Responding to a Small-scale Bioterrorist Anthrax Attack

Cost-effectiveness Analysis Comparing Preattack Vaccination With Postattack Antibiotic Treatment and Vaccination

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Background: In 2001, a small-scale bioterrorism-related anthrax attack was perpetrated via the US mail. The optimal future response may require strategies different from those required in a large-scale attack.

Methods: We conducted a cost-effectiveness analysis using Monte Carlo simulation during a 10-year time frame from a societal perspective to determine the optimal response strategy for a small-scale anthrax attack perpetrated against US Postal Service distribution centers in a large metropolitan area. Three strategies were compared: preattack vaccination of all US distribution center postal workers, postattack antibiotic therapy followed by vaccination of exposed personnel, and postattack antibiotic therapy without vaccination of exposed personnel. Outcome measures were costs, quality-adjusted life-years, and incremental cost-effectiveness. The probabilities for anthrax exposure and infection; vaccine and antibiotic benefits, risks, and costs; and associated clinical outcomes were derived from the medical literature and from bioterrorism experts.

Results: Postattack antibiotic therapy and vaccination of exposed postal workers is the most cost-effective response compared with other strategies. The incremental cost-effectiveness is $59,558 per quality-adjusted life-year compared with postattack antibiotic therapy alone. Preattack vaccination of all distribution center workers is less effective and more costly than the other 2 strategies. Assuming complete adherence to preattack vaccination, the incremental cost-effectiveness compared with postattack antibiotic therapy alone is almost $2.6 million per quality-adjusted life-year.

Conclusion: Despite uncertainties about a future anthrax attack and exposure risk, postattack antibiotic therapy and vaccination of exposed personnel seems to be the optimal response to an attack perpetrated through the US Postal Service.

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attacks perpetrated through the US Postal Service (USPS), simulating the postal attacks of October 2001. Detection of the attack was assumed to occur similarly to the 2001 attacks (base case scenario). We then reanalyzed for early detection through autonomous detection systems recently installed by the USPS to detect anthrax spores.16

### METHODS

#### STUDY DESIGN AND MODEL PARAMETERS

A Markov model was used to estimate the cost-effectiveness of response strategies to reduce morbidity and mortality from a small-scale anthrax attack during a 10-year time frame. A societal perspective with a 3% annual discount factor for costs of all outcomes was adopted.17 Results were expressed as incremental cost-effectiveness ratios (ICER), calculated as the incremental cost per additional quality-adjusted life-year (QALY). The willingness-to-pay threshold was set at $100 000 per additional year of life. Analyses were conducted using TreeAge Pro Healthcare software (version 2006; TreeAge Software, Williamstown, Mass). Sensitivity analyses were conducted using 1- and 2-way analyses, and Monte Carlo simulation. Model parameters and ranges are given in Table 1.

