Cost-Effectiveness of Defending against Bioterrorism: A Comparison of Vaccination and Antibiotic Prophylaxis against Anthrax

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Background: **Weaponized *Bacillus anthracis* is one of the few biological agents that can cause death and disease in sufficient numbers to devastate an urban setting.**

Objective: **To evaluate the cost-effectiveness of strategies for prophylaxis and treatment of an aerosolized *B. anthracis* bioterror attack.**

Design: **Decision analytic model.**

Data Sources: **We derived probabilities of anthrax exposure, vaccine and treatment characteristics, and their costs and associated clinical outcomes from the medical literature and bioterrorism-preparedness experts.**

Target Population: **Persons living and working in a large metropolitan U.S. city.**

Time Horizon: **Patient lifetime.**

Perspective: **Societal.**

Intervention: **We evaluated 4 postattack strategies: no prophylaxis, vaccination alone, antibiotic prophylaxis alone, or vaccination and antibiotic prophylaxis, as well as preattack vaccination versus no vaccination.**

Outcome Measures: **Costs, quality-adjusted life-years, life-years, and incremental cost-effectiveness.**

Results of Base-Case Analysis: **If an aerosolized *B. anthracis* bioweapon attack occurs, postexposure prophylactic vaccination and antibiotic therapy for those potentially exposed is the most effective (0.33 life-year gained per person) and least costly ($355 saved per person) strategy, as compared with vaccination alone. At low baseline probabilities of attack and exposure, mass previous vaccination of a metropolitan population is more costly ($815 million for a city of 5 million people) and not more effective than no vaccination.**

Results of Sensitivity Analysis: **If prophylactic antibiotics cannot be promptly distributed after exposure, previous vaccination may become cost-effective.**

Limitations: **The probability of exposure and disease critically depends on the probability and mechanism of bioweapon release.**

Conclusions: **In the event of an aerosolized *B. anthracis* bioweapon attack over an unvaccinated metropolitan U.S. population, postattack prophylactic vaccination and antibiotic therapy is the most effective and least expensive strategy.**

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Anthrax is one of the few biological agents identified by the U.S. Working Group on Civilian Biodefense and the Centers for Diseases Control and Prevention (CDC) as being capable of causing death and disease in sufficient numbers to cripple a developed region or urban setting (1, 2). Research into the use of *Bacillus anthracis* as a bioweapon is at least 80 years old, and several nations are believed to have weaponized anthrax (3). The 1979 accidental release of aerosolized anthrax spores from a military microbiology facility in Sverdlovsk, of the former Soviet Union, caused at least 68 deaths and demonstrated the lethal potential of aerosolized *B. anthracis* (4). A World Health Organization report estimated that aircraft release of 50 kg of *B. anthracis* over a city of 5 million would result in 250 000 deaths, 100 000 of whom would likely die before receiving treatment (5). The U.S. Congressional Office of Technology Assessment estimated that between 130 000 and 3 million deaths would follow the release of 100 kg of *B. anthracis* spores upwind of Washington, DC, matching the lethality of a hydrogen bomb (6). More recently, the Aum Shinrikyo terrorist group is believed to have ineffectively released aerosolized *B. anthracis* in Tokyo (7).

In September 2001, the first of 22 cases of bioterrorism-related anthrax were identified in the United States (8). Five people died and 11 cases of inhalational anthrax and 11 cases of cutaneous anthrax occurred (8). More than 10 000 persons potentially exposed to anthrax in Connecticut; Florida; New Jersey; New York City; and Washington, DC, were recommended to take postexposure antibiotic prophylaxis (9). If inhalational anthrax is untreated, the mortality approaches 100%, and the costs associated with a real or perceived *B. anthracis* bioterror attack have been estimated at more than $26 billion per 100 000 persons exposed (10–12).

The U.S. Department of Defense previously directed that all military services begin an anthrax vaccination pro-

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Context

The best strategies for preventing infection in the event of bioterrorism with aerosolized *Bacillus anthracis* are unknown. Given the paucity of data, the development of strategies must rely heavily on hypothetical models.

Contribution

This decision model evaluated postattack strategies (no prophylaxis, vaccination alone, antibiotic prophylaxis alone, or both plus preattack vaccination) and identified postexposure vaccination and antibiotics as the most effective and least expensive strategy. Mass preattack vaccination did not seem cost-effective.

Cautions

The model is based on many assumptions, and the results depend heavily on probabilities that are difficult to estimate, such as the probability of an attack.

