Cost-effectiveness of defending against bioterrorism: a comparison of vaccination and antibiotic prophylaxis against anthrax


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Pre- and post-attack strategies against anthrax were examined. The four post-attack strategies were no vaccination, vaccination alone, antibiotic prophylaxis alone, and vaccination plus antibiotic prophylaxis. The two pre-attack strategies were vaccination and no vaccination. Antibiotic prophylaxis was based on 60 days of oral doxycycline or ciprofloxacin.

Type of intervention
Primary prevention and treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of persons residing or working in a large metropolitan US city with a gender distribution (53% women), mean age (36 years) and age-specific life expectancy similar to those for New York City.

Setting
The setting was primary care. The economic study was carried out in the USA.

Dates to which data relate
The clinical data were estimated using studies published between 1970 and 2005. The economic data were derived from studies published from 1994 to 2005. The price year was 2004.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and experts' opinions.

Modelling
A decision model was constructed to simulate a large-scale aerosolised release of anthrax over a US metropolitan area. Also, to examine the costs and benefits of the pre- and post-attack strategies. The structure of the model was depicted. A hypothetical cohort of individuals could receive or not receive pre-attack vaccination against anthrax. In the case of no attack, individuals followed normal age-specific mortality or disability. In the case of attack, individuals could receive or not receive post-attack antibiotics and then suffer or not from anthrax-related illness. The time horizon of the model was the individuals' lifetime.
Outcomes assessed in the review
The outcomes estimated from the literature were:

- the rate of clinical inhalational anthrax with different strategies,
- the mortality and morbidity associated with anthrax,
- the exposure rate,
- antibiotic side effects,
- vaccine side effects,
- the utility values, and
- life expectancy.

Study designs and other criteria for inclusion in the review
It was unclear whether a systematic review of the literature was undertaken to identify the primary estimates. Life tables were used to derive all-cause mortality. Limited information on the design of the primary studies and patient characteristics was provided. For the assessment of utility values, data from similar health states were used when primary data were unavailable.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
Not stated.

Methods used to judge relevance and validity, and for extracting data
Not stated.

Number of primary studies included
Twenty-nine primary studies provided clinical evidence.

Methods of combining primary studies
The primary estimates appear to have been combined using a narrative approach.

Investigation of differences between primary studies
Not stated.

Results of the review
The rates of clinical inhalational anthrax after attack and exposure were:

- with no vaccination and no antibiotics, 0.95 (range: 0.5 - 1.0);
- with antibiotic therapy alone, 0.2 (range: 0.1 - 0.5);
with vaccination alone, 0.07 (range: 0.0 - 0.5); and
with both vaccination and antibiotic therapy, 0.02 (range: 0.0 - 0.2).

Other probability values were as follows:
baseline mortality, given clinical disease, 0.45;
non-disabled state if survive clinical illness, 0.85 (range: 0.6 - 1.0);
rate of Bacillus anthracis bioterror attack per year, 0.01 (range: 0.0 - 1.0); and
rate of exposure, given attack, 0.10 (range: 0.0 - 1.0).

The rate of antibiotic side effects was 0.19 (range: 0.1 - 0.4) for mild effects, 0.01 (range: 0.01 - 0.1) for moderate effects, and 0.0001 (range: 0.0 - 0.001) for severe effects.

The rate of vaccine side effects was 0.04 (range: 0.01 - 0.05) for mild effects, 0.01 (range: 0.01 - 0.1) for moderate effects, and 0.0001 (range: 0.0 - 0.001) for severe effects.

The utility values were as follows:
population baseline, 0.92 (range: 0.9 - 1.0);
antibiotic treatment, 0.90 (range: 0.7 - 1.0);
mild antibiotic side effects, 0.9 (range: 0.8 - 0.92);
moderate antibiotic side effects: 0.8 (range: 0.6 - 0.9);
severe antibiotic side effects, 0.6 (range: 0.4 - 0.8);
mild vaccination side effects, 0.9 (range: 0.8 - 0.92);
moderate vaccination side effects, 0.8 (range: 0.6 - 0.9);
severe vaccination side effects, 0.6 (range: 0.4 - 0.8);
severe inhalational anthrax, 0.64 (range: 0.5 - 0.8);
post-anthrax healthy state, 0.9 (range: 0.7 - 1.0);
post-anthrax disabled state, 0.8 (range: 0.6 - 0.9); and
death, 0.

Methods used to derive estimates of effectiveness
The authors stated that published evidence was supplemented with experts' opinions.

Estimates of effectiveness and key assumptions
No explicit effectiveness estimates were derived from experts' opinions, but the rate of bioterror attack used in the base-case was influenced by experts.

Measure of benefits used in the economic analysis
The summary benefit measure used was the quality-adjusted life-years (QALYs). An annual rate of 3% was used to discount benefits that were incurred in the future. The utility values were derived from the literature. Life-years were also reported.

**Direct costs**
The cost analysis was carried out using a societal perspective. The direct costs included in the economic analysis were vaccination- or booster-related costs (vaccine, vaccine administration and treatment of side effects), antibiotic and administration costs, pharmacy dispensing costs, treatment of antibiotic side effects, outpatient physician follow-up, inpatient costs due to anthrax-related disease, age-specific medical care, and death from any cause. The unit costs were presented separately from the quantities of resources for vaccine and antibiotics, while other categories of costs were reported as macro-categories. The costs and quantities of resources used were mainly derived from published sources. Discounting was relevant, owing to the long timeframe of the analysis, and an annual rate of 3% was applied. All the costs were inflated to 2004 values using the gross domestic product deflator.