#### TARGET POPULATION

The USPS employed 351 470 field career employees in 2004, excluding delivery carriers, motor vehicle operators, and maintenance personnel.18 The base case analysis considers a postal service workforce of 350 000 persons aged 18 to 60 years. Workforce turnover was estimated at 10% annually, and all workers were assumed to have no previous exposure to anthrax.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Sensitivity Analysis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scenario</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual probability of an attack</td>
<td>10</td>
<td>1-50</td>
<td>...</td>
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<tr>
<td>Postal service field career employees</td>
<td>350 000</td>
<td></td>
<td>18</td>
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<tr>
<td>Probability of exposure in an attack</td>
<td>0.57</td>
<td>0.01-1</td>
<td>19, 20</td>
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<tr>
<td>Percentage of total exposure that is inhalational anthrax</td>
<td>50</td>
<td>0-100</td>
<td>20</td>
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<tr>
<td>Probability of inoculation after exposure, infectious dose</td>
<td>1</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Anthrax prophylaxis and treatment adverse events and outcomes</td>
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<td></td>
<td></td>
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<tr>
<td>Probability of mild adverse reaction to vaccine</td>
<td>0.0456</td>
<td>0-12</td>
<td>21-24</td>
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<tr>
<td>Probability of severe adverse reaction to vaccine</td>
<td>0.0369</td>
<td>0-1</td>
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<td>Probability of mild adverse reaction to oral antibiotic therapy</td>
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<td>10-25</td>
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<tr>
<td>Duration of adverse events</td>
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<td>2-6 wk</td>
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<tr>
<td>Infection rate</td>
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<td></td>
<td></td>
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<tr>
<td>No vaccine</td>
<td>32</td>
<td>32-100</td>
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<tr>
<td>Postattack vaccine</td>
<td>31</td>
<td>31-94</td>
<td>9</td>
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<tr>
<td>Pretreatment vaccine</td>
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<td>7.5-45</td>
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<td>Probability of being dead on arrival after inhalational anthrax infection</td>
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<td>0-10</td>
<td>...</td>
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<tr>
<td>Probability of dying from inhalational anthrax after hospitalization</td>
<td>45</td>
<td>0-100</td>
<td>20</td>
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<td><strong>Utilities</strong></td>
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<tr>
<td>Acute inhalational anthrax</td>
<td>0.40</td>
<td>0.16-0.64</td>
<td>29</td>
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<tr>
<td>Acute cutaneous anthrax</td>
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<td>0.40-0.88</td>
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<td>Long term after inhalational anthrax</td>
<td>0.60</td>
<td>0.40-0.80</td>
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<tr>
<td>Long term after cutaneous anthrax</td>
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<td>Mild adverse reaction to vaccine</td>
<td>0.90</td>
<td>0.80-1.00</td>
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<tr>
<td>Severe adverse reaction to vaccine</td>
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<td>0.40-0.88</td>
<td>29</td>
</tr>
<tr>
<td>Mild adverse reaction to oral antibiotic therapy</td>
<td>0.90</td>
<td>0.80-1.00</td>
<td>29</td>
</tr>
<tr>
<td>Severe adverse reaction to oral antibiotic therapy</td>
<td>0.64</td>
<td>0.40-0.88</td>
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<tr>
<td><strong>Cost</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Anthrax vaccine (BioThrax; BioPort Corp, Lansing, Mich) absorbed, per dose, $</td>
<td>24.50</td>
<td>0-24.50</td>
<td>30</td>
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<tr>
<td>Vaccine administration, per dose, $</td>
<td>20.35‡</td>
<td>0-20.35</td>
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</tr>
<tr>
<td>Ciprofloxacin, 500 mg twice daily for 60 d, $</td>
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<td>5.74-12</td>
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<td>89.64</td>
<td>89.64-233-130.03</td>
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<tr>
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<td>3841.62</td>
<td>3841.62-25†</td>
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<tr>
<td>Mild adverse reaction to oral antibiotic therapy, $</td>
<td>89.64</td>
<td>89.64-233-130.03</td>
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</tr>
<tr>
<td>Severe adverse reaction to oral antibiotic therapy, $</td>
<td>3841.62</td>
<td>3841.62-25†</td>
<td>31</td>
</tr>
<tr>
<td>Cutaneous anthrax treatment, no vaccine and pretreatment vaccine arms, $</td>
<td>957.24</td>
<td>957.24-25†</td>
<td>31, 32</td>
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<tr>
<td>Cutaneous anthrax treatment, posttreatment vaccine arms, $</td>
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<td>1050.21-25†</td>
<td>31, 32</td>
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<tr>
<td>Inhalational anthrax treatment, died from anthrax, $</td>
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<td>5493.50-25†</td>
<td>32, 33</td>
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<td>Inhalational anthrax treatment, survived, $</td>
<td>26 343.34</td>
<td>26 343.34-25†</td>
<td>31-33</td>
</tr>
<tr>
<td>Discount rate, %</td>
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<td></td>
<td>...</td>
</tr>
<tr>
<td>Time frame, y</td>
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<td></td>
<td>...</td>
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</tbody>
</table>

Abbreviation: ellipses, not applicable.