–The Editors

gram (13). Live attenuated endospore–based vaccines were widely used in the former Soviet Union for both humans and livestock and remain in use in the Russian Federation (14). In 1970, the U.S. Food and Drug Administration licensed the anthrax vaccine adsorbed (BioThrax, BioPort Corporation, Lansing, Michigan) for human use (15). The U.S. military has now given more than 2 million anthrax vaccinations to more than 500 000 personnel since beginning the program, and an active system of reporting side effects and complications has accompanied this program (16). Although the U.S. military has determined that its troops have sufficient risk for exposure to warrant the costs and side effects associated with vaccination, the optimal strategies of prophylaxis and treatment against a potential bioterror attack for civilian U.S. populations are highly controversial.

We aimed to evaluate the cost-effectiveness of anthrax prevention and treatment strategies for urban centers at risk for bioterror attacks. We simulated a large-scale aerosolized release of *B. anthracis* over a U.S. metropolitan area. This method may incur rapid and wide-reaching exposure and, accordingly, a large burden on the health care system. We evaluated the cost-effectiveness of postattack strategies of antibiotic prophylaxis or vaccination, alone or in combination, and we assessed how high the probability of attack must be for preattack vaccination strategies to be cost-effective.

METHODS

Decision Model

We developed a decision analytic model to compare outcomes of pre- and postattack anthrax prevention and treatment strategies for urban centers at risk for a large-scale bioterror attack of similar or greater potential magnitude than that experienced through the U.S. mail. Following the recommendations of the Panel on Cost-Effectiveness in Health and Medicine, we adopted a societal perspective for costs and benefits, discounted at 3% annually (17). We used a decision model to capture the costs and benefits of the different strategies immediately after an attack and for the remaining expected lifespan of an individual within the cohort (**Figure 1**). We developed the simulation models and performed analyses by using DATA Pro (TreeAge Software, Inc., Williamstown, Massachusetts) and Excel 2000 (Microsoft, Inc., Redmond, Washington).

Strategies

We compared the costs, harms, and benefits of 4 postattack strategies (no vaccination, vaccination alone, antibiotic prophylaxis alone, or vaccination plus antibiotic prophylaxis) and 2 preattack strategies (vaccination vs. no vaccination). We performed sensitivity analyses on key model variables.

