Finding Risk-Based Switchover Points for Response Decisions for Environmental Exposure to *Bacillus anthracis*

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Risk Management Articles

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ABSTRACT

In the wake of the 2001 terrorist attacks, the use of *Bacillus anthracis* (anthrax) in bioterrorism attacks has emerged as a realistic concern. Thus, a contingency plan is needed to inform decision-makers about which response actions are appropriate and justified under which circumstances. This study considers the decisions: (1) to undertake prophylactic antibiotic treatment; (2) to vaccinate individuals; or (3) to decontaminate the building. While these response actions are clearly justified for highly exposed individuals, a very large number of individuals exposed to very small risks in areas outside of the immediate vicinity of the release are also likely. Our results indicate that there are non-negligible risk thresholds below which response actions produce more costs than benefits. For the base case, the thresholds range from a risk of 1 in 33 for decontamination by fumigation to 1 in 6,547 for antibiotic prophylaxis and 1 in 7,108 for vaccination. A one-way sensitivity analysis on uncertain variables indicates less than an order of magnitude change in these thresholds. Benefit–cost analysis is a useful tool for assessing tradeoffs among alternative decisions, but cannot be the sole criterion in responding to incidents because of inherent limitations.

Key Words: *Bacillus anthracis*, decision model, risk threshold, cost–benefit analysis, bioterrorism, response strategies.

BACKGROUND

The threat of an anthrax attack and the necessity to prepare for such an event are major public health concerns (Moran *et al.* 2008; Wallin *et al.* 2007). These events are historically rare, but the social and economic consequences can be so catastrophic that preparedness is imperative (Webb 2003). The limited number of real-world events necessitates the mathematical modeling of emergency preparedness strategies. The literature establishes through the use of a myriad of mathematical models that certain treatment or environmental decontamination strategies will be more or less effective given an anthrax attack and a certain exposure scenario. These models are briefly summarized below. In addition, the discussion highlights a remaining research priority, the need for a risk-informed action level for response. An exposure threshold below which zero risk exists has not been established for *B. anthracis*. Thus, current dispersion and risk models allow for very low, but not zero, risk estimates at any finite distance from a release. Some means of deciding where to respond and where not to respond is needed, so that a single small release does not require remediation of an entire city, region, or nation.

Brookmeyer *et al.* (2004) used a probability model to predict the impact of different anthrax antibiotic and vaccination policies. Similar preventable cases were observed for each alternative at thee levels of exposure with the lowest of these exposure levels being the infectious dose ID (1) which results in 100 cases in 10,000. In a four paper series (Craft *et al.* 2005; Wein and Craft 2005; Wein *et al.* 2003, 2005), both a complex and simplified computational model were developed and evaluated to assess emergency response strategies to an airborne anthrax attack. Cost was not considered in this analysis. Baccam and Boechler (2007) also conducted an analysis to evaluate the number of lives that can be saved by a post-exposure prophylaxis campaign using a discrete time deterministic compartmental model. Their model addresses some limitations in previous studies by exposing individuals to one of ten different exposure levels corresponding to infectious doses ranging from 1% to 90%. Their model also allows for the uninfected "worried well" population but does not consider costs or the side effects associated with the treatments. Nevertheless, their findings reveal that regardless of the vaccination policy adopted, rapid and effective post-attack medical response has a large impact on the number of people who can be saved. A method for determining who needs treatment and who does not was arbitrarily set at those individuals who have inhaled enough spores to have at least a 1% chance of becoming ill.

In studies that do contain cost and benefit information, a need for an established threshold is implied, but not presented. Bravata *et al.* (2006) evaluated strategies for stockpiling and dispensing medical and pharmaceutical supplies using a cost–benefit analysis and found that mortality was highly dependent on the number of people requiring prophylaxis. However, a method of determining who should receive prophylaxis was not put forth. An effort to compare strategies using cost-effectiveness measures was presented by Braithwaite *et al.* (2006) for an intentional release of *Bacillus anthracis*. While it considers a new mitigation strategy and includes both variable attack probabilities and variable exposure levels, 10% is the lowest probability of infection considered in the sensitivity analysis. The conclusions indicate that the emergency surveillance and response system strategy is only cost effective at high

probabilities of large exposures, which implies the need for an established threshold. Another important result of this study is that more lives were lost than saved because of vaccine toxicity at very low attack probability and for small exposures. Schmitt *et al.* (2007) conducted a cost-effectiveness analysis comparing pre-attack vaccination with post-attack antibiotic treatment and vaccination for a small scale postal facility attack, using a constant exposure assumption consistent with the fixed low exposure level of Brookmeyer *et al.* (2004). Schmitt *et al.* recommend post-attack treatment with antibiotics for a small scale attack due to the high cost of vaccinating, but did not answer when (*i.e.*, at what risk level) this treatment is no longer justified. Zaric *et al.* (2008) developed a compartmental model to evaluate the costs and benefits of stockpiling, distributing and dispensing medical and pharmaceutical supplies in case of an anthrax bioterrorism attack. One of the key findings is that the number of unexposed individuals seeking prophylaxis and treatment significantly affected mortality. However a systematic approach for determining sufficient exposure for treatment was not established.

In general the literature fails to establish when treatment or environmental decontamination is required. In the post-9/11 attacks, more than 33,000 people received post-exposure prophylaxis (Heyman *et al.* 2002) and billions of dollars were spent on decontamination efforts. Modeling efforts (Wein *et al.* 2003) have predicted that 100,000 deaths would occur in a city of 10 million people with the release of 1 kg of anthrax spores even with relatively efficient post-attack medical response. With only a fraction of 1 g being used in the year 2001 anthrax mail attacks, the cost to decontaminate the U.S. postal facilities in Brentwood, Washington, D.C., and Hamilton Township, New Jersey, required more than 2 years and cost more than $200M (Webb 2003). Other direct costs are estimated to exceed $3B in the case of the postal facilities alone (Heyman 2002). A total of seven buildings on Capitol Hill—the Dirksen, Hart, and Russell Senate Office Buildings; the Ford and Longworth House Office Buildings; the U.S. Supreme Court Building; and the P Street Warehouse required a total expenditure of $28M (GAO 2003; Schmitt *et al.* 2007). Consideration of this exorbitant direct cost should bring light to the need for economic analysis in the development of guidelines for environmental concentrations of *Bacillus anthracis*. Wein *et al.* (2005) compared two indoor environmental decontamination strategies—fumigation and a HEPA/vaccine approach, based on cost and potential reduction of anthrax cases. Wein *et al.* showed that the HEPA/vaccine approach is more cost effective except in the most heavily contaminated spaces, but do not identify a benefit–cost threshold for decontamination.