†Value given as a percentage.
RESPONSE STRATEGIES

Three response strategies were compared: preattack vaccination of all distribution center workers; postattack antibiotic therapy followed by vaccination of exposed personnel; and postattack antibiotic therapy without vaccination. Postattack vaccination alone was not modeled because it would not prevent early spore germination. The first strategy uses the cell-free anthrax vaccine absorbed given in a series of 6 inoculations, at 1 day, 2 and 4 weeks, and 6, 12, and 18 months. The efficacy of this approach has been demonstrated in several animal models. The second strategy uses an appropriate antibiotic (ciprofloxacin; Bayer Pharmaceutical, Westhaven, Conn) for 60 days and 3 inoculations of anthrax vaccine absorbed at 1, 14, and 28 days in exposed individuals. The therapeutic efficacy as well as protection against repeat challenge provided by combining postexposure antibiotic therapy with vaccination has been demonstrated in animal models. The third strategy uses only the described antibiotic regimen for 60 days in exposed individuals.

In the 2001 postal attack, prophylactic antibiotic adherence was approximately 44%. Partial adherence to antibiotic therapy postattack was assumed, with 23% of treated persons completing 15, 30, 45, and 60 days of antibiotic therapy. Partial adherence (50%) was also assumed for preattack vaccination. A rapid attack response was assumed in the base case, with postattack antibiotic therapy distribution to all exposed persons by 6 days. Predicted inhalational anthrax infection rates for no vaccination and postattack vaccination using a 60-day regimen of oral antibiotic therapy were 34% and 29%, respectively. The predicted anthrax infection rate for preattack vaccination was 56%. Cutsaneous infection rates were assumed to be equal to inhalational infection rates. Infection rates derived from simulations conducted by Brookmeyer et al under different assumptions of infectious dose, response time, and adherence to prophylactic therapy are given in Table 2. Sensitivity analyses were conducted under each scenario and for a substantially more rapid response to an attack.

PROBABILITIES OF ATTACK, EXPOSURE, AND INOCULATION

Because the likelihood and nature of a future postal attack are unknown, scenario probabilities are based on the best subjective estimates of the investigative team (Table 1). An attack was assumed to occur with 10% annual probability (1 attack expected during the 10-year time frame) at multiple USPS distribution centers, exposing 2000 postal workers. A 1% infectious dose, described by Brookmeyer et al as low, was assumed in the base case analysis and is within the range observed in the 2001 attacks at the New Jersey and Washington, DC, postal facilities. Without intervention, 1% of exposed persons would become infected with anthrax.

ANTHRAX INFECTION OUTCOMES

Outcomes for the preattack and postattack vaccination strategies are shown in the Figure (4 more figures are available from the corresponding author on request). Patients with inhalational anthrax die without treatment, die after inpatient treatment, or survive after inpatient treatment. Inhalational anthrax mortality in the 2001 attack was 45% despite intensive medical care. The probability of being dead on arrival, dead after hospitalization, or surviving inhalational anthrax was estimated at 0%, 45%, and 55%, respectively. For cutaneous anthrax exposure, lack of treatment could result in severe disease with mortality as high as 20%, whereas with appropriate treatment, mortality is less than 1%. Consistent with the 2001 attack, we assumed that all persons with cutaneous anthrax exposure in our model were treated with oral antibiotics and survived. Survivors of both inhalation and cutaneous exposure to anthrax are assumed to have immunity to subsequent infection.

ANTIBIOTIC THERAPY, VACCINATION, AND MEDICAL TREATMENT COSTS

Treatment assumptions were made based on the 22 anthrax cases from the 2001 postal attacks. Inhalational anthrax survivors would be hospitalized for 14 days, receive parenteral antibiotic therapy for 7 days followed by oral ciprofloxacin therapy for 53 days, and receive biannual outpatient visits after recovery for the duration of the study. Patients who died were assumed to have been hospitalized for 3 days before death. Patients with cutaneous anthrax exposure were treated as outpatients with oral antibiotic therapy.