**Statistical analysis of costs**
The costs were treated deterministically in the base-case.

**Indirect Costs**
The indirect costs (i.e. work losses due to disease or the treatment of side effects) were included in the economic evaluation. They were estimated using data coming from the US Bureau of Labor Statistics and the US Census Bureau. The unit costs were not presented separately from the quantities of resources used. The price year was 2004 and an annual discount rate of 3% was applied.

**Currency**
US dollars ($).

**Sensitivity analysis**
The robustness of the model results was tested using univariate and multivariate sensitivity analyses over plausible ranges of values. In general, these ranges were derived from the literature. A Monte Carlo simulation was also carried out using 10,000 iterations to calculate approximate confidence intervals (CIs) for the primary results.

**Estimated benefits used in the economic analysis**
Among post-attack strategies, the expected QALYs (life-years) were 20.61 (22.40) with no vaccination or antibiotics, 21.05 (22.89) with vaccination alone, 21.24 (23.09) with antibiotic prophylaxis alone, and 21.36 (23.23) with both vaccination and antibiotic prophylaxis. Antibiotic plus vaccination was thus the most effective strategy.

For pre-attack strategies, the expected QALYs (life-years) were 21.51 (23.39) with no vaccination and 21.50 (23.38) with vaccination. The difference in QALYs was 0.01 (95% CI: 0.009 - 0.201).

**Cost results**
Among post-attack strategies, the expected lifetime costs were $46,958 with no vaccination or antibiotics, $46,434 with vaccination alone, $46,102 with antibiotic prophylaxis alone, and $46,099 with both vaccination and antibiotic prophylaxis. Antibiotic plus vaccination was thus the less expensive strategy.

For pre-attack strategies, the expected lifetime costs were $45,579 with no vaccination and $45,742 with vaccination. The cost-difference was $163 (95% CI: 121 - 205).
Synthesis of costs and benefits
It was not necessary to combine the costs and benefits since a strategy of both vaccination and antibiotic prophylaxis was dominant (both more effective and less costly) among post-attack strategies, while no vaccination was the dominant strategy among the pre-attack strategies.

The sensitivity analysis showed that a combination of vaccination and antibiotic therapy remained the most effective and least expensive strategy, even when vaccination added only marginally increased effectiveness to antibiotic therapy or when the costs of the antibiotics increased.

The incremental cost-effectiveness ratio of pre-attack vaccination of the population decreased to $50,185 per QALY only when individuals had a probability of exposure of greater than 1 in 200. If adherence to antibiotic therapy decreased to less than 50% (it was 100% in the base-case), the strategy of no pre-attack vaccination was no longer dominant, but adherence would need to decrease to approximately 20% before the incremental cost per QALY gained of prior vaccination approached $100,000.

The probabilistic sensitivity analysis showed that the strategy of post-attack vaccination and antibiotic prophylaxis (versus vaccination alone) was preferred in 77% of cases, at an incremental cost-effectiveness threshold of $50 000 per QALY. The strategy of no pre-attack vaccination was dominant or the preferred strategy in 81% of simulations.

Authors' conclusions
The use of vaccination plus antibiotic prophylaxis was the most effective and least expensive option among post-attack strategies, while no vaccination was the most cost-effective strategy among pre-attack strategies. However, the authors noted that the cost-effectiveness of no vaccination depended critically on the probability of an attack and on the proportion of the population exposed during the attack.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparators was appropriate. It appears that all possible comparators have been included in the analysis, both in the pre- and post-attack scenarios. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence was derived from published studies, although it was not explicitly stated whether a systematic review of the literature was undertaken. In effect, the primary estimates appear to have been identified selectively. Details of the design of the primary studies and the patient samples were not reported. Thus it was difficult to assess the validity of the primary sources of clinical evidence. Survival data came from US statistics. Differences between the primary studies were not investigated and a narrative approach was used to combine the primary estimates. Some assumptions were also made. The issue of uncertainty was addressed in the sensitivity analysis.

Validity of estimate of measure of benefit
QALYs were used as the summary benefit measure. This was appropriate as they capture the impact of survival and quality of life in a single measure. Discounting was applied, as recommended in US guidelines. Utility adjustments were derived from the literature, but limited information on the source of the data was reported. QALYs are comparable with the benefits of other health care interventions.

Validity of estimate of costs
A societal perspective was adopted in the analysis and indirect costs due to vaccine side effects were considered. The source of the data was reported for all categories of costs; much of the data came from published studies. A detailed breakdown of the costs was given. However, the unit costs were not presented separately from the quantities of resources used for all items because some costs were reported as macro-categories. The costs were treated deterministically, but several sensitivity analyses were carried out on the economic estimates. The price year was
reported, which aids reflation exercises.

**Other issues**
The authors stated that their findings were consistent with a published study that had estimated greater than 50% increases in post-attack mortality rate when either the distribution of antibiotics was delayed or prophylactic adherence to antibiotics was substantially diminished. The issue of the generalisability of the study results to other settings was not explicitly addressed, although extensive sensitivity analyses were performed. These, in part, enhance the external validity of the analysis. The authors noted some limitations of their study. First, the analysis was carried out in the scenario of a large-scale anthrax release, but other potential mechanisms of attack are possible. Second, the effectiveness of the vaccine with an abbreviated vaccination schedule that would be used after an attack is less certain. However, it was pointed out that the base-case results were robust to changes in the model inputs.

**Implications of the study**
The study results supported the use of post-attack prophylactic vaccination and antibiotic therapy in the event of an aerosolised anthrax attack over an unvaccinated metropolitan US population.

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**Bibliographic details**

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**Other publications of related interest**


Watson A, Keir D. Information on which to base assessments of risk from environments contaminated with anthrax spores. Epidemiology and Infection 1994;113:479-90.

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