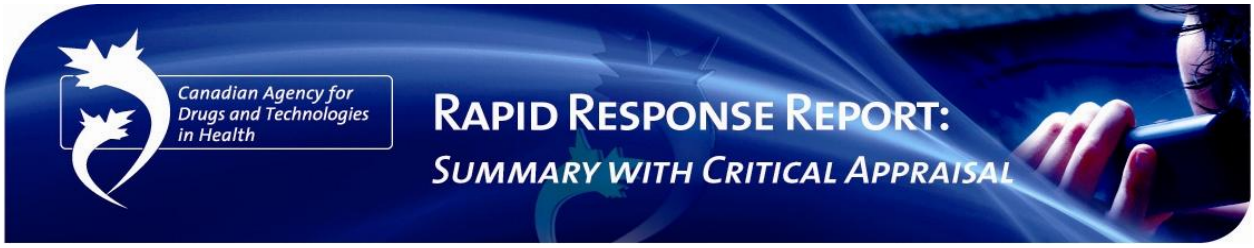

TITLE: Ciprofloxacin or Doxycycline for the Treatment of Anthrax: A Review of the Clinical and Cost-Effectiveness

DATE: 27 November 2012

CONTEXT AND POLICY ISSUES

The potential use of anthrax as a biological terrorist attack has prompted health authorities to investigate different treatment protocols and discuss which antibiotic agent should be used in the event of an attack.[1] Ciprofloxacin, and doxycycline were the primary agents used after the 2001 attack in the US, and amoxicillin was reserved for pregnant or breast feeding women, children, and those with adverse effects associated with ciprofloxacin or doxycycline.[2] Re-evaluation of these agents is required over time considering changes in resistance patterns, costs, or other factors. This report will review the clinical and cost-effectiveness literature of ciprofloxacin and doxycycline for anthrax.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of ciprofloxacin for the treatment or prophylaxis of anthrax in adult and pediatric populations?

2. What is the cost-effectiveness of ciprofloxacin for the treatment or prophylaxis of anthrax in adult and pediatric populations?

3. What is the clinical effectiveness of doxycycline for the treatment or prophylaxis of anthrax in adult and pediatric populations?

4. What is the cost-effectiveness of doxycycline for the treatment or prophylaxis of anthrax in adult and pediatric populations?

KEY MESSAGE

No controlled clinical studies on the effectiveness of ciprofloxacin or doxycycline for the treatment or prevention of anthrax infections were found. Surveillance data on post-exposure prophylaxis with ciprofloxacin and doxycycline suggests that the short-term incidence of serious adverse events in adults is infrequent (<1%). Two US economic models reported that antibiotics

plus vaccination was the most cost-effective strategy following a small or large bioterrorist attack; however, the generalizability of these findings to Canada is unclear.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, Embase, The Cochrane Library (2012, Issue 10), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. The search was also limited to English language documents published between January 1, 2002 and October 29, 2012.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to the selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients of any age exposed to anthrax
Intervention	Ciprofloxacin, doxycycline
Comparator	No treatment with ciprofloxacin or doxycycline
Outcomes	Health outcomes, percentage change in health outcomes, length of effect, number of treatments for control of symptoms, disability adjusted life years (DALYs), