptomatics in queue, is defined by Eq. 28 for $i = H, j = \tilde{2}, \hat{2}, 3$, and by

$$S_j^A(x, y, a, t) = \mu_A \min\left(1, \frac{[n_A(x, y) - Q_2^A(x, y, t) - Q_3^A(x, y, t)]^+}{Q_0^A(x, y, t) + Q_1^A(x, y, t)}\right) \text{ for } j = 0, 1, \quad [29]$$

$$S_j^A(x, y, a, t) = \mu_A \min\left(1, \frac{n_A(x, y)}{Q_2^A(x, y, t) + Q_3^A(x, y, t)}\right) \text{ for } j = 2, 3. \quad [30]$$

The symptomatic/prodromal policy, which builds on the symptomatic policy by giving priority to prodromal patients over fulminant patients in the hospital queue (i.e., prodromals are served locally; then excess prodromals are served by mobile servers; then spare local servers serve fulminants; and finally spare mobile servers serve fulminants), is defined by Eqs. 29 and 30 and

$$S_j^H(x, y, a, t) = \mu_H \min\left(1, \frac{n_H(x, y)}{Q_2^H(x, y, t)}\right) + \frac{\mu_H}{Q_2^H(x, y, t)} [Q_2^H(x, y, t) - n_H(x, y)]^+ \min\left(1, \frac{m_H}{\int_0^X \int_{-Y}^Y [Q_2^H(x, y, t) - n_H(x, y)]^+ dy dx}\right) I_{\{t \geq \tau + \tau_m\}} \quad [31]$$

for $j = \tilde{2}, \hat{2}$, and

$$S_3^H(x, y, a, t) = \mu_H \min\left(1, \frac{[n_H(x, y) - Q_2^H(x, y, t)]^+}{Q_3^H(x, y, t)}\right) + \frac{\mu_H}{Q_3^H(x, y, t)} [Q_3^H(x, y, t) - (n_H(x, y) - Q_2^H(x, y, t))^+]^+ \min\left(1, \frac{[m_H - \int_0^X \int_{-Y}^Y (Q_2^H(x, y, t) - n_H(x, y))^+ dy dx]^+}{\int_0^X \int_{-Y}^Y [Q_3^H(x, y, t) - (n_H(x, y) - Q_2^H(x, y, t))^+]^+ dy dx}\right) I_{\{t \geq \tau + \tau_m\}}, \quad [32]$$

where the first term on the right side of Eq. 32 represents service of fulminant patients by spare (i.e., not serving prodromals) local servers and the second term is due to processing by spare mobile servers. The symptomatic-age policy and the symptomatic-age/prodromal

policy incorporate on top of the symptomatic and symptomatic/prodromal policies, respectively, a second layer of age-based priority at the antibiotics queue. Because this priority layer is conceptually similar to the disease-based priority at the antibiotics queue, we omit the detailed specifications of the symptomatic-age and symptomatic-age/prodromal policies.

References

1. Hanna, S. R., Briggs, G. A. & Hosker, R. P. (1982) *Handbook on Atmospheric Diffusion*, U.S. Department of Energy report no. DOE/TIC-11223 (U.S. Department of Energy, Washington, DC).
2. Meselson, M., Guillemin, J., Hugh-Jones, M., Langmuir, A., Popova, I., Shelokov, A. & Yampolskaya, O. (1994) *Science* **266**, 1202-1208.
3. Office of Technology Assessment, U.S. Congress (1993) *Proliferation of Weapons of Mass Destruction*, U.S. Government Printing Office Pub. OTA-ISC-559 (U.S. Government Printing Office, Washington, DC).
4. United States Census (2000) Geographic Comparison Table (GCT)-P5. Age and Sex: 2000 Data Set: Census 2000 Summary File 1 (SF 1) Geographic Area: United States and Puerto Rico – Metropolitan Area.
5. Jernigan, J. A., Stephens, D. S., Ashford, D. A., Omenaca, C., Topiel, M. S., Galbraith, M., Tapper, M., Fisk, T. L., Zaki, S., Popovic, T. *et al.* (2001) *Emerging Inf. Dis.* **7**, 933-944.

6. Rickmeier, G., McClennan, G. & Anno, G. (2001) *Mil. Oper. Res.* **6**, 35-47.
7. Glassman, H. N. (1966) *Bacteriol. Rev.* **30**, 657-659.
8. Cox, D. R. (1970) *Analysis of Binary Data* (Methuen, London).
9. Webb, G. F. & Blaser, M. J. (2002) *Proc. Natl. Acad. Sci. USA* **99**, 7027-7032.
10. Brachman, P. (1980) *Ann. N.Y. Acad. Sci.* **353**, 83-93.
11. Henderson, D. W., Peacock, S. & Belton, F. C. (1956) *J. Hyg.* **54**, 28-36.
12. Gleiser, C. A., Berdjis, C. C., Hartman, H. A. & Gochenour, W. S. (1963) *Br. J. Exp. Pathol.* **44**, 416-426.
13. Brookmeyer, R., Blades, N., Hugh-Jones, M. & Henderson, D. A. (2001) *Biostatistics* **2**, 233-247.
14. Inglesby, T. V., O'Toole, T., Henderson, D. A., Bartlett, J. G., Ascher, M. S., Eitzen, E., Friedlander, A. M., Gerberding, J., Hauer, J., Hughes, J. *et al.* (2002) *J. Am. Med. Assoc.* **287**, 2236-2252.
15. Friedlander, A. M., Welkos, S. L., Pitt, M. L. M., Ezzell, J. W., Worsham, P. L., Rose, K. J., Ivins, B. E., Lowe, J. R., Howe, G. B., Mikesell, P. *et al.* (1993) *J. Inf. Dis.* **167**, 1239-1242.
16. Williams, J. L., Noviello, S. S., Griffith, K. S., Wurtzel, H., Hamborsky, J., Perz, J. F., Williams, I. T., Hadler, J. L., Swerdlow, D. L. & Ridzon, R. (2002) *Emerging Infect. Dis.*

8, 1133-1137.

17. Jefferds, M. D., Laserson, K., Fry, A. M., Roy, S., Hayslett, J., Grummer-Strawn, L. & Kettel-Khan, L. (2002) *Emerging Infect. Dis.* **8**, 1138-1144.

18. Advisory Committee on Immunization Practices (2001) *Clin. Toxicol.* **39**, 85-100.