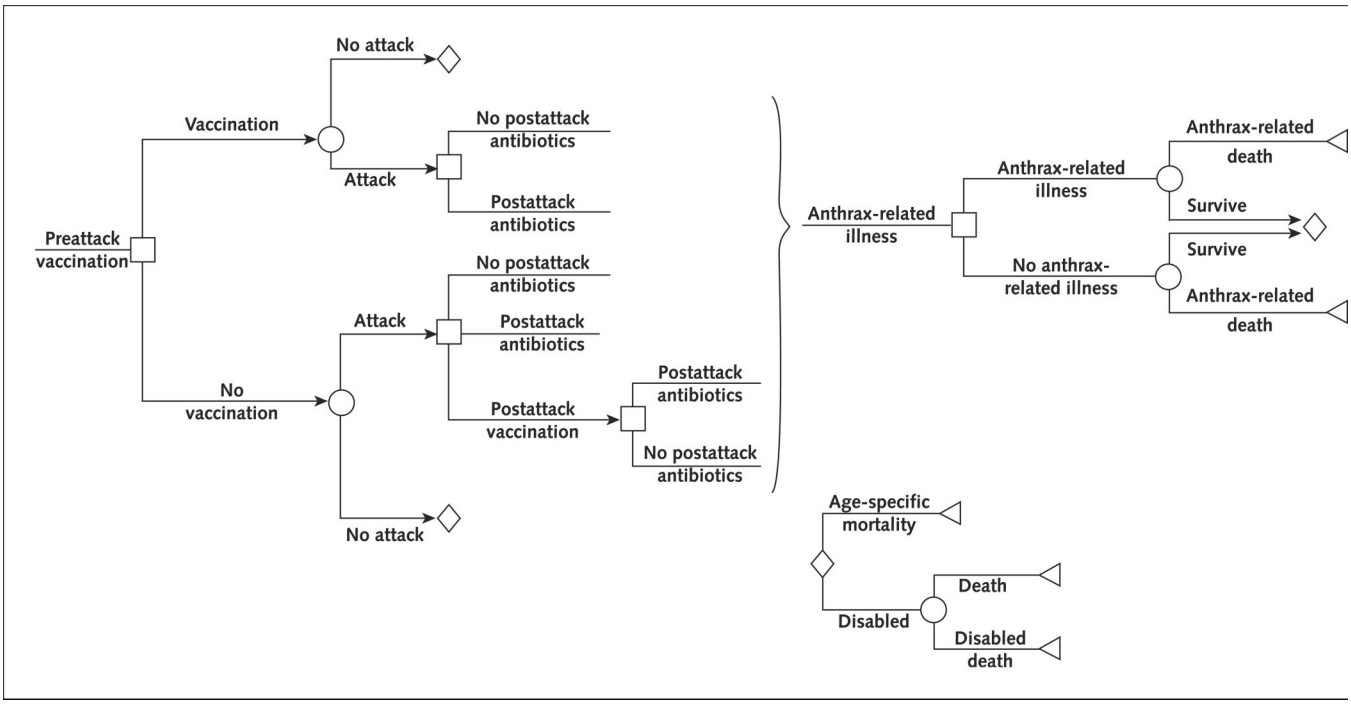
Base-Case Assumptions

Our model followed a hypothetical cohort of persons residing or working in a large metropolitan U.S. city with a sex distribution (53% women), mean age (36 years), and age-specific life expectancy similar to those of New York City (18, 19). We assumed a mean influx of new residents through immigration and birth of less than 5% of the total population per year (18, 20, 21). **Table 1** summarizes our other model inputs (1, 5, 6, 8, 10–12, 16, 22–53).

Probabilities of Attack and Exposure

Despite the widespread discussion of *B. anthracis* as an important potential agent of bioterror attacks (1), there are no well-established estimates of the probability of an attack on any U.S. metropolitan area or the probability of exposure for given types of attacks. To the extent possible, we chose estimates derived from reviews of the literature and, when necessary, opinion of experts in public health and bioterrorism-preparedness planning. To illustrate the cost-effectiveness of alternative strategies for a city that is judged to be at relatively low but non-negligible risk, we assumed a 1% per year baseline probability of attack and varied this probability over a wide range in sensitivity analyses (1, 4, 10, 23). Although anthrax bioterror attacks have already occurred in the United States, the risk for a large-scale aerosolized release may be much lower or may vary substantially among metropolitan areas. The probability that a person is exposed, given that an attack occurs, may also vary widely. Recent modeling of an urban airborne anthrax attack, accounting for population density, size and height of release, and downwind and crosswind dispersion, estimated that 13% of a metropolitan population could be infected (23). In our base-case scenario, we assumed that 10% of the population would have sufficient exposure to *B. anthracis* spores to cause clinical disease. Because exposure rates would probably vary substantially on the basis of the type of attack and local environmental factors, we var-

Figure 1. **Decision model for prophylactic vaccination and antibiotic strategies before and after a hypothetical anthrax bioterror attack.**



Circles represent chance nodes, and squares represent decision nodes. Patients who have no exposure to *Bacillus anthracis* or who survive acute infection enter a process (represented by the diamond) that models pathway-specific annual probabilities of death and health, costs, and utilities for those who are healthy or disabled.

ied this probability widely in sensitivity analyses (1, 4, 10, 11, 23).

Probabilities of Health Outcomes

We estimated the probabilities of anthrax-related morbidity and mortality from the published literature on the untreated and treated morbidity and mortality of inhalational and clinical anthrax in humans, nonhuman primates, animal models, and the recent anthrax bioterrorism experience (1, 8, 11, 22, 24, 30) (**Table 1**). We estimated the probability of surviving clinical anthrax from reports of the recent U.S. anthrax cases (30, 32) and clinical outcomes of similar disease states (31, 54, 55). Without prophylaxis, clinical disease given a sufficient spore inhalation is nearly uniform, and the mortality from inhalational anthrax approaches 100%. We therefore assumed that 95% of individuals who had sufficient exposure during an attack would develop severe inhalational anthrax without prophylaxis or vaccination (**Table 1**) (1, 8, 11, 22, 24). With postattack treatment, the case-fatality rate of the inhalational anthrax contracted through letter contamination in 2001 was 45% (**Table 1**) (1, 22, 25, 30). Pre- and postattack antibiotic and vaccination strategies further attenuate this risk (23). Appropriate prophylactic antibiotics may prevent disease in more than 80% of patients, depending on individual adherence; thus, 20% of people may still develop disease in this case (**Table 1**) (1, 8, 22, 25). Where the probabilities for clinical morbidity and mortality were more uncertain (for example, for probabilities associated with the combination of vaccination and antibiotic prophylaxis), we consulted experts in the fields of public health and bioterrorism preparedness (**Table 1**). We derived the age-specific life expectancy in the absence of a bioterror attack from the U.S. Life Tables (51).

