

Evaluation of Public Health Interventions for Anthrax: A Report to the Secretary's Council on Public Health Preparedness

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To aid in understanding how best to respond to a bioterror anthrax attack, we analyze a system of differential equations that includes a disease progression model, a set of spatially distributed queues for distributing antibiotics, and vaccination (preevent and/or postevent). We derive approximate expressions for the number of casualties as a function of key parameters and management levers, including the time at which the attack is detected, the number of days to distribute antibiotics, the adherence to prophylactic antibiotics, and the fraction of the population that is preimmunized. We compare a variety of public health intervention policies in the event of a hypothetical anthrax attack in a large metropolitan area. Modeling assumptions were decided by the Anthrax Modeling Working Group of the Secretary's Council on Public Health Preparedness. Our results highlight the primary importance of rapid antibiotic distribution and lead us to argue for ensuring postattack surge capacity to rapidly produce enough anthrax vaccine for an additional 100 million people.

THIS ARTICLE COMPARES THE NUMBER of inhalation anthrax casualties under four attack scenarios for the four policy options set forth by the Anthrax Modeling Working Group (AMWG) of the Secretary's Council on Public Health Preparedness (SCPHP). The Council hired two groups to perform this task: the coauthors of the present paper, and Dr. Sid Baccam and Dr. Michael Boechler from Innovative Emergency Management (Baton Rouge, Louisiana). We derive approximate analytical formulas for the number of casualties under various policy options, which is complementary to the detailed simulation study performed by Baccam and Boechler.¹ Through an iterative process requiring two onsite meetings and preliminary results from earlier versions of the models, the Working Group decided on the attack scenarios and the various policy options, and they determined most of the modeling assumptions and the parameter values used in the model.

We define a casualty as a seriously ill person (see

Methods for a more precise definition) who requires aggressive medical treatment to survive. The model does not explicitly address the availability of medical treatment for seriously ill patients. The analysis in previous work^{2,3} suggests that, for the attack sizes considered in the present article, the medical care facilities would be overwhelmed, and a very small fraction of seriously ill patients would survive under the medical care capacity assumed in the earlier article.² Hence, in our view, casualties can be interpreted as deaths. Relative to the analysis in the earlier article,² the main contribution of the present study is to assess a vaccine that can be used before or after an event. The policy issues regarding the use of a vaccine are discussed at the end of this article. Although most of the modeling assumptions were determined by the AMWG, the results and views stated in this article are the authors' own and do not represent a consensus or official opinion of the AMWG.

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METHODS

Attack Scenarios

The four attack scenarios stem from a scenario of a dry anthrax release originally developed by Dr. Fred Harper (Sandia Laboratories) and Dr. Arnold Kaufmann (Centers for Disease Control and Prevention), which incorporates an atmospheric release model, a spatial population density, and a dose-response curve. In this scenario, approximately 10^{14} anthrax spores (assumed to be 1 kg, with 50% dissemination efficiency) are released from a 1-km long line source over a large U.S. city, exposing 1.39 million people to various amounts of agent. We create four scenarios from the original Harper-Kaufmann scenario by varying the probit slope of the dose-response curve (either 0.7, as derived from monkey data,⁴ or 1.82, as proposed by Harper and Kaufmann) and the building protective factor (either 50, as proposed by Harper and Kaufmann, or 10). In all four scenarios, it is assumed that, at the time of the attack, 85% of the people are indoors and inhale only 2% or 10% (depending on the building protective factor) as many spores as the 15% who are outdoors.

We briefly performed a few calculations suggesting that the 0.7 slope is perhaps more realistic than the 1.82 slope. For an ID_{50} of 10,000 spores, the probability that someone is infected by a single spore is $\Phi(-4\beta)$, where $\Phi(\cdot)$ is the standard normal cumulative distribution function and β is the probit slope. This probability is $\Phi(-2.8) = 0.0026$ if the probit slope is 0.7, and $\Phi(-7.28) \approx 10^{-12}$ if the probit slope is 1.82. It has been estimated that approximately 5,000 letters were cross-contaminated during the 2001 postal attack.⁵ If we assume that each of these letters went to a single person and caused the inhalation of a single spore (some of these letters were handled by multiple people and caused the inhalation of multiple spores), then the mean number of people infected by these cross-contaminated envelopes would be 13 if the slope is 0.7, and 5×10^{-9} if the slope is 1.82. The fact that a 94-year-old Connecticut woman appeared to have been infected by a very small number of spores⁶ suggests that the 0.7 slope may be closer to the actual value than the 1.82 slope—that is, the probability of at least one person getting infected if the probit slope is actually 1.82 is essentially zero.