Fowler *et al.* (2005) evaluated the cost-effectiveness of strategies for prophylaxis and treatment of an aerosolized release of *B. anthracis* for urban centers at risk for bioterrorism events. This study (Fowler *et al.* 2005) investigated the value of pre-attack vaccination assuming that a successive opportunity for treatment is available at a later point, after the attack. The strategy of pre-attack vaccination did not become cost effective until the probability of clinically significant exposure reached 1 in 200. This model assumed that an attack would be detected and allowed for pre-symptomatic treatment after an attack, an option that reduces the value of pre-attack vaccination. In contrast, the decision to re-occupy an area with some residual contamination assumes that the attack has already been detected and that the last opportunity for pre-symptomatic treatment is being considered. Under

such circumstances, a much lower threshold for the preventative treatment, such as vaccination, is warranted. A threshold has yet to be proposed with regard to this post-attack re-occupation scenario.

In this article we evaluate the cost-effectiveness of strategies for vaccine and antibiotic prophylaxis under two different exposure scenarios (1) a re-occupation scenario that looks at vaccination and decontamination as strategies for preventing illness due to a potential future exposure to *B. anthracis*; and (2) a retrospective scenario that looks at antibiotics as a means of preventing illness among people who have already been exposed to *B. anthracis*. Once identified, these thresholds can also be used in concert with a fate and transport model to inform decontamination standards, detection limits and sampling strategies (Huang *et al.* 2010) that can guide medical treatment decisions.

The Fowler *et al.* (2005) simulation applies to a large scale release of *B. anthracis* over a U.S. city, causing wide-spread and significant exposure. Their conclusion over a wide range of monetary values for a quality adjusted life year (QALY) was that the combination of post-attack vaccination and antibiotic prophylaxis is the most effective and least costly alternative when compared to vaccination alone. While sensitivity analysis was conducted on a number of uncertain variables, the probability of post-attack infection used in their analysis for the no action alternative was fixed at 0.95. In reality, this risk of infection is highly variable depending on how close individuals are to the point of release. In many situations there will be a few highly exposed individuals and a much larger number of individuals who receive much lower exposures. While it is clear that highly exposed people should receive immediate treatment or prophylaxis, at lower risks, the "no action" alternative must be considered. The intent of this analysis is to conduct a sensitivity analysis on the probability of infection for three different response strategies—antibiotic prophylaxis, vaccination, and environmental decontamination strategies. By determining the risk of infection when the "no action" alternative becomes the preferred alternative (the switchover point), we establish at what point medical treatment or decontamination become unjustified based on benefit–cost analysis. A benefit–cost action threshold such as this may be one input into the development of response plans for bioterrorism incidents.

While this study uses a benefit–cost approach to determine these risk thresholds, it is recognized that benefit–cost analysis should not be the sole basis for such decisions (Arrow *et al*. 1996). Factors such as societal equity and the high visibility and public concern associated with terrorism can and should inform the development of response guidelines.

METHODS

Exposure Scenario

The base case scenario assumes that an attack has occurred resulting in exposure to some people in the immediate vicinity of the attack as well as contaminated buildings/areas that may cause future exposures. A single release creates two related but distinct decision problems: (1) What action should be taken to protect those already exposed to this release? and (2) What actions should be taken to protect against future exposures that might result from residual environmental

contamination associated with this release? For the first decision, termed here the retrospective decision, antibiotic therapy is the relevant option. For the second decision, termed the re-occupancy decision, vaccination and environmental decontamination are both options. It would also be possible to combine both vaccination and decontamination. This combined option is not modeled in detail here but is discussed in the results section. In the post-exposure scenario, we assume that individuals have already been exposed to *Bacillus anthracis* spores. In the re-occupancy scenario, it is assumed that a release of spores has contaminated a building but there is no longer ongoing exposure because the occupants have left the building. In such cases the spores will settle and deposit on surfaces, but future exposure can occur when these particles become re-aerosolized (Weiss *et al.* 2007). Two alternatives are considered to prevent future exposures upon re-occupancy of the building—vaccination of the re-occupants and decontamination of the building.

Decision Model Design

Decision trees (Figures 1 and 2) were developed to compare the no action alternative to each of the post-attack strategies being investigated—antibiotic prophylaxis, vaccination, and decontamination. Decision trees are analytic tools that support the process of decision-making by structuring alternatives (*e.g.,* response strategies), uncertainties, and consequences. The expected value function is calculated for each possible outcome, incorporating the effect of risk into the calculations (Clemen and Reilly 2001). A decision between alternatives is rendered by selecting the alternative with the highest expected value. The analysis was performed using Precision Tree v. 1.0.9 Decision Analysis Add In (Palisade Corp., Ithaca, New York) for Microsoft Excel 2003 (Microsoft, Inc., Redmond, Washington).

Each tree begins with a decision node (shown as a rectangular box) with two alternatives, response or no response. All other nodes (represented by circles) are chance nodes with the likelihood of different outcomes described by different probabilities. For Figure 1 (antibiotic treatment and vaccination) chance nodes describe the probabilities of: contracting anthrax without treatment (p_1), contracting anthrax with treatment (p_2), survival or death following illness (p_3), disability or complete recovery following anthrax (p_4), and for the treatment alternatives, suffering side effects from the antibiotics or vaccination (p_5-p_8). The probability of contracting anthrax with treatment is the product of the probability of anthrax without treatment (p_1) and the probability that the treatment is effective.

The decision to decontaminate or not is depicted in Figure 2. The probability of contracting anthrax when no remediation is performed is represented by p_9. When environmental decontamination is performed a 5-log reduction in the probability of getting anthrax-related illness is represented by p_{10}, which is calculated as the product of p_9 and 0.00001. The complementary probability of not becoming ill when decontamination is performed is 1-p_{10}. In this model, the same probabilities used in Figure 1, p_3 and p_4, represent the probabilities associated with survival or death and healthy or disabled states following illness.