Medical costs were estimated in 2005 US dollars and adjusted for inflation as needed using the medical care component of the Consumer Price Index. Hospital costs were based
ANTIBIOTIC THERAPY AND VACCINATION

ADVERSE EFFECTS

Mild adverse reactions to oral antibiotic therapy or vaccination are defined as those treated in the outpatient setting with 1 physician visit. Severe adverse reactions require a 2-day hospitalization and 2 outpatient follow-up visits. The model assumed a 16% probability of a mild adverse reaction to the antibiotic therapy, a 0.3% probability of a severe adverse reaction, and no deaths from antibiotic prophylaxis. The model assumed that mild adverse reaction to the vaccine occurred in 0.03% of the population and that severe adverse reaction occurred in 0.04% of the population, based on reports of adverse events in US military personnel. Effects of potential adverse events are assessed in the sensitivity analyses.

QOL ADJUSTMENTS

Short-term adjustments in QOL were made for mild and severe adverse reactions to oral antibiotic therapy and vaccination and were based on utilities reported for similar health states. Estimation of the short-term QOL effect of inhalational anthrax exposure was made by selecting a value 1 SD below the mean utility reported for acute illness, to capture the QOL effect of having an illness with a high probability of death. Long-term adjustments were based on reports from anthrax survivors 1 year after infection. Inhalational and cutaneous anthrax survivors reported QOL that was 60% and 71%, respectively, of the normal value and were assumed to have utility in the years after infection of 0.6 and 0.71, respectively. Variations in QOL were explored in sensitivity analyses.

SENSITIVITY ANALYSES

One-way sensitivity analyses were conducted for all variables, based on the ranges given in Table 1. Brookmeyer et al estimated the effect of simultaneous variations in infectious dose, adherence, and response time on the expected infection rates for the 3 strategies we evaluated. Two-way analyses based on adherence and response time assumptions were conducted separately for 1% and 10% inoculation rates (Table 2). Costs and QALYs for each of the 3 strategies were calculated for the 10 scenarios defined by these variables.

Another sensitivity analysis assessed longer (4 months) antibiotic therapy required for higher spore exposure. The USP has recently deployed autonomous detection systems to promptly identify mailed anthrax. A sensitivity analysis was conducted assuming administration of postattack prophylaxis as rapidly as 12 hours after exposure. Using the algorithm of Brookmeyer et al, spor germination would occur in 2.4% of exposed persons by 12 hours. Sensitivity analyses estimated the minimal improvement in effectiveness conveyed by the addition of postattack vaccination to postattack antibiotic therapy required for combined postattack antibiotic therapy and vaccination to remain cost-effective.

Two analyses were conducted to model scenarios that would most favor preattack vaccination. The effect of a mass vaccination of postal workers before an attack on the probability of an attack targeted at postal workers was tested. In addition, a sensitivity analysis was conducted assuming a positive probability of attack but zero probability of adverse reaction to vaccination, slow attack response, no adherence to postattack antibiotic therapy, and complete adherence to vaccination.

Monte Carlo simulations of 1000 randomly selected observations were conducted by varying 36 variables simultaneously for the 10 scenarios defined by infectious dose, response time, and adherence to prophylactic treatment to test the sensitivity of the results for the entire range of possible parameter values. Uniform distributions were assumed for each variable (Table 1). Strategies that were both more costly and less effective or were more costly and had a higher ICER than a remaining strategy were excluded from the Monte Carlo simulations. The optimal strategy was identified based on a willingness-to-pay threshold of $100 000. The percentage of simulations in which each strategy was optimal was calculated.
RESULTS

Our base case analysis indicates that postattack antibiotic therapy without vaccination is the least costly strategy but that combined postattack antibiotic therapy and vaccination is the most cost-effective strategy (Table 3). Preattack vaccination is dominated by both remaining strategies, reflecting the higher infection rate in the reference case analysis that assumes partial adherence. Even if a preattack vaccination program entirely prevents any anthrax attack on the postal service and there is complete adherence to the preattack vaccination program, it costs nearly $2.6 million per QALY for postattack antibiotic therapy alone. In contrast, the incremental cost-effectiveness of combined postattack antibiotic therapy and vaccination vs postattack antibiotic therapy alone was $59 558 per QALY.