For our purposes, we only need to know the total number of infected people (in the absence of intervention) for each scenario. This is because our analytical results are expressed as the fraction of infected people who are casualties, and this fraction turns out to be independent of the number of infected people.² The number of infected people for the four scenarios was computed in Baccam and Boechler¹ and appears in Table 1.

The Model

The model is described below, and the base-case values of all parameters are in Table 1.

- The natural disease progression is divided into four stages. The first stage is the incubation period, which has a log-normal distribution with a median of 10.95 days and a dispersion factor of 2.04 (i.e., $e^\sigma = \sqrt{2}$, where σ is the standard deviation of the underlying normal distribution).⁷ People enter the early symptomatic phase on leaving the incubation phase.
- The early symptomatic period has a log-normal distribution with a median of 1.175 days and a dispersion factor of $\sqrt{2}$. Absent intervention, people enter the intermediate disease phase on leaving the early symptomatic phase. The median of the early disease phase equals half the median of the early plus intermediate phases reported by Brookmeyer and colleagues.⁷ People entering the intermediate phase proceed to the fulminant stage and then eventually die unless intensive medical care is provided. The availability of aggressive medical care to prevent progression from the intermediate disease phase to the fulminant disease phase was not addressed in our model.
- Antibiotic distribution begins at time τ . We consider three values of τ : 2 days, 3.5 days, and 5 days. At this time, all people in the exposed region enter the antibiotics queue, and antibiotic distribution is initiated. People in the antibiotics queue who have, or develop, early symptoms (i.e., fever) still wait in the queue along with people who are asymptomatic.
- Let t_e be the time that the antibiotic queue becomes empty. Then it takes $t_e - \tau$ amount of time to distribute antibiotics to the entire population. We consider three values of $t_e - \tau$: 2 days, 6 days, and 10 days.
- There is partial antibiotic adherence (less than 50% of postal workers adhered to the full antibiotic regimen during the 2001 mail attack^{8,9}), which applies regardless of the stage of disease: Among people receiving antibiotics, 10% take no antibiotics, 15% take the antibiotics for exactly 15 days, 25% take them for exactly

TABLE 1. THE NUMBER INFECTED IN THE FOUR SCENARIOS¹

<i>Probit Slope</i>	<i>Building Protective Factor</i>	<i>Number Infected</i>
0.7	10	312,996
0.7	50	205,835
1.82	10	115,970
1.82	50	83,601

30 days, 25% take them for 45 days, and 25% take them for the full 60 days.

- Antibiotics, if taken, are effective at preventing people in the incubation stage or early disease stage from proceeding to later stages (we are assuming that spores can remain in the lungs for several weeks). Antibiotics do not prevent people in the intermediate or fulminant stages from disease progression or death.
- The vaccine, which is administered in 2 doses spaced 2 weeks apart, is assumed to protect either 80% or 90% of the vaccinated population—that is, the vaccine efficacy is either $e_v = 0.8$ or $e_v = 0.9$. This protection starts 3 weeks after the first dose for 50% of the successfully vaccinated people, and the protection starts 4 weeks after the first dose for the remaining 50%.
- Vaccine administration begins 5 days after the attack. It takes 7 days to distribute each vaccine dose to the entire population.

Policy Options

The four public health interventions considered here are:

1. **PostA:** Postexposure prophylaxis with antibiotics for 60 days.
2. **PostA+PostV:** Postexposure prophylaxis with antibiotics for 60 days and 2 doses of postexposure vaccine spaced 2 weeks apart.
3. **PreV+PostA:** Two levels of preemptive (or preexposure) vaccination: 50% and 80% of the population (of these 50% and 80%, only 80% or 90% will be effectively preimmunized given the imperfect vaccine efficacies), followed by 60 days of postexposure prophylaxis.
4. **PreV+PostA+PostV:** Two levels of prerelease vaccination: 50% and 80% of the population (of these

50% and 80%, only 80% or 90% will be effectively preimmunized), followed by 60 days of postexposure prophylaxis and 2 doses of postexposure vaccine spaced 2 weeks apart.

Analysis

In the Appendix, we derive the fraction of infected people who are casualties for the PostA and PostA+PostV policy options; the derivation of the other two policy options is described in the next paragraph. A person becomes a casualty by entering the intermediate disease stage, which can occur either by not receiving antibiotics in a timely fashion, or by receiving them but not successfully adhering to the antibiotic regimen.