A switchover analysis is conducted to determine the level of risk (*i.e.*, probability of clinical anthrax infection) at which the preferred option switches between the response strategy and the no action alternative. The expected values of the response and no response options are calculated as a function of the risk of infection when
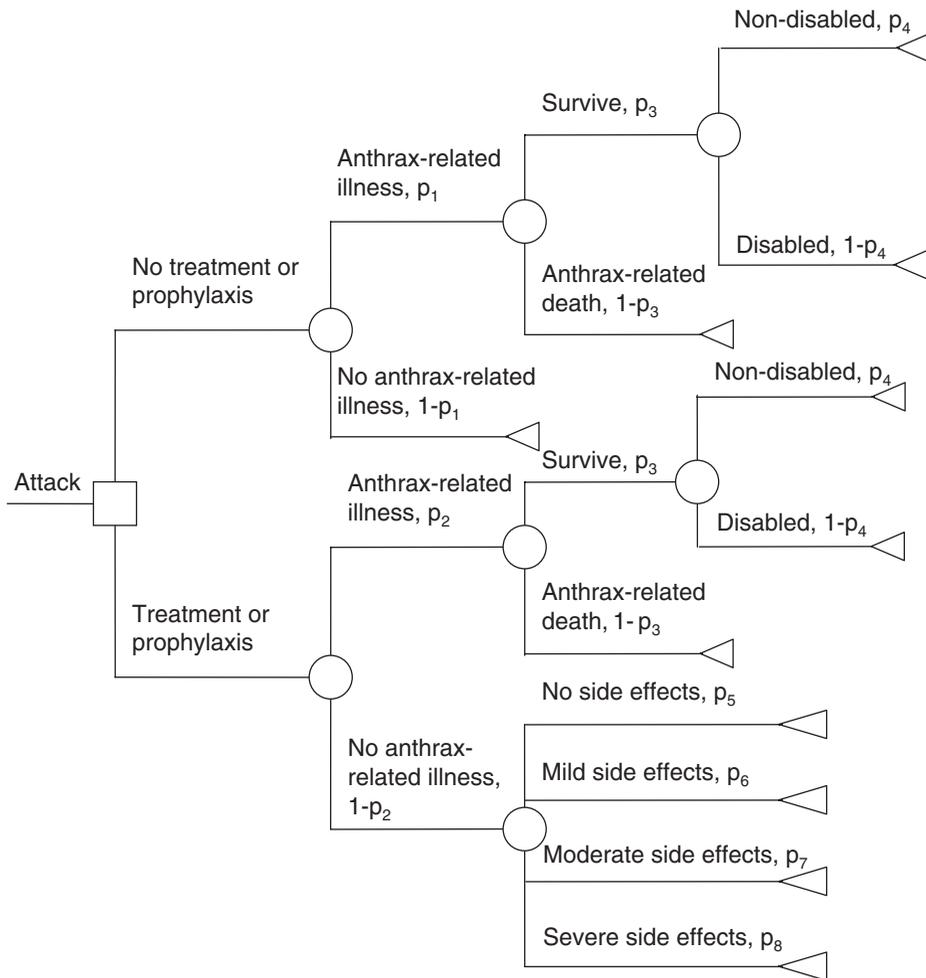
Figure 1. Prophylactic strategies following an anthrax attack.

no action is taken. The switchover point is the point at which the expected values of response and non-response options become equivalent (Eq. (1)). This switchover point is the lowest level of risk at which a response is justified based on benefit–cost considerations.

$$\mathrm{EV(action)} = \mathrm{EV(no\,action)}, \tag{1}$$

where:

$$\mathrm{EV(action\;or\;no\,action)} = \mathrm{cost\;of\;action} + \sum \mathrm{probability} * \mathrm{consequence} \tag{2}$$

A sensitivity analysis is then conducted to identify the impact of uncertainties in model inputs on this switchover point.

Figure 2. Environmental decontamination strategies following an anthrax attack.

Model Parameters

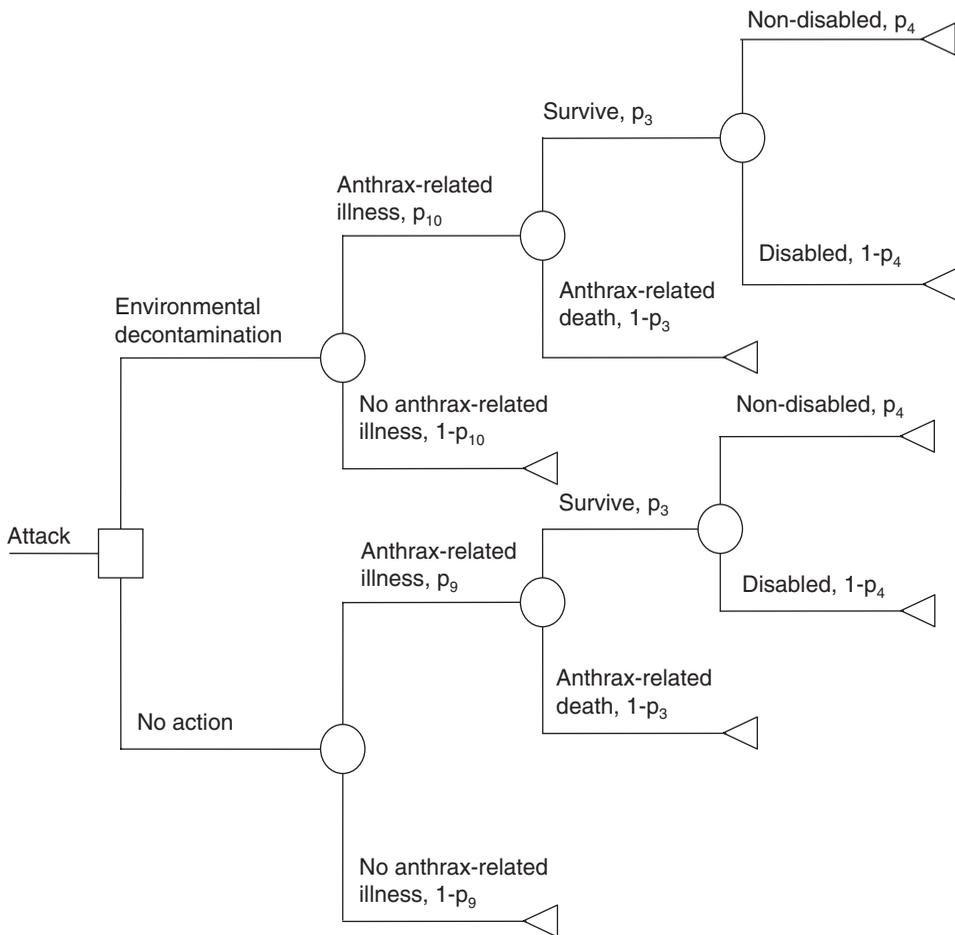A summary of the parameters values used in this model is included in Table 1. Probabilities, costs, and utilities for the baseline cases are consistent with those of Fowler *et al.* (2005). For the baseline analysis the model considers a hypothetical cohort of individuals living and working in a major metropolitan center, like New York City, based on similar assumptions presented by Fowler *et al.* (2005). An average age of 36 and average life expectancy of 76 years were assumed for the baseline analysis.