Vaccine Efficacy and Side Effects

The efficacy of the currently available anthrax vaccine depends on the number of boosters that a person has received and the time since receiving them (11, 26, 27, 56, 57). The primary vaccine series includes 6 subcutaneous inoculations at 0, 2, and 4 weeks and at 6, 12, and 18 months (11). Boosters can be given annually, although protection after the primary series may remain for many years (26, 27). The anthrax vaccine has been 93% to 100% effective against aerosolized *B. anthracis* in some human and animal studies (26, 27). In the base-case analysis, we assumed 93% vaccine effectiveness for full adherence with a 6-dose vaccination schedule administered before an attack (**Table 1**). Nearly complete protection has been demonstrated in primates after the first 3 doses (1), and antibody titers among vaccinated persons peak at 14 days after the third dose (58). The Advisory Committee on Immunization Practices endorses making the anthrax vaccine available in a 3-dose regimen (0, 2, and 4 weeks), in combination with antibiotic therapy for postexposure prophylaxis (58). However, immediately after a bioterror attack,

Table 1. **Probabilities, Utilities, and Costs**

Variable	Base Case (Range)	References
Probabilities		
Clinical inhalational anthrax after attack and exposure		
No vaccination, no antibiotics	0.95 (0.5–1.0)	1, 8, 11, 22, 24
No vaccination, receive antibiotics	0.2 (0.1–0.5)	1, 8, 22, 25
Vaccination, no antibiotics	0.07 (0.0–0.5)	8, 26–29
Vaccination, receive antibiotics	0.02 (0.0–0.2)	1, 22, 24–28
Baseline mortality given clinical disease	0.45	1, 22, 25, 30
Nondisabled state if survive clinical illness	0.85 (0.6–1.0)	8, 30, 31
Bacillus anthracis bioterror attack (base case, per y)	0.01 (0.0–1.0)	1, 4, 10
Exposure, given attack	0.10 (0.0–1.0)	1, 4–6, 10
Antibiotic side effects		
Mild	0.19 (0.1–0.4)	8, 16, 32–34
Moderate	0.01 (0.01–0.1)	8, 16, 32–34
Severe	0.0001 (0.0–0.001)	8, 16, 32–34
Vaccine side effects		
Mild	0.04 (0.01–0.05)	1, 25–29
Moderate	0.01 (0.01–0.1)	1, 25–29
Severe	0.0001 (0.0–0.001)	1, 25–29
Utilities		
Population baseline	0.92 (0.9–1.0)	35–37
Antibiotic treatment	0.90 (0.7–1.0)	35–37
Antibiotic side effects		
Mild	0.9 (0.8–0.92)	32–37
Moderate	0.8 (0.6–0.9)	32–37
Severe	0.6 (0.4–0.8)	32–37
Vaccination side effects		
Mild	0.9 (0.8–0.92)	27, 29, 35–37
Moderate	0.8 (0.6–0.9)	27, 29, 35–37
Severe	0.6 (0.4–0.8)	27, 29, 35–37
Severe inhalational anthrax	0.64 (0.5–0.8)	30, 35–37
Postanthrax healthy state	0.9 (0.7–1.0)	30, 35–38
Postanthrax disabled state	0.8 (0.6–0.9)	30, 35–38
Death	0	35, 37
Costs, $		
Vaccination- or booster-related costs		
Vaccine costs (6 doses)	18 (1–600)	39
Vaccine administration	46 (0–200)	40–43
Vaccination side effects costs		
Mild side effects	8 (0–30)	44
Moderate side effects	18 (0–50)	44
Severe side effects	2473 (1000–3000)	44, 45
Disease or treatment side effect–related and loss of work costs (per h)	25 (0–300)	46, 47
Antibiotic and administration costs (adult dosing)		
Doxycycline, 100 mg, orally twice daily	0.10 for 100 mg; 12.00 for 60 d	1, 8, 11, 22, 33, 44
Doxycycline, 100 mg, intravenously twice daily	4.50 for 100 mg; 540.00 for 60 d	1, 8, 11, 22, 33, 44
Amoxicillin, 500 mg, orally twice daily	0.58 for 500 mg; 104.40 for 60 d	1, 8, 11, 22, 33, 44
Penicillin G, 24 million U, intravenously daily	11.32 for 10 million U; 1630.08 for 60 d	1, 8, 11, 22, 33, 44
Ciprofloxacin, 500 mg, orally twice daily	5.47 for 500 mg; 656.40 for 60 d	1, 8, 11, 22, 33, 44
Ciprofloxacin, 400 mg, intravenously twice daily	30.00 for 400 mg; 3600.00 for 60 d	1, 8, 11, 22, 33, 44
Pharmacy dispensing costs	10 (0–20)	48
Antibiotic side effects cost		
Mild side effects	10 (0–100)	44
Moderate side effects	103 (0–200)	44
Severe side effects	2473 (1000–3000)	44, 45
Outpatient physician follow-up	123 (0–600)	43, 47, 49
Inpatient costs		
Moderate inhalational anthrax estimated cost of care	5361 (±25%)	12, 31, 45, 50
Severe inhalational anthrax estimated inpatient cost of care	28 731 (±25%)	12, 31, 45, 50, 53
Age-specific medical care	*(±25%)	19, 46, 51
Death from any cause	6270 (4703–7838)	52

* Adjusted age-specific health care costs.

immunity would initially be incomplete. We estimated that postattack vaccination would be half as effective as immunity provided by the complete vaccination series. This estimate corresponds to the observed survival reduction in animal models given a single inoculation before aerosolized exposure of *B. anthracis* (59).