RESULTS

The fraction of infected people who are casualties is given in Table 2 for the PostA policy and in Table 3 for the PostA+PostV policy. These results are graphically depicted in Figure 1. Because the fraction of infected people who are casualties is essentially independent of the number infected, the analysis of preevent vaccination is straightforward as long as preimmunized people receive the same postattack treatment as the rest of the population,³ which is the case here. Let v be the level of preexisting immunity. Because we consider two values of prerelease vaccination coverage (50% and 80%) and two values of vaccine efficacy (0.8 and 0.9), we have four possible levels of preexisting immunity: $v = 0.4, 0.45, 0.64,$ and 0.72 . The number of casualties under the PreV+PostA policy is simply $1 - v$ times the number of casualties under the PostA policy, and the number of casualties under the PreV+PostA+PostV policy is $1 - v$ times the number of casualties under the PostA+PostV

TABLE 2. RESULTS FOR THE POSTA POLICY

<i>Time of Antibiotic Initiation</i>	<i>Time to Distribute Antibiotics</i>	<i>Fraction of Infected Who Are Casualties</i>	<i>Casualties Slope = 0.7 Protect = 10</i>	<i>Casualties Slope = 0.7 Protect = 50</i>	<i>Casualties Slope = 1.82 Protect = 10</i>	<i>Casualties Slope = 1.82 Protect = 50</i>
2 days	2 days	0.170	53,296.6	35,049.3	19,747.2	14,235.5
2 days	6 days	0.236	73,926.	48,615.8	27,390.8	19,745.6
2 days	10 days	0.332	103,904.	68,330.2	38,498.1	27,752.7
3.5 days	2 days	0.203	63,677.9	41,876.4	23,593.7	17,008.3
3.5 days	6 days	0.297	93,083.7	61,214.4	34,489.	24,862.6
3.5 days	10 days	0.397	124,405.	81,812.3	46,094.	33,228.5
5 days	2 days	0.266	83,145.6	54,678.9	30,806.8	22,208.1
5 days	6 days	0.371	116,198.	76,414.8	43,053.1	31,036.3
5 days	10 days	0.467	146,269.	96,190.8	54,195.1	39,068.4

The last four columns give the number of casualties for the four scenarios described in Table 1.

TABLE 3. RESULTS FOR THE POST A+POSTV POLICY

<i>Vaccine Efficacy</i>	<i>Time of Antibiotic Initiation</i>	<i>Time to Distribute Antibiotic</i>	<i>Fraction of Infected Who Are Casualties</i>	<i>Casualties Slope = 0.7 Protect = 10</i>	<i>Casualties Slope = 0.7 Protect = 50</i>	<i>Casualties Slope = 1.82 Protect = 10</i>	<i>Casualties Slope = 1.82 Protect = 50</i>
0.8	2 days	2 days	0.095	29,711.9	19,539.4	11,008.7	7936.
0.8	2 days	6 days	0.167	52,214.8	34,337.9	19,346.4	13,946.5
0.8	2 days	10 days	0.271	84,915.2	55,842.6	31,462.4	22,680.8
0.8	3.5 days	2 days	0.131	41,036.	26,986.4	15,204.5	10,960.7
0.8	3.5 days	6 days	0.233	73,112.3	48,080.7	27,089.3	19,528.2
0.8	3.5 days	10 days	0.343	107,278.	70,549.1	39,748.2	28,653.9
0.8	5 days	2 days	0.199	62,271.6	40,951.6	23,072.6	16,632.7
0.8	5 days	6 days	0.314	98,325.3	64,661.5	36,431.1	26,262.6
0.8	5 days	10 days	0.419	131,128.	86,233.5	48,585.	35,024.2
0.9	2 days	2 days	0.086	26,765.9	17,602.	9917.1	7149.1
0.9	2 days	6 days	0.158	49,502.8	32,554.4	18,341.6	13,222.2
0.9	2 days	10 days	0.264	82,543.2	54,282.8	30,583.6	22,047.2
0.9	3.5 days	2 days	0.122	38,207.7	25,126.5	14,156.6	10,205.2
0.9	3.5 days	6 days	0.226	70,617.6	46,440.1	26,164.9	18,861.9
0.9	3.5 days	10 days	0.336	105,139.	69,142.2	38,955.6	28,082.5
0.9	5 days	2 days	0.191	59,664.2	39,236.9	22,106.5	15,936.3
0.9	5 days	6 days	0.307	96,092.8	63,193.4	35,603.9	25,666.3
0.9	5 days	10 days	0.413	129,237.	84,989.7	47,884.2	34,519.

The last four columns give the number of casualties for the four scenarios described in Table 1.

policy. Hence, the number of casualties in Figure 1 is reduced by the factors 0.28, 0.36, 0.55, or 0.6 by the addition of preattack vaccination.