A 3% annual discount factor is used in the base case scenario calculations and all costs are given in year 2004 dollars. Benefits were calculated using monetized QALYs over the remaining lifespan of the individual. Short-term adjustments in QALY values were made for adverse side effects and affliction with anthrax-related illness. Long-term adjustments were made for people suffering from permanent disability due to anthrax. The probabilities of mortality and disability were generated from the 11 cases resulting from the 2001 anthrax letters (Lustig *et al.* 2001).

Table 1. Baseline model parameters for the cost-effectiveness analysis of response strategies (Fowler *et al.* 2005).

Parameter	Baseline values from Fowler *et al* (2005) unless otherwise noted
Efficacy of Vaccination	**93%** (0%–100%)
Efficacy of Antibiotic	**80%** (0%–100%)
Utility for Severe Inhalational Anthrax	**0.6**
Utility for Population Baseline	**0.92**
Utility for Postanthrax healthy state	**0.9**
Utility for Postanthrax disabled state	**0.8**
Utility for Vaccination Side Effects—Mild	**0.9**
Utility for Vaccination Side Effects—Moderate	**0.8**
Utility for Vaccination Side Effects—Severe	**0.6**
Utility for Antibiotic Side Effects—Mild	**0.9**
Utility for Antibiotic Side Effects—Moderate	**0.8**
Utility for Antibiotic Side Effects—Severe	**0.6**
Cost of Antibiotic	**$22**
Cost of Vaccination	**$64**
Cost of Anthrax Related Illness	**$28,731** ($1,000–$300,000)
Cost of Death	**$6,270**
Cost for Antibiotic Side Effects—Mild	**$10**
Cost for Antibiotic Side Effects—Moderate	**$103**
Cost for Antibiotic Side Effects—Severe	**$2,473**
Cost for Vaccination Side Effects—Mild	**$8**
Cost for Vaccination Side Effects—Moderate	**$18**
Cost for Vaccination Side Effects—Severe	**$2,473**
Cost of Environmental Decontamination per Person	**$16,714** ($10,700–$29,633) (see Table 2)
Length of Mild Antibiotic Side Effects—Days	**60** (7–60)
Length of Moderate Antibiotic Side Effects—Days	**60** (7–60)
Length of Severe Antibiotic Side Effects—Days	**7**
Length of Mild Vaccine Side Effect—Days	**7**
Length of Moderate Vaccine Side Effect—Days	**21** (7–28)
Length of Severe Vaccine Side Effect—Days	**21** (7–28)
Value of a QALY	**$50,000** ($50,000, $298,770) (USEPA 2000))
Discount Interest Rate	**3%** (~0%, 7%) (USEPA 1999)
Remaining Life Years	**40** (3.6–77.8) (U.S. Census Bureau 2009)

Response Strategies

The first response strategy, vaccination, is based on administration of the Anthrax Vaccine Adsorbed (AVA) vaccine, which has been used since 1970 (BioThrax, Bio-Port Corporation, Lansing, Michigan). Full immunity is assumed to be achieved in 93% of individuals in the base case scenario (Fowler *et al.* 2005). The AVA vaccine consists of a "noninfectious sterile filtrate from the culture of an attenuated strain *B. anthracis*, adsorbed to the adjuvant, aluminum hydroxide," which is given in six doses over a period of 18 months (Friedlander *et al.* 1999). The AVA vaccine has been associated with acute reactions including swelling, headache, fever, and chills. The AVA vaccine may also be associated with long-term neurological damage, but these effects were not considered in this analysis (Joellenbeck *et al.* 2002). In this study, side effects were assumed to reduce the value of a quality adjusted life year utility for a period of 7 days for mild and moderate side effects and 21 days for severe side effects.

The antibiotic response strategy is based on the use of doxycycline, which has a lower cost than ciprofloxacinin. The recommended duration of the treatment is 60 days. Full compliance with the regimen is assumed in this model, although studies indicate that adherence is problematic (Shepard *et al.* 2002). Adverse side effects reported with antimicrobial prophylaxis includes gastrointestinal (diarrhea or stomach pain, nausea, or vomiting) and neurologic (headache, dizziness, light-headedness, fainting, and seizures) symptoms primarily. Reduced quality adjusted life year utilities were considered for a period of 60 days for mild and moderate and 7 days for severe side effects.

The third strategy, environmental decontamination, is based on fumigation with a combination of chlorine dioxide and paraformaldehyde. To determine a base case value of the environmental decontamination costs per person, the total expenses reported from two main sources (Canter 2005; Martin 2008) were used to calculate square footage costs based on an assumed ceiling height of 10 feet, except for one building (the AMI building), where an actual square footage of the building was reported (Price *et al.* 2009). The total expenditures reported for the 2001 attacks are associated with five different tasks (some of which extend beyond the volume/areas requiring fumigation). These tasks include pre-environmental decontamination, which involves dry wipe sampling and assessment; post-environmental decontamination repeats sampling following cleanup depending on the effectiveness of the environmental decontamination; disposal of contaminated materials by hazmat teams and offsite treatment of these materials; and physical environmental decontamination, the actual process of fumigating with chlorine dioxide (GAO 2003). We then applied an occupant load factor of 234 ft²/person, which is a mean estimate for government office buildings in Washington, D.C. (Milke and Caro 1997). Upper and lower bounds on each estimate were produced using 5th percentile and 95th percentiles occupant load factors of 214 ft²/person and 254 ft²/person, respectively. The results of this analysis for the different buildings are presented in Table 2. The median value of $16,714 per person was selected for the base case corresponds to the AMI Building decontamination cost.

In order to model the targeted population for this study, a cohort of people working in an office building in a metropolitan area, we used the actual costs reported for decontamination after the 2001 attacks. In reality, postal facilities have

Table 2. Environmental decontamination cost breakdown.