In a recent comprehensive evaluation of the vaccine's safety and efficacy, the Institute of Medicine found no evidence of adverse long-term health effects (28). However, the literature is inconsistent with respect to the types and severity of potential reactions (16, 26, 28, 29, 60, 61). In a study of military recruits and individuals with occupational exposure to anthrax, the vaccine caused mild local reactions (for example, erythema) in up to 4% of recipients and systemic reactions (for example, malaise and fevers) in less than 0.2% of recipients (26, 29, 60). One study found that serious events possibly related to the vaccine that required hospitalization have been reported in fewer than 0.002% of recipients (61). The vaccine seems safe for pregnant women, and no evidence suggests that the safety and efficacy profile differs in children (16). On the basis of the available evidence, we assumed that 4% of recipients may have minor vaccine-related side effects and that less than 1% may experience moderate or severe side effects (**Table 1**).

Antibiotic Prophylaxis and Treatment

The CDC recommends empirical prophylaxis against all asymptomatic patients (including children and pregnant women) with suspected exposure to *B. anthracis* spores, with 60 days of oral doxycycline or ciprofloxacin (22). Because of the potential association of fluoroquinolones with arthropathy in children, therapy may subsequently be changed to amoxicillin if an isolated *B. anthracis* strain proves susceptible (22). A postexposure treatment course might be shortened to 30 to 45 days if 3 rounds of vaccination were a component of the postexposure therapy (25, 58). Treatment for inhalational anthrax consists of intravenous ciprofloxacin or doxycycline, in combination with 1 or 2 additional appropriate antimicrobial drugs, with subsequent step-down therapy, depending on clinical response and strain susceptibilities, to complete a 60-day course (22). We assumed the initial mass antibiotic prophylaxis would be performed by using the least expensive appropriate oral antibiotic. Choices for individual patients may vary depending on age, allergy, and comorbid conditions; regional supply and recommendations; and nature of suspected strain of *B. anthracis*. We examined the effects of varying antibiotic choices and costs within the model and through sensitivity analyses.

For our initial analyses, we assumed rapid distribution and dispensing of postattack therapy, previously shown essential in limiting morbidity and mortality after an anthrax bioterror attack (23). However, recognizing that logistic distribution problems may occur in the aftermath of a bioterror attack, we explored how delays in distribution and dispensing influence the benefits and costs of alternative strategies.

Cost Estimates

Medical cost estimates in the model include costs associated with prophylactic vaccination and antibiotic therapy, inpatient and outpatient medical care, potential lost earnings, death costs, and age-specific medical costs (**Table 1**). We converted all costs to 2004 U.S. dollars by using the gross domestic product deflator (62).

The vaccine costs approximately $18 for a complete immunization series ($3 per dose) (39). The cost of administering the vaccine series is higher if the vaccine is given by individual clinicians rather than as part of mass public vaccinations. For the base-case analysis, we use estimates from mass vaccination programs (**Table 1**) (40–43, 63). We estimated expenditures for adverse reactions on the basis of estimated outpatient and inpatient costs, medication costs, and loss of work costs associated with commonly reported adverse reactions (12, 44, 45). We estimated inpatient medical costs from a review of the published records of hospital stays and care for patients with cutaneous and inhalational anthrax in the United States in 2002 (30) and from comparison of the costs of care for similar disease states, derived from the Centers for Medicare & Medicaid Services Provider Specific File (8, 12, 31, 43, 45, 50, 53). We estimated future health care costs for patients who survive the initial anthrax illness by using adjusted, age-specific medical expenditure data from the 1998 Statistical Abstract of the United States (46, 51).

Quality-of-Life Adjustments

We adjusted life expectancy for quality of life by using health state utilities (**Table 1**) (35, 36). We calculated quality-adjusted life-years (QALYs) by applying utility weights to each year of life to reflect quality of life. We derived baseline utilities and antibiotic- or vaccination-associated utilities from known and validated utilities for similar health states (36, 37). We adapted utilities for clinical anthrax from similar disease states, such as acute severe contagious illness that requires hospitalization and respiratory isolation (37) (**Table 1**). We adjusted utilities during the acute and convalescent period to account for the differences in severity and duration of illness and used knowledge of 1-year health assessment of adult survivors of *B. anthracis* infection (38) (**Table 1**).

Sensitivity Analyses

We assessed the effects of uncertainty in key variables by performing 1-way sensitivity analyses over plausible ranges. We selected pairs of variables that were influential and correlated for multiway sensitivity analyses. We performed Monte Carlo analyses to vary parameters simultaneously over a specified probability distribution. We assumed normal or log-normal distributions for cost inputs and normal or logistic distributions for probabilities and health state utilities, as appropriate (64). We assigned variables without a definite distribution as the normal distribution. We performed 10 000 simulations to calculate approximate CIs for the primary results.