Our results reveal four main points:

- In the absence of (preevent or postevent) vaccination, we predict that between 17% and 47% of the infected people will be casualties during an airborne anthrax attack, assuming that antibiotic distribution is initiated between days 2 and 5 and can be distributed in 2–10 days. Approximately 5% of infected people become casualties for each additional day it takes to initiate antibiotic distribution or to distribute antibiotics. The primary importance of rapid antibiotic distribution echoes the recommendations in earlier studies.^{2,10}
- The total number of casualties in the absence of (preevent or postevent) vaccination ranges from 20,000 to 140,000, depending on the fraction of infected people who are casualties (see the previous point) and the total number infected, which depends on the probit slope and the building protection factor (see Table 1).
- Because of partial drug adherence, postattack vaccination achieves a 5–7% reduction in the fraction of infected people who are v casualties, which represents between 4,000 and 20,000 averted casualties.

- In this study, everyone—preimmunized or not—receives the same postattack treatment. Consequently, if a fraction v of the population is preimmunized, then the number of casualties is reduced by the factor $1 - v$. For the parameter values considered here, $1 - v$ ranges from 0.28 to 0.6—that is, the number of casualties can be cut from almost one-half to almost one-quarter. This represents from 5,000 to 100,000 lives saved.

DISCUSSION

Approximate Analytical Formulas Versus Stochastic Simulation

Our approach of deriving approximate analytical formulas for the number of casualties is complementary to the detailed stochastic simulation study reported in Baccam and Boechler.¹ We view both as valuable, with their own strengths and weaknesses. Our approach is less accurate, cannot accommodate some detailed and complicated assumptions used in a simulation model, and cannot quantify the uncertainty (e.g., 95% confidence intervals) in outcomes for a given set of parameter values. However, the simplicity of our model makes it more transparent to policymakers.

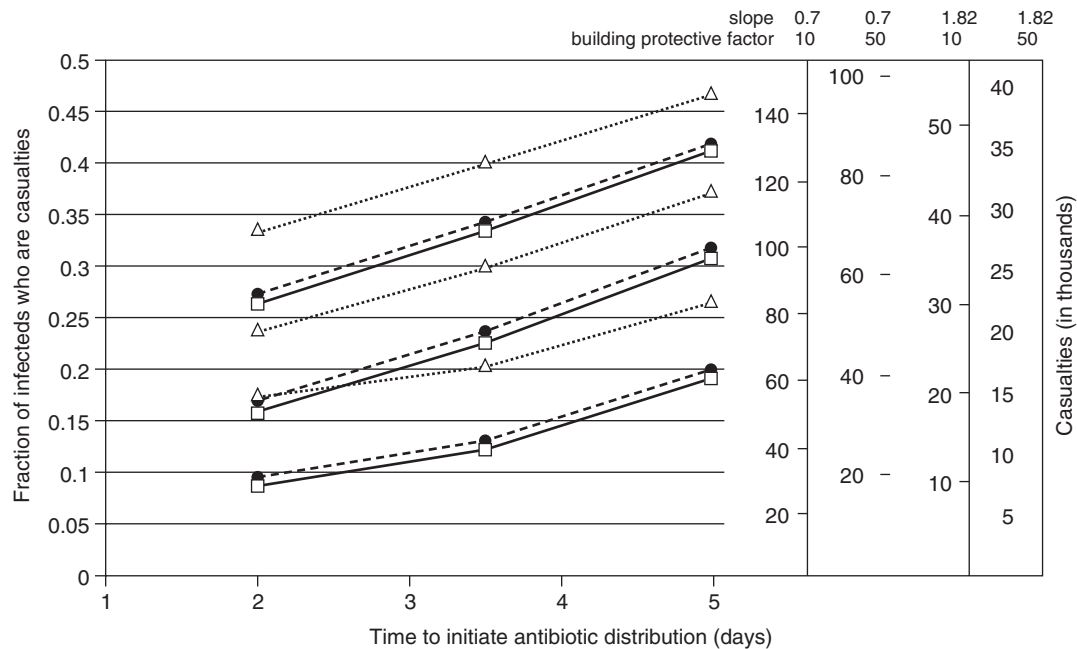


FIGURE 1. A GRAPHIC DEPICTION OF THE RESULTS IN TABLES 2 AND 3

Interestingly, the quantitative results for the two models are virtually indistinguishable (see Figure 2 of Baccam and Boechler¹). The analytical model also can provide insights that are difficult to obtain via simulation. A key analytical insight from Craft et al.³ is that the number of casualties is nearly linear in the number of infected people—that is, the fraction of infected people who are casualties is nearly a constant. This linearity holds for the models in our earlier studies,^{2,3} in which aggressive medical treatment can save symptomatic people before they enter the fulminant phase, because the medical care facilities would be overwhelmed in a modest or large attack and would save a negligible fraction of infected people.