Location	Volume Fumigated (ft³)	Square footage	Height	Cost	Cost/SF	Cost per person*	References
Generic 10 × 10 office space	1000	100	10	$5000	$50.00	$11,700 ($10,700–$12,700)	(Martin 2008)
DOS SA-32	1,400,000	140,000	10	$9,000,000	$64.29	$15,043 ($13,757–$16,329)	(Canter 2005)
AMI Building	670,000	70,000	9.57	$5,000,000	$71.43	$16,714 ($15,286–$18,143)	(Canter 2005; Price et al. 2009)
Brentwood only	14,000,000	1,400,000	10	$130,000,000	$92.86	$21,729 ($19,871–$23,586)	(Canter 2005; Wein et al. 2005)
Trenton only	6,000,000	600,000	10	$70,000,000	$116.67	$27,300 ($24,967–$29,633)	(Canter 2005)
DOJ Mail Room*	8330	833	10	$463,916	$556.92	$130,320 ($119,181–$141,458)	(Canter 2005; Canter et al. 2005)

Calculations based on mean and 95% confidence intervals of occupancy load factors for government buildings (234 sf/person, 214 sf/person-254 sf/person) (Milke and Carol 1997).
*This value represents an extreme case in a much smaller facility and was considered an outlier in this analysis.

much lower occupancy and higher cost per occupant than office buildings. Such buildings would require specific analyses that accounted for the benefit of restoring the use of the specialized capabilities of the facility. Total remediation costs for such buildings (not used in this analysis) include complete renovation, equipment replacement, and enhanced security measures, in some cases. These investments produced benefits beyond protecting the immediately exposed workers, such as protecting the recipients of mail handled by these facilities. Thus, these values are not considered applicable to the office building scenario considered here. Variation in remediation costs is also dependent on the amount of anthrax spores released, as well as the size of the building.

Sensitivity Analyses

One-way sensitivity analyses were conducted for a number of uncertain variables to assess the effect of variation over a range of plausible values for these parameters (indicated in Table 1) on the switchover point (*i.e.*, lowest level of risk at which the benefits of response exceed the costs) for each model. Base case values were taken from Fowler *et al.* (2005). The value of a quality adjusted life year was varied from $50,000 to $298,700. The lower bound/base case value of $50,000 is common in medical cost effectiveness. The upper bound of $298,000 is based on annualizing the estimated value of a statistical life of $6.9 million in year 2004 dollars over 40 years of remaining life expectancy using a 3% discount rate. The discount rate was varied from 0% to 7% to represent the range of values most often presented in the literature. Zero percent is a natural lower bound and 7% is the upper bound for U.S. Environmental Protection Agency (USEPA) benefit–cost analysis (USEPA 1999). Although the model was derived for a hypothetical cohort of office workers with a median age of 36, the number of remaining life years was also varied from 3.6 to 77.8 to consider a range of individuals from elderly to infants. To represent the degree of uncertainty in the length of side effects and the cost of environmental decontamination, ranges given in Table 1 were chosen to assess their affect on the switchover points for each model as well.

RESULTS AND DISCUSSION

Switchover Points

Shown in Figures 3, 4, and 5 are the values of response and no response options as a function of the risk of infection in order to emphasize the switchover between the two alternatives, the point when response becomes unjustified. In all cases the no response action slopes downward sharply with risk (*i.e.,* doing nothing becomes rapidly less favorable as risk increases). This fact is highlighted by Figure 6, which illustrates the net benefits of the no action alternatives over the full range of risk from 0 to 100% probability of infection. A very small range of low probability exists where the no action alternative has positive benefits. The antibiotic prophylaxis option also slopes downward but more gradually. As this option is ineffective in 20% of cases, higher initial infection probabilities lead to greater numbers of individuals who become ill even with treatment (and hence less favorable outcomes). The
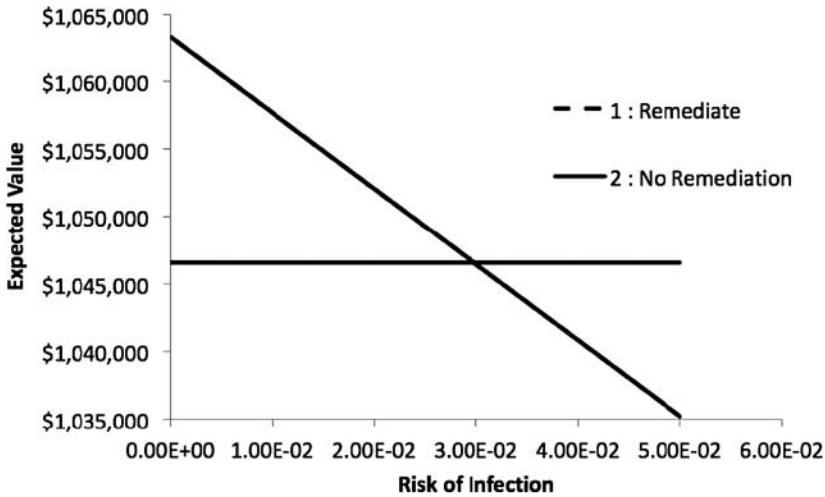
Figure 3. Switchover risk of infection for environmental decontamination combined.

vaccination and remediation options are less dependent on risk. These options are highly effective (decontamination is assumed to achieve 5 log reductions of the risk and vaccination is assumed to be 93% effective). Hence, most of the costs are the fixed costs of the response action, rather than the loss of QALYs caused by illness. In the antibiotic prophylaxis tree, the switchover point is estimated at 1 in 6547 people or when the probability of infection is 0.015% (Figure 5). For risks less than this level the costs and risks of side effects due to treatment are estimated to outweigh the benefits of reducing the risk due to the environmental exposure. In the vaccination
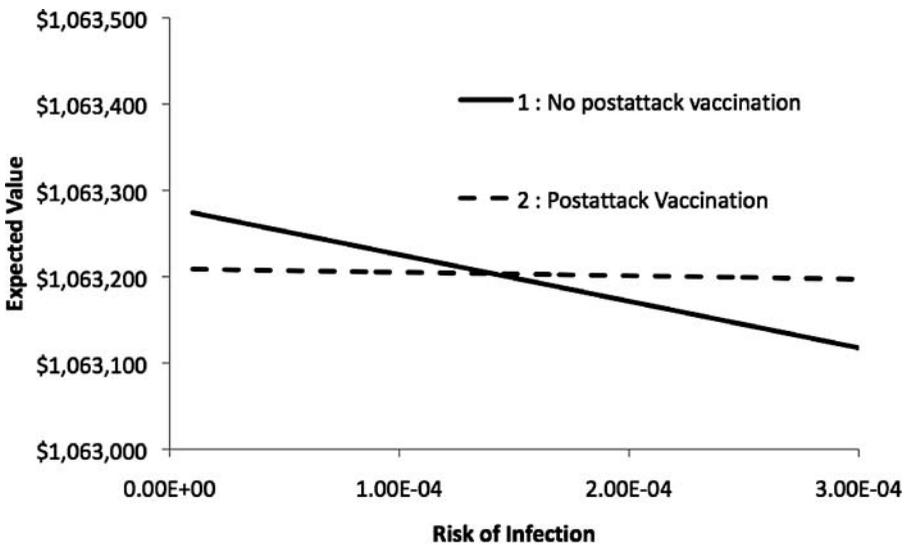

Figure 4. Switchover risk of infection for vaccination.