Role of the Funding Sources

The authors were funded by the University of Toronto and Sunnybrook and Women's College Health Sciences Centre, The Laughlin Fund, and the Agency for Healthcare Research and Quality. The funding sources had no

Table 2. **Lifetime Costs and Effectiveness of Vaccination and Antibiotic Strategies against an Aerosolized *Bacillus anthracis* Bioterror Attack for Individuals of Urban Areas***

Variable	Costs, *$*	Effects, *QALYs*	Effects, *life-years*
Postattack strategies			
No vaccination or antibiotics	46 958	20.61	22.40
Vaccination alone	46 434	21.05	22.89
Antibiotic prophylaxis alone	46 102	21.24	23.09
Both vaccination and antibiotic prophylaxis†	46 099	21.36	23.23
Preattack strategies			
No vaccination‡	45 579	21.51	23.39
Vaccination	45 742	21.50	23.38

* QALYs = quality-adjusted life-years.
† Dominant postattack strategy.
‡ Dominant preattack strategy.

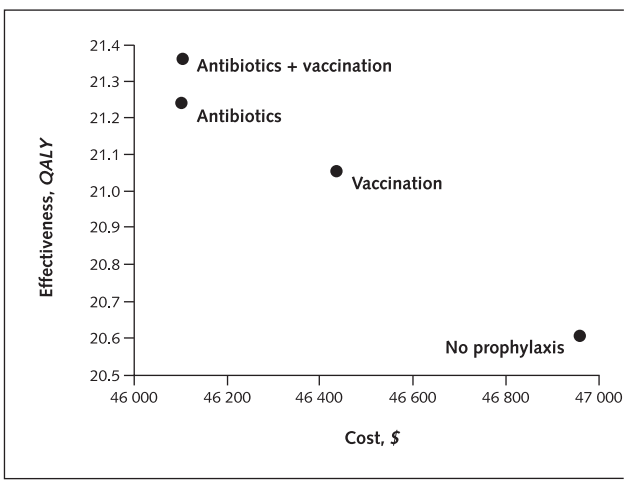
role in its design, conduct, or reporting or in the decision to submit the manuscript for publication.

RESULTS

Postattack Vaccination and Antibiotic Prophylaxis Strategies

Table 2 and **Figure 2** present the results of our 4 postattack strategies: no prophylaxis, antibiotic prophylaxis alone, vaccination alone, and both antibiotics and vaccination. Use of vaccine plus antibiotic prophylaxis was the most effective strategy and had lower costs than other strategies. This combination strategy was less expensive because it prevented more cases of inhalational anthrax and more deaths than the individual strategies and resulted in a gain of 0.33 life-year and cost saving of $355 per person as compared with vaccination alone. No prophylaxis was the least effective and most expensive strategy. Costs were higher without vaccination or antibiotic prophylaxis because of the high cost of treating inhalational anthrax. Postattack vaccination alone was less effective than antibiotic prophylaxis alone (**Table 2**, **Figure 2**).

Figure 2. **Cost-effectiveness of prophylactic vaccination and antibiotic strategies after a *Bacillus anthracis* bioterror attack.**



QALY = quality-adjusted life-year.

Sensitivity Analyses

The efficacy of vaccination after a bioterror attack may vary depending on the timing of vaccination and the strain of anthrax. However, even when vaccination added only marginally increased effectiveness to antibiotic therapy (for example, vaccine efficacy < 10%), a combination of vaccination and antibiotic therapy remained the most effective and least expensive strategy. The additional effects gained through vaccination when an attack has occurred (even at low vaccine efficacy) outweighed any effects lost through vaccine-associated side effects.

We assessed the sensitivity of the model to estimates of the cost of antibiotic and vaccination therapies. Assuming similar efficacy among recommended antimicrobial drugs (**Table 1**), the least expensive medication (doxycycline) was always the dominant treatment strategy. However, when we varied the drug cost between the least and most expensive antibiotic considered (ciprofloxacin), the incremental cost-effectiveness of strategies containing antibiotic prophylaxis remained less than $20 000 per QALY, compared with a strategy of vaccination alone. Even if the cost of the vaccine increased from the base-case estimate of $3 per dose to $150 per dose, the strategy of vaccination plus antibiotic prophylaxis remained the most effective strategy and cost $7000 per QALY gained as compared with antibiotics alone, if an attack did occur.