In the present model, medical intervention does not reduce the number of casualties, and the linearity between the number of casualties and the number of infected people is more obvious. Nonetheless, within the AMWG, this result led the policymakers to decompose the threat assessment and consequence management aspects of the problem and to focus on how the management levers affect the fraction of infected people who are casualties, rather than the number of casualties. Because of the huge uncertainty in the magnitude of an attack (e.g., it depends on terrorists' capabilities and the weather), this decomposition led to more focused, and less political, discussion within the Working Group.

We conclude this article by addressing some of the key policy issues pertaining to vaccine use that are informed by our model. The previous discussion notwithstanding, some of these issues depend critically on the likelihood of a future attack of the size assumed in this article.

While it is nearly impossible to support different scenarios with strong evidence, we note that some of the Department of Health and Human Services members of the AMWG insisted that we use the Harper-Kaufmann scenarios, which arose out of an earlier government-funded project. We conclude from this that there are at least some bioterror experts within the government who believe that an attack of the assumed size is not out of the realm of possibility.

Should Prevaccinated People Receive Postattack Prophylactic Antibiotics?

If the prevaccinated receive no postattack prophylaxis, then there is a tradeoff between logistics (those getting antibiotics will do so more quickly) and false negatives (prevaccinated but unprotected people who get infected will not receive antibiotics until they develop symptomatic illness). Hence, if the fraction preimmunized is *less* than a critical threshold, then there are fewer casualties if the prevaccinated do not get antibiotics. If the fraction preimmunized is *greater* than this threshold, then there are fewer casualties if the prevaccinated receive antibiotics. Although we cannot easily compute this critical threshold with the existing model, the difference in outcomes between the two policies may be dwarfed by the mayhem that could result if the prevaccinated insist on receiving prophylactic antibiotics. One possible way around this is to somehow give priority in the antibiotics queue to those who have yet to receive a vaccine, but this could also be problematic.

Postattack Vaccination Versus No Postattack Vaccination

In the presence of partial drug adherence, postattack vaccination offers some benefit beyond postattack antibiotic prophylaxis, although it would be costly to deliver. This is consistent with a third paper (in addition to Baccam and Boechler¹ and the present paper) that arose out of the AMWG,¹⁰ which shows that postattack vaccination will help only if drug adherence is low, as it is here (Table 4). However, the vaccine may need to be administered for purposes of reoccupation and remediation. Indeed, we have recently argued that vaccination needs to be a critical component of an indoor remediation plan that is both quick and reasonably reliable.¹¹ Hence, in our view, the PostA+PostV policy dominates the PostA policy, and the PreV+PostA+PostV policy dominates the PreV+PostA policy.

Preattack Vaccination Versus Postattack Vaccination

The most challenging and important issue is whether to deploy the next-generation vaccine when it becomes available, or wait until an attack occurs. The preattack versus postattack vaccination decision depends on five factors: (1) the likelihood of a future attack, (2) the scale of a future attack, (3) the adverse events (and deaths) that would be generated by voluntary preattack vaccination, (4) the cost, and (5) the preattack vaccination coverage. Before addressing these five factors, let us first note that there is the possibility that the anthrax strain will be anti-

biotic-resistant (although we have no evidence that intentionally released anthrax might be resistant to antibiotics, developing an antibiotic-resistant strain appears to be straightforward¹²), which would be catastrophic in a reasonably sized attack if there is no prevent vaccination.

Regarding the first factor, we conclude that the likelihood of an attack is nontrivial, given that the 2001 attack occurred and no one has been apprehended, and given the interest that terrorists and several nations have taken in this biological agent.

A second factor is how many casualties would be incurred in such an attack. This analysis suggests that 100,000 casualties is within the feasible range, particularly if this is a simultaneous multicity event, although this is based on the debatable assumption that the attack sizes in Table 1 are plausible.

Regarding the third factor, it would appear that the next-generation vaccine should be safer than the smallpox vaccine;¹³ we do not yet know whether the adverse events (e.g., swollen arms) from the anthrax vaccine will be mitigated in this new vaccine.¹⁴

If the vaccine is very safe, then it would appear that the main downside of prevent vaccination is the fourth factor, cost, which includes not only the out-of-pocket cost, but also the opportunity cost with respect to countermeasures for both competing bioterror scenarios (since this may come out of a fixed budget, such as BioShield) and for naturally occurring diseases such as pandemic influenza. A cost-effectiveness analysis of anthrax countermeasures¹⁵ concluded that PostA+PostV was the most cost-effective option if the distribution of countermea-