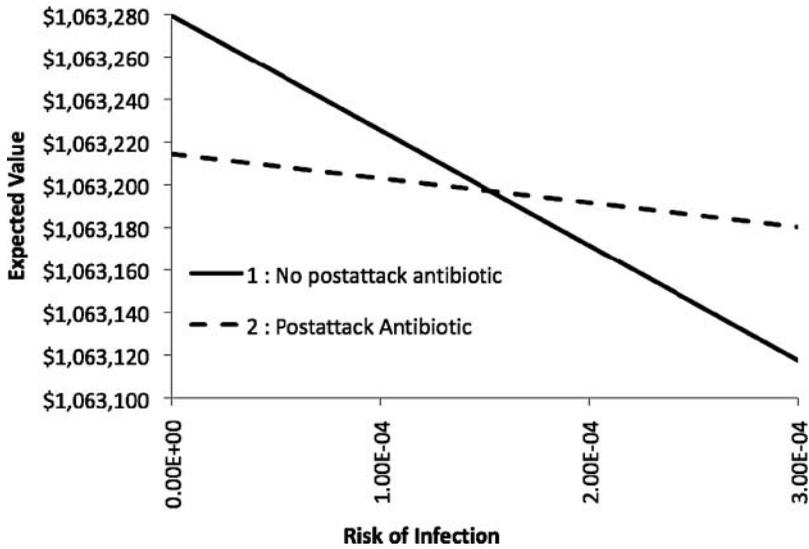**Risk-Based Switchover Points for Response to *B. anthracis***

Figure 5. Switchover risk of infection for antibiotics.

model, the switchover point is identified at 1 in 7108 people or when the probability of infection is 0.014% (Figure 4).

The switchover for environmental decontamination was estimated to be 1 in 32 people or a probability of infection of 2.9% (Figure 3). In other words, the
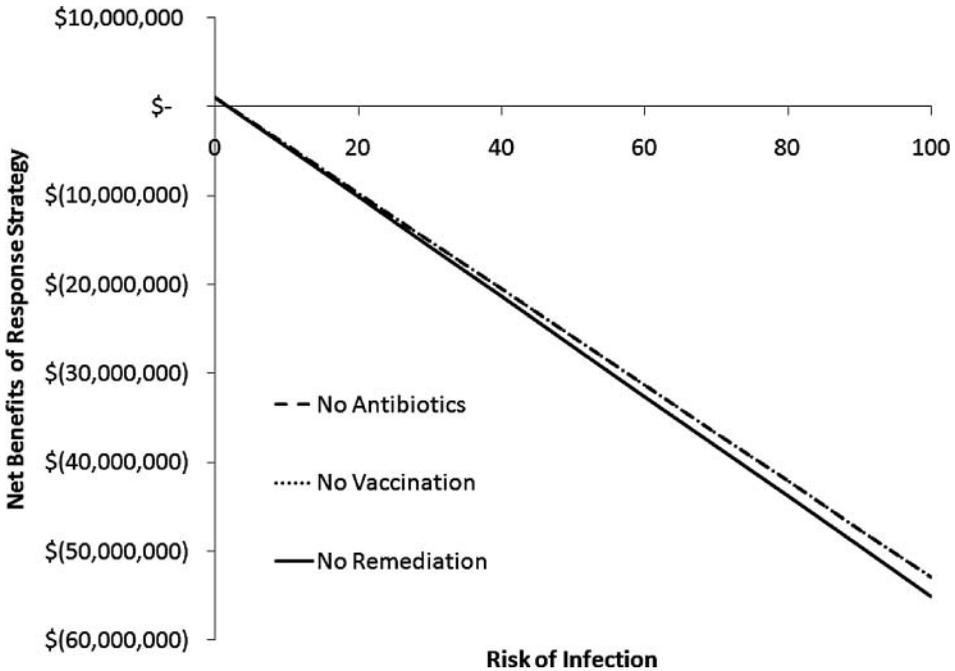

Figure 6. Net benefits of the no action alternative.

model predicts that unless the risk is close to 1 in 32 people, the expenditure of environmental decontamination at the historical costs for fumigation used in this model are not justifiable. This is a very high action level. It may be worthwhile to further explore lower cost remediation techniques and develop action levels for a variety of different approaches, such as HEPA vacuuming, and so on. Even if these alternative remediation techniques are less effective than fumigation, they may be less costly and therefore justifiable at lower risk levels.

A comparison of the action levels for vaccination and environmental decontamination indicates that vaccination is preferred over environmental decontamination for low probabilities of infection (*i.e.*, at risks less than 1 in 32 and greater than 1 in 7108, vaccination would pass a benefit–cost test while remediation would not). This would require restricting building access to vaccinated individuals, which is clearly problematic but not out of the question, particularly as a short term measure in response to an attack.

Combining vaccination with environmental decontamination was not considered quantitatively here. In general multiple responses will be justified at higher levels of risk than single response options (*i.e.*, as carrying out two responses will cost more than a single response). Thus dual response options will not define the lower bound of actionable risk, which is the primary goal of this paper. Nevertheless, such approaches do merit consideration as response options. The inclusion of both vaccination and decontamination in a single decision tree for the re-occupancy decision would not change the switchover point for vaccination (as vaccination would continue to be the sole response for low risks). It would further increase the risk needed to justify fumigation (*i.e.*, as the alternative would not be the risk if no response is taken but the substantially reduced risk of a vaccination only response). Thus a consideration of multiple response options should serve to further highlight the need for less costly decontamination strategies, strategies that are suitable for widespread use and cost-effective even at low risk levels.

Sensitivity Analysis

One-way sensitivity analysis was performed on each model to determine how different input parameters affected the switchover points. Outlined in Table 3 are the upper and lower bounds of the probabilities of infection found by the analysis. Percent change in the switchover level of risk is also presented graphically in Figures 7–9 by rank. These plots indicate the most significant uncertainties as they pertain to the individual models and tell which variables need to be considered more closely. In the antibiotic model, the length of mild and moderate side effects is the most important uncertainty followed by the number of remaining life years and the interest rate. For both the vaccination and decontamination models, the most important uncertainty is the value of the quality adjusted life year. Remaining life years and discount rate rank second in these models as well. The length of mild and moderate side effects is an epistemic uncertainty, for which further research could provide better information. Remaining life years is highly variable (from individual to individual as a function of age), but is subject to little epistemic uncertainty. This implies that actionable levels might be variable for different age groups. The suggestion that older people would tolerate higher risks before taking action could be seen

Table 3. One-way sensitivity analyses.

| Parameter	Base case (Parameter value range)	Probability of infection (1:X = 1 in X number of people)
Antibiotic prophylaxis:		Base Case 1:6547
Value of a QALY	50,000 (50,000–298,770)	1:6547 to 1:9186
Discount Interest Rate	3% (~0%–7%)	1:10,787 to 1:4067
Remaining Life Years	40 (3.6–77.8)	1:1359 to 1:8353
Length of Mild & Moderate Side Effects	60 (7–60)	1:14,274 to 1:6547
Vaccination:		Base Case 1:7108
Value of a QALY	50,000 (50,000–298,770)	1:7108 to 1:28,920
Discount Interest Rate	3% (~0% –7%)	1:11,898 to 1:4327
Remaining Life Years	40 (3.6–77.8)	1:1475 to 1:9068
Length of Moderate & Severe Side Effects	21 (7–28)	1:7509 to 1:6925
Environmental decontamination:		Base Case 1:32
Value of a QALY	50,000 (50,000–298,770)	1:32 to 1:184
Discount Interest Rate	3% (~0%–7%)	1:54 to 1:20
Remaining Life Years	40 (3.6–77.8)	1:7 to 1:41
Cost of Environmental decontamination (2004 $)	16,714 (10,700–29,633)	1:50 to 1:18
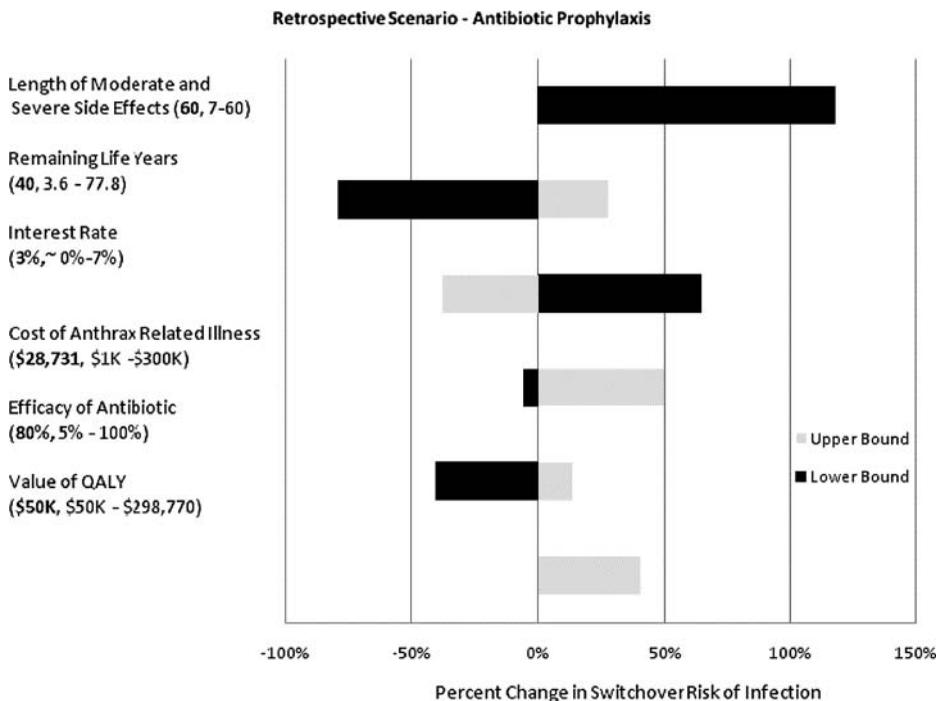
Figure 7. One-way sensitivity analysis on antibiotic model.
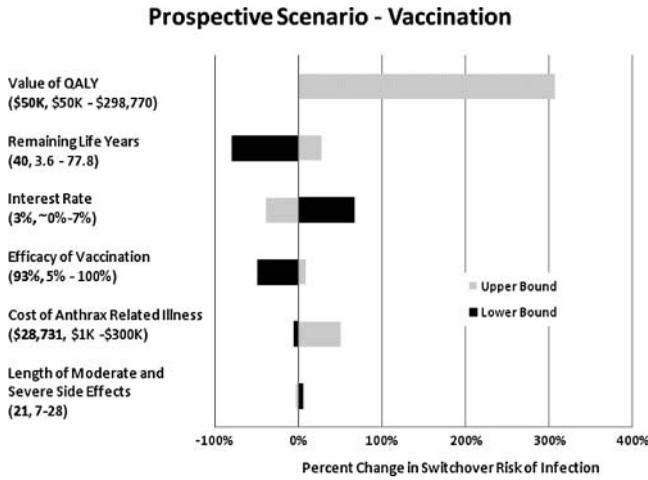
Prospective Scenario - Vaccination

Figure 8. One-way sensitivity analysis on vaccination model.

as highly controversial. It is important to note that these action levels are intended to represent guidance for individuals and would not constitute centrally mandated response decisions. The use of a value of statistical life approach would avoid providing different recommendations for different age groups. However, some individuals might prefer to account realistically for the fact that the duration of time suffering side effects is a larger proportion of remaining lifespan for older individuals (*i.e.*, the quality adjusted life years approach might better account for the preferences of these individuals).