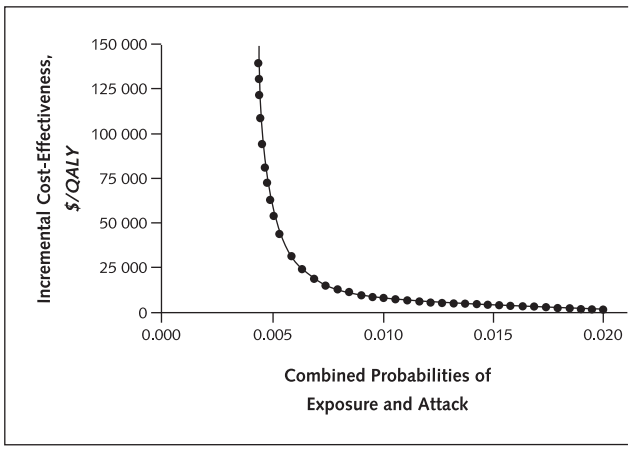
Preattack Vaccination versus No Vaccination Strategies

For a scenario in which the annual risk for attack was 1%, and 10% of the population had an exposure sufficient to cause infection, the no-vaccination strategy was less expensive and resulted in marginally higher QALYs gained per person (**Table 2**). The probability that any individual received a clinically significant exposure in this scenario is the product of the probability of an attack (1%) and the probability of exposure given an attack (10%) or 1 in 1000. At this risk for attack, the preattack vaccination strategy cost an additional $163 (95% CI, $121 to $205) per person, but because of potential adverse effects of the vaccine, reduced QALYs by 0.01 (CI, 0.009 to 0.201). For a city with a population of 5 million, the incremental cost of previous vaccination would be $815 million without appreciable health benefits.

Sensitivity Analyses

Because the risks for exposure and attack are uncertain (4–6, 23, 65), we simultaneously varied both variables in a sensitivity analysis to determine their effects on the costs and benefits of preattack strategies (**Figure 3**). Previous vaccination did provide net health benefit when overall probability of exposure for an individual was greater than 1 in 500. However, the incremental cost-effectiveness ratio of preattack vaccination of the population decreased to $50 185 per QALY only when individuals had a probabil-

Figure 3. **Sensitivity analysis of combined probabilities of attack and exposure on the incremental cost-effectiveness ratio of prophylactic vaccination before a *Bacillus anthracis* bioterror attack.**



QALY = quality-adjusted life-year.

ity of exposure greater than 1 in 200. If the efficacy of vaccination increased from our base-case estimate of 93% to 100%, the strategy of no previous vaccination remained less costly and more effective because of vaccine-associated side effects.

The Effect of Adherence and Distribution of Postattack Strategies on the Decision to Forgo Preattack Vaccination

Among 8424 postal employees who were offered antibiotic prophylaxis against anthrax in 2001, approximately 66% initiated it (32, 34). Fewer than half of respondents to follow-up questionnaires reported taking antibiotic prophylaxis against anthrax for at least 60 days, and adherence ranged from 21% to 64% (66). In our model, as adherence to antibiotic therapy decreased from a base case of 100% to less than 50%, the strategy to forgo previous vaccination was no longer dominant. However, adherence to the suggested regimen would need to decrease to approximately 20% before the incremental cost-effectiveness ratio of previous vaccination approached $100 000 per QALY gained, depending on the specific nature of nonadherence. Similarly, if the ability to distribute antibiotics for prophylaxis after a *B. anthracis* bioterror attack was limited and fewer than 50% of the exposed population could receive antibiotics (that is, if antibiotic prophylaxis could be delivered to fewer than 250 000 of the 500 000 people exposed in a city of 5 million people), previous vaccination would become cost-effective at a threshold of $100 000 per QALY gained, underscoring the importance of an organized and timely treatment distribution plan.