TABLE 4. PARAMETER VALUES FOR THE MODEL

<i>Parameter</i>	<i>Description</i>	<i>Value</i>
	Median incubation	10.95 days
	Dispersion factor of incubation	2.04
	Median of early symptomatic phase	1.175 days
	Dispersion factor of early symptomatic phase	$\sqrt{2}$
τ	Intervention delay	2, 3.5, or 5 days
$t_e - \tau$	Time to distribute antibiotics	2, 6, or 10 days
a_0, f_0 a_1, f_1 a_2, f_2 a_3, f_3 a_4, f_4	Antibiotic adherence for a_i days with probability f_i	0 days, 0.1 15 days, 0.15 30 days, 0.25 45 days, 0.25 60 days, 0.25
e_v	Vaccine efficacy	0.8 or 0.9
θ	Spore clearance rate	0.07/day

sure was very rapid. However, this analysis did not include a detailed temporal model of the interaction of antibiotics and vaccine (as in earlier studies^{1,10} and the present article). Some of the Department of Health and Human Services members of the AMWG did not want us to incorporate costs into the analysis.

Finally, an argument has been made to take the most dangerous bioterror threats off the table.^{16,17} However, preattack voluntary mass vaccination would be a big step toward taking this threat off the table and deterring terrorists from using anthrax only if preattack vaccination coverage is high. Given the resistance to smallpox vaccination among front-line workers and the resistance to anthrax vaccination among the military, in the absence of a large future terrorist attack, it is possible that the preattack vaccination coverage would be an order of magnitude lower than the 50% and 80% figures considered here. Moreover, even if several cities achieved high coverage, terrorists could choose other cities to attack.¹⁸ Taken together, although the preattack vaccination of the next-generation vaccine may be capable of greatly mitigating the threat at a large financial cost, the biggest barrier may not be cost but public acceptance.

How Much Vaccine Should Be Made?

Whether or not there is voluntary preattack vaccination, we will need enough vaccine stockpiled to perform postattack vaccination: We do not want the bottleneck for reoccupation to be unavailability of the vaccine. Moreover, if an attack of this magnitude occurs, then it is quite plausible that the terrorists will have the capacity to “reload,” or to carry out a campaign of attacks.^{16,19} Even if the culprits are caught, it seems likely that the public—in the target city as well as throughout the country—will demand voluntary vaccination before the next attack. Hence, it is conceivable that the total demand during and after a large attack could be 100 to 200 million people. Project BioShield legislation calls for the stockpiling of enough vaccine for 25 million people.²⁰ Given the immense cost of the vaccine and its limited shelf life, the most reasonable approach may be to ensure surge postattack capacity to quickly manufacture enough vaccine for another 100 million people.

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APPENDIX

We combine the analysis of a similar anthrax response model in an earlier study³ with the competing risks analysis in Brookmeyer and Johnson²¹ to evaluate the two post-exposure policy options: policies PostA and PostA+PostV. Let X_1 and X_2 denote the random duration of the incubation period and the early symptomatic period, respectively, and let $f_1(t)$ and $f_2(t)$ be the corresponding probability density functions and $F_1(t)$ and $F_2(t)$ denote the corresponding cumulative distribution functions. Also, let T_S denote the random time that a typical infected person receives antibiotics. By equation (43) in Reference 3, $T_S \sim U[\tau, t_e]$, i.e., T_S has a uniform distribution that ranges from τ to t_e . If we let e_a denote the probability that antibiotics are successful at preventing progression to the intermediate disease stage (e_a will be investigated more thoroughly later in this section), then by equation (66) of Reference 3, the fraction of infected people who are casualties is given by

$$\begin{aligned} \frac{C}{I} &= P(X_1 + X_2 < T_S) + (1 - e_a)P(X_1 + X_2 > T_S), \\ &= 1 - e_a \left(1 - \frac{\int_{\tau}^{t_e} \int_0^S f_1(t)F_2(s-t)dt ds}{t_e - \tau} \right), \end{aligned} \quad (1)$$

where C is the number of casualties and I is the number of infected people.

Substituting the values from Table 3 into this equation gives the simple linear equations (the values for τ and $t_e - \tau$ are in days)

$$\frac{C}{I} = \begin{cases} 1 - 0.991e_a & \text{if } \tau = 2, t_e - \tau = 2; \\ 1 - 0.912e_a & \text{if } \tau = 2, t_e - \tau = 6; \\ 1 - 0.798e_a & \text{if } \tau = 2, t_e - \tau = 10; \\ 1 - 0.951e_a & \text{if } \tau = 3.5, t_e - \tau = 2; \\ 1 - 0.839e_a & \text{if } \tau = 3.5, t_e - \tau = 6; \\ 1 - 0.719e_a & \text{if } \tau = 3.5, t_e - \tau = 10; \\ 1 - 0.877e_a & \text{if } \tau = 5, t_e - \tau = 2; \\ 1 - 0.751e_a & \text{if } \tau = 5, t_e - \tau = 6; \\ 1 - 0.636e_a & \text{if } \tau = 5, t_e - \tau = 10. \end{cases} \quad (2)$$

The remainder of the Appendix is devoted to deriving an approximate expression for the antibiotic efficacy e_a

for the two postexposure policy options. There are two key steps in the approximation, both of which are made for purposes of analytical tractability (although the latter is also made for lack of data): We ignore the interperson variability in antibiotic distribution time and consider a typical person whose antibiotic delivery time is the mean of the uniform distribution, and we ignore the interperson variability in infectious dose and consider a typical person who inhales the ID₅₀. We suspect that the accuracy of our resulting estimates is due to the fact that both of these probability distributions (antibiotic distribution time and infectious dose) are symmetric about their mean.

It is important to review the timing of events. Let us first consider a typical person under policy PostA and assume the attack happens on (i.e., at the beginning of) day 0. Assuming an intervention delay of τ days, and assuming it takes $t_e - \tau$ days to distribute antibiotics, this typical person will start antibiotics on day $\tau + \frac{t_e - \tau}{2} = \frac{\tau + t_e}{2}$. As described earlier, 10% of the people will not take antibiotics, and 15%, 25%, 25%, and 25% will stop taking antibiotics after 15, 30, 45, and 60 days, respectively.

According to the competing risks model in Reference 21, spores are cleared from the lung at rate $\theta = 0.07/\text{day}$, and someone who receives the dose of ID_{100p} and who is protected (via antibiotics and/or vaccine) from day t_1 to day t_2 and from day t_3 onwards, will not progress to the intermediate disease stage with probability

$$(1 - p)^{(1 - e^{-\theta t_1 + e^{-\theta t_2 - e^{-\theta t_3}}})}. \tag{3}$$

We now describe how to combine this result with our previous work. First, we plan to replace the antibiotic prophylactic efficacy e_a in Equation 1 by the probability (as predicted by the competing risks model) that an infected person who starts antibiotics while in the pre-symptomatic or early symptomatic phase (and may receive a postexposure vaccination) does not progress to the intermediate stage. To do that, we must focus on the people who get their antibiotics before developing symptoms; that is, we must condition on the fact that these people got their antibiotics before reaching the intermediate disease stage. Consequently, since a typical person starts antibiotics on day $\frac{\tau + t_e}{2}$, we subtract $\frac{\tau + t_e}{2}$ days

for the true values of t_1 , t_2 , and t_3 in Equation 3. Moreover, we have to apply Equation 3 for each subset of the population, according to how long they adhere to their antibiotic regimen. Finally, note that the quantity in Equation 3 depends on the inhaled dose ID_{100p}. To get the exact fraction of people who get disease after their antibiotics are finished requires detailed knowledge of everyone's dose, which is not provided in the Harper-Kauf-

mann model. Hence, we simply substitute $p = 0.5$, and consider this probability for someone who inhales the ID₅₀. Our resulting estimate for the antibiotic efficacy for policy PostA is

$$e_a = \sum_{i=1}^4 f_i (0.5)^{e^{-\theta a_i}} = 0.837, \tag{4}$$

where $(f_1, f_2, f_3, f_4) = (0.15, 0.25, 0.25, 0.25)$ and $(a_1, a_2, a_3, a_4) = (15, 30, 45, 60)$ days are the probabilities and durations for drug adherence (see Table 3). Equations 2 and 4 can be combined to give an estimate for the fraction of infected people who are casualties under policy PostA. Multiplying this fraction times the number of people infected in Table 1 gives an estimate for the number of casualties. These estimates are given in Table 4 and Figure 1.

Now consider a typical person under policy PostA+PostV. We assume that vaccine administration begins 5 days after the attack. Further assuming that it takes 7 days to distribute each of the two vaccine doses to the entire population, this typical person will get his two vaccine doses on days 8.5 and 22.5. We assume that protective immunity takes hold on day 29.5 for 50% of the successfully vaccinated people (where the vaccine efficacy is either 0.8 or 0.9), and day 36.5 for the other 50%.