Value of a quality adjusted life year and discount rate are not epistemic uncertainties but value parameters, which reflect the preferences of the decision-maker. They
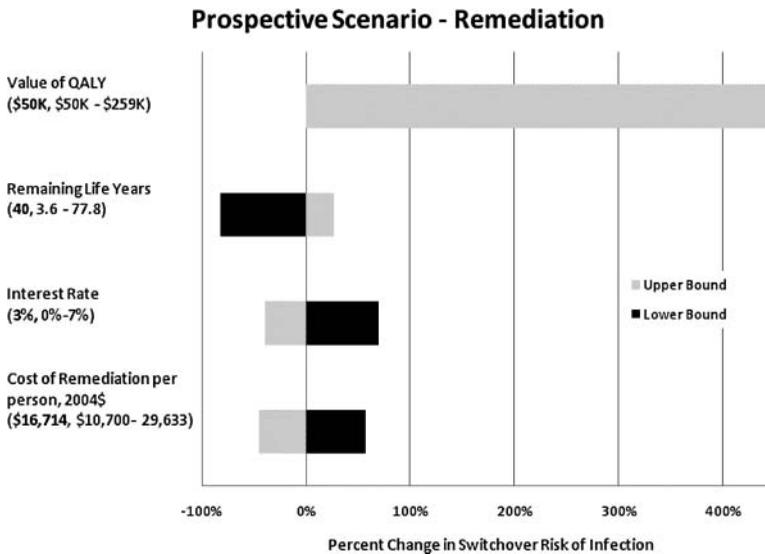
Prospective Scenario - Remediation

Figure 9. One-way sensitivity analysis on remediation model.

should be set to reflect the values of the individuals for which recommendations are being made. A great deal of variability and disagreement exists regarding how to value life and health. Substantial literature exists on this topic (Blomqvist 2002; Dockins *et al.* 2004; Graham and Vaupel 1981; Johansson 2001; Viscusi 2004, 2008). Our sensitivity analysis illustrates that even with the disparities in the assignment of this value; the switchover risk varies by less than a factor of 10 (or a single order of magnitude) from the base case estimate for the vaccination and environmental decontamination models. The maximum variation in risk estimates was produced by the remediation model, but even in this case, the estimate changed by less than a factor of ten. The range of results is much closer for the antibiotic decision. While an order of magnitude would appear to be a very substantial uncertainty, previous research suggests that it may not be overwhelming. A study by Graham and Vaupel (1981) found that for the 57 life saving policies evaluated, the specific value of a life used in a benefit–cost analysis had not altered the policy implications of the study in approximately four-fifths or five-sixths of the cases despite the considerable range of values chosen. Furthermore, this finding was consistent with a previous statement by Zeckhauser (1975, p. 436) "In many circumstances policy choices may not change substantially if estimates of the value of life vary by a factor of ten."

In the event of a release environmental dispersion would produce exposures ranging over many orders of magnitude. Given this huge range of exposures, having even a rough estimate of actionable risk levels may allow many individuals to be identified as having exposures well below actionable levels and many individuals to be identified as having exposures well above actionable.

Huang *et al.* (2010) presents an analysis for the pathogen *Yersinia pestis*. The action risk level established by their decision model was 1.5×10^{-4}, based on the switchover point between the decisions to apply a first line antibiotic immediately as post-exposure prophylaxis or wait until symptoms are manifest. At the point when symptoms have manifested one would apply a second line antibiotic are estimated to be sufficient to justify treatment. When the Huang *et al.* result is compared to those presented in this analysis, we find that for the antibiotic model a very similar result is obtained.

CONCLUSIONS

Switchover points were identified for the three decision models—providing antibiotics, vaccination, or remediating a contaminated facility. In each case, the decision was evaluated against a no action alternative in order to establish a threshold at which action is warranted. The switchover risk can be associated with a dose of spores using a dose–response function, which correlates the risk of infection or death associated with a specific dose of spores (Bartrand *et al.* 2008). An environmental concentration can then be associated with this dose using a fate-and-transport model (Hong 2009). The switchover establishes a risk threshold above which action is warranted. If a measured environmental concentration is less than the number of spores that warrants action, then treatment may not be required. Non-zero cleanup levels are possible based on the actionable risk level. These action levels can be offered as guidance to individuals and building owners facing difficult decisions after

a bioterrorism incident. However, this type of approach may not be appropriate for all decision-makers due to the amount of assumptions and numerical values placed on non-market goods. Exceedance of these values should clearly not be considered mandatory for an exposed individual or building owner to take action. These risk-informed action levels may be useful as recommendations or guidance values and may even help to establish minimum standards for response (*i.e.*, individuals would remain free to address lower risks but would be encouraged to address risks over particular action levels).

We found that the resulting risk thresholds established by the retrospective and prospective strategies, providing antibiotics or vaccination, differed only subtlety. This result could have been expected because the specific properties of the treatments—efficacy, probability of side effects, costs, and costs of side effect treatment—vary within a small range and are of the same scale. However, when we considered fumigation as a strategy, the cost per person differs by at least two orders of magnitude.

Overall, the results of the model are clearly sensitive to many factors including the value of a QALY and the discount rate, which are dictated by the decision-maker or agency. Scenario-specific parameters can be adjusted appropriately for a given situation on a case by case basis. For instance, decisions regarding a school for young children may be different than decisions regarding an office building.

A few limitations should be mentioned:

- The probabilities of mortality and disability were generated by a small pool of data (11 cases from year 2001) (Lustig *et al.* 2001; Reissman *et al.* 2004).
- The model assumes prompt identification and dissemination of medical countermeasures in the retrospective case.
- The model assumes adherence to the prescribed prophylactic treatment regimen, while 100% compliance was not observed in 2001.
- The cost to remediate a building is based on historical data and likely will become less expensive with emerging technologies. At the cost per unit area used in these calculations, one might consider demolition and reconstruction as an alternative. However, this strategy has the environmental consequences of potentially producing bio-aerosols and a large quantity of solid waste that must be treated as hazardous. Alternative strategies, such as the HEPA filter approach (Wein *et al.* 2005), which is less effective and expensive, may therefore have a role to play.
- The analysis did not address intangible social, physical and economic factors and other direct societal costs, which may be relevant (Burns and Slovic 2007; Kaufmann *et al.* 1997). This article acknowledges the complexities associated with predicting the costs of closing a business or several businesses or even a section of a city for a long period of time after an anthrax release. Not only are direct business interruption costs expected but also indirect costs due to disruption of extended linkages to the region (Rose 2009).

It should also be noted that our calculations are based on the AVA vaccine, which has many side effects. As a result, several companies in the past 5 years have publicly announced initiatives to fund the discovery and development of new treatments

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against anthrax-related illness. Development of a vaccine that is immunogenic, unlike the current vaccine and has reduced side effects in addition to protecting both pre- and post-exposure to anthrax has shown promise (Grabenstein 2008; Weiss *et al.* 2007).

A framework is presented herein to provide a risk-based approach that speaks directly to the question "How clean is clean?" Even with the limitations of this model, the fact that the U.S. government spent hundreds of millions of dollars and 3 years to decontaminate a handful of buildings should warrant a closer look at how these decisions are made. The similarities found between our results for medical treatment and the Huang *et al.* (2010) result might suggest that further analyses should be conducted to determine if risks on the order of 10^{-4} generally represent the point at which medical responses to microbial risk become justified.

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