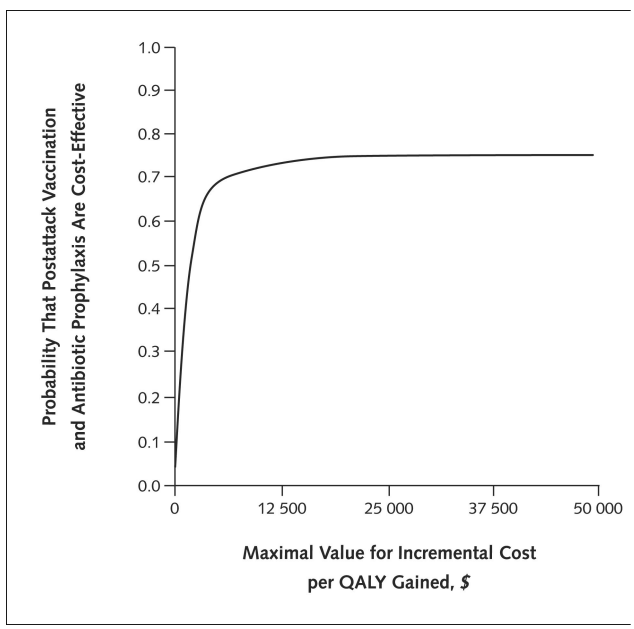
Probabilistic Sensitivity Analyses

We performed a probabilistic sensitivity analysis by using Monte Carlo simulation to generate CIs for the uncertain variables used in the model. If an attack occurred, probabilistic sensitivity analysis indicated that, of 10 000 simulations, the strategy of vaccination and antibiotic prophylaxis (vs. vaccination alone) was preferred in 77% of simulations, at an incremental cost-effectiveness threshold of $50 000 per QALY. **Figure 4** shows the results of our Monte Carlo simulation as an acceptability curve, which allows decision-makers to determine the probability that postattack vaccination and antibiotic prophylaxis are cost-effective at various willingness-to-pay thresholds (the highest incremental cost-effectiveness ratio that people would be willing to accept as reasonable value for the health care dollar). Before a potential *B. anthracis* bioterror attack, the strategy of no preattack vaccination was dominant or the preferred strategy in 81% of simulations, assuming an incremental cost-effectiveness threshold of $50 000 per QALY.

Discussion

In this analysis, we assessed the costs and benefits of postattack and preattack strategies for an anthrax release of a greater magnitude than that previously experienced in the United States. The main finding of our analyses of postattack strategies is that use of vaccine plus antibiotic prophylaxis is the most effective and least expensive therapy. The savings associated with preventing cases of inhalational anthrax offset the cost of using both vaccination and antibiotics. This finding is robust even with reasonable changes in our estimates of the cost and efficacy of the vaccine and antibiotics. Our most important finding about preattack vaccination is that the net health benefit and cost-effective-

Figure 4. **Cost-effectiveness acceptability curve of vaccination and antibiotic prophylaxis after a *Bacillus anthracis* bioterror attack.**



QALY = quality-adjusted life-year.

ness depended critically on the probability of an attack and on the proportion of the population exposed during the attack. For a large metropolitan U.S. city, vaccination provides reasonable value for the health care dollar only when the probability of clinically significant exposure reaches about 1 in 200 (for example, when the probability of attack is 0.01 and the probability of exposure during an attack is 0.5, the joint probability of clinically significant exposures would be 0.005 or 1 in 200). Our findings highlight the inherent difficulties in decision making about anthrax vaccination. Several factors influence the probability that an individual will receive a clinically significant exposure during an attack, including the quantity of spores released, method of dissemination, and environmental factors (such as geography, wind conditions, and time of day of the dispersal) (4–6, 23, 65). Although it is difficult to judge the likelihood of a release and the probability of exposure given a release, clearly some individuals are at higher risk than others. Our finding that vaccination provides a net health benefit at even relatively low probabilities (1 in 500) may help decision-makers assess the desirability of vaccination of military and emergency services personnel, who are probably at greater risk for exposure than the general population. If a vaccine with fewer adverse reactions became available, the probabilities of exposure at which there may be net benefit would be lower.

Our results suggest that if distribution of antibiotics or adherence to antibiotics is substantially impaired, previous vaccination may become cost-effective. In addition, antibiotic prophylaxis would still be a cost-effective component of postattack therapy, even for those who had previously received vaccination. Our finding is consistent with the work of other authors who have estimated greater than 50% increases in postattack mortality rate when either the distribution of antibiotics is delayed or prophylactic adherence to antibiotics is substantially diminished (23). These findings highlight the critical need for distribution systems that can rapidly provide prophylaxis and vaccination for hundreds of thousands, perhaps millions, of exposed people.

Our study has 2 primary limitations. First, our analysis assessed vaccination and prophylaxis strategies in response to a large-scale anthrax release. We did not assess other potential mechanisms of attack. However, our results provide insights that might be generalized to alternate mechanisms of release that have different probabilities of exposure. Second, although human and animal studies indicate that the human anthrax vaccine is effective when administered in the scheduled dosing regimen, the effectiveness of the vaccine with an abbreviated vaccination schedule that would be used after an attack is less certain. However, our sensitivity analyses indicate our results are robust to substantial changes in vaccine efficacy. In addition, a vaccine-resistant strain of *B. anthracis* could conceivably be used for an aerosolized attack. We assumed that the strain used is not resistant to antibiotics or the vaccine. Less evidence exists about the efficacy of the vaccine in very young and very old people and in people with comorbid conditions.

If an aerosolized *B. anthracis* bioterror attack does occur, a combination of vaccination and antibiotic therapy provided the most health benefit at the lowest cost. The cost-effectiveness of a program of mass preattack vaccination of the population of large U.S. cities against the threat of an aerosolized *B. anthracis* bioterror attack depends critically on the likelihood of attack and the proportion of the population exposed, given that an attack occurs. Until the individual probability of exposure reaches about 1 in 200, adverse effects of the vaccine outweigh potential benefit.

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