One-way sensitivity analyses indicate that postattack combined antibiotic therapy and vaccination is also cost-effective compared with postattack antibiotic therapy alone over the entire range of most model parameters (Table 4). However, postattack antibiotic therapy alone is optimal when the proportion of infected persons dying from anthrax is very low (<1.4%). Preattack vaccination is not cost-effective over the range of any of the model parameters, including vaccination cost. Although the cost-effectiveness of postattack combined antibiotic therapy and vaccination compared with postattack antibiotic therapy alone is relatively unchanged with increases in the probability of exposure (scope of the attack), preattack vaccination becomes cost-effective compared with postattack antibiotic therapy alone (ICER<$100,000) only with complete adherence to preattack vaccination and with a probability of exposure equal to or greater than 18.5%, or 64,750 of the 350,000 USPS employees.

Table 5 gives the ICER between postattack combined antibiotic therapy and vaccination compared with...
Infection rates with postattack strategies were reduced substantially to reflect what might be expected in a rapid (12-hour) response scenario with complete adherence. Postattack combined antibiotic therapy and vaccination was no longer cost-effective compared with postattack antibiotic therapy alone, with an ICER of more than $2.3 million per QALY.

Despite the uncertainties of an anthrax attack and the efficacy of human vaccination, postattack combined antibiotic therapy and vaccination of exposed persons seems to be the most cost-effective strategy after a small-scale anthrax attack. When adherence to postattack antibiotic therapy is high, the incremental benefit of postattack vaccination is small and postattack antibiotic therapy alone may be optimal, depending on response time and infectious dose. However, the overall adherence after the 2001 attacks on the USPS was 44%.

Several factors should be considered when interpreting our findings. In small-scale attacks, the effect of low adherence to postattack antibiotic therapy and vaccination on lives saved is small (1 life) compared with a large-scale attack,12 in which the number of lives saved is substantial (85,000 lives) with complete adherence. Even with substantial reductions in vaccination cost and adverse events, postattack strategies are preferred. Consequently, new vaccines (eg, from VaxGen Inc, Brisbane,
Calif) with reduced cost per dose and number of required doses would not alter the optimal response strategy for a small-scale postal attack.

Autonomous detection systems substantially lower expected infection rates in the postattack strategies by promptly identifying mailed anthrax. With the infectious dose observed in the 2001 postal attacks, early detection and rapid response (12 hours to initiation of treatment) reduces the added benefit of postattack vaccination to almost zero and changes the optimal response to postattack antibiotic therapy alone. Similar to large-scale attacks in which early recognition, antibiotic distribution, and adherence to antibiotic therapy all influence the optimal strategy, the choice between postattack strategies is affected by adherence to preattack and postattack prophylaxis and a prompt response. However, unlike a large-scale attack, preattack vaccination is never preferred in a small-scale attack with reasonable assumptions of exposure risk, infectious dose, and adherence, because of the expected low infection rate and the high total vaccine cost. Even assuming terrorists would not attack a worksite where the employees had been vaccinated, preattack vaccination resulting in zero probability of an attack is not cost-effective.

Two limitations should be mentioned. First, the duration of postattack antibiotic therapy may be inadequate for victims exposed to high spore concentrations. Expanding the duration of antibiotic therapy from 2 to 4 months would add to costs and likely reduce adherence. However, the recommended strategy would not change because the additional $688.00 per additional 60-day regimen is negligible compared with the costs of preattack vaccination. Second, our model evaluated a small-scale attack while the United States remains at risk of a large-scale attack. The preferred treatment strategy identified in this study, postattack combined antibiotic therapy and vaccination, is also recommended for a mass attack, although the implications of the sensitivity analyses in the 2 settings differ.

While the military has determined that exposure risk is sufficient to warrant preattack vaccination in Iraq and Afghanistan, anthrax vaccination of civilian populations at risk for a small-scale attack is likely to be controversial because of safety concerns. Targeted preattack vaccination of U.S. postal workers at highest risk may increase its cost-effectiveness. However, identification of postal distribution centers at risk of attack is impossible; this option is not cost-effective in any reasonable circumstances. Our results suggest that postattack antibiotic therapy alone may be preferred when response time is rapid (≤12 hours), which is feasible given the presence of the autonomous detection systems in postal offices. Development of a plan for rapid delivery of treatment (vaccination and antibiotic therapy) is critical for successful mitigation of a future attack.

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REFERENCES