As above, this person will start antibiotics on day $\frac{\tau + t_e}{2}$ and will have random drug adherence. Summing up over all the different possible outcomes, we get

$$e_a = (1 - e_v) \left(\sum_{i=1}^4 f_i (0.5)^{e^{-\theta a_i}} \right) + \frac{e_v}{2} \left((0.1)0.5^{(1 - e^{-\theta 25.5})} + (0.15)0.5^{(e^{-\theta 15.5} - e^{-\theta 25.5})} + 0.75 \right) + \frac{e_v}{2} \left((0.1)0.5^{(1 - e^{-\theta 32.5})} + (0.15)0.5^{(e^{-\theta 15} - e^{-\theta 32.5})} + (0.25)0.5^{(e^{-\theta 30} - e^{-\theta 32.5})} + 0.5 \right), \tag{5}$$

which reduces to

$$e_a = \begin{cases} 0.9135 & \text{if } e_v = 0.8; \\ 0.9230 & \text{if } e_v = 0.9. \end{cases} \tag{6}$$

Combining Equation 6 with Equation 2 gives the number of casualties appearing in Table 3 and Figure 1.

REFERENCES

1. Baccam S, Boechler M. Analysis of public health policies: evaluation of impact on anthrax casualties. Baton Rouge, LA: Innovative Emergency Management, Inc.; 2004.
2. Wein LM, Craft DL, Kaplan EH. Emergency response to an anthrax attack. *Proc Natl Acad Sci U S A* 2003;100: 4346-4351.

3. Craft DL, Wein LM, Wilkins AH. Analyzing bioterror response logistics: the case of anthrax. *Manage Sci* 2004; 51:679–694.
4. Glassman HN. Discussion. *Bacteriol Rev* 1966;30:657–659.
5. Webb GF, Blaser MJ. Mailborne transmission of anthrax: Modeling and implications. *Proc Natl Acad Sci USA* 2002; 99:7027–7032.
6. Griffith KS, Mead P, Armstrong GL, et al. Bioterrorism-related inhalational anthrax in an elderly woman, Connecticut, 2001. *Emerg Infect Dis* 2003;9:681–688.
7. Brookmeyer R, Blades N, Hugh-Jones M, Henderson DA. The statistical analysis of truncated data: application to the Sverdlovsk anthrax outbreak. *Biostatistics* 2001;2: 233–247.
8. Williams JL, Noviello SS, Griffith KS, et al. Anthrax post-exposure prophylaxis in postal workers, Connecticut, 2001. *Emerg Infect Dis* 2002;8:1133–1137.
9. Jefferds MD, Laserson K, Fry AM, et al. Adherence to antimicrobial inhalational anthrax prophylaxis among postal workers, Washington, D.C., 2001. *Emerg Infect Dis* 2002;8:1138–1144.
10. Brookmeyer R, Johnson E, Bollinger R. Public health vaccination policies for containing an anthrax outbreak. *Nature* 2004;432:901–904.
11. Wein LM, Liu Y, Leighton T. Evaluation of a HEPA-vaccine plan for indoor remediation after an airborne anthrax attack. *Emerg Infect Dis* 2005;11:69–76.
12. Brook I, Elliott TB, Pryor HI, et al. *In vitro* resistance of *Bacillus anthracis* Sterne to doxycycline, macrolides and quinolones. *Int J Antimicrob Agents* 2001;18:559–562.
13. Grabenstein JD. Anthrax vaccine: a review. *Immunol Allergy Clin North Am* 2003;23:713–730.
14. Pittman PR, Kim-Ahn G, Pifat DY, et al. Anthrax vaccine: immunogenicity and safety of a dose-reduction, route-change comparison study in humans. *Vaccine* 2002;20: 1412–1420.
15. Fowler RA, Sanders GD, Bravata DM, et al. Cost-effectiveness of defending against bioterrorism: a comparison of vaccination and antibiotic prophylaxis against anthrax. *Ann Intern Med* 2005;144:601–610.
16. Danzig R. *Catastrophic Bioterrorism—What Is To Be Done?* Washington, DC: Center for Technology and National Security Policy, National Defense University; August 2003.
17. Henderson DA. The looming threat of bioterrorism. *Science* 1999;283:1279–1282.
18. Webb GF. Being prepared: modeling the response to an anthrax attack. *Ann Intern Med* 2005;142:667–668.
19. Danzig R. *Reload and the Post-attack Environment*. Washington, DC: Center for Strategic and International Studies; September 2004.
20. Kaufman M. U.S. awards anthrax vaccine deal. *Washington Post* November 5, 2004:A4. Available at: www.washingtonpost.com/wp-dyn/articles/A26564-2004Nov4.html. Accessed September 21, 2005.
21. Brookmeyer R, Johnson E. Computer program to evaluate public health policy options in response to an anthrax outbreak: the impact of post exposure antibiotics and vaccine. Baltimore, Md: Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, January 23, 2004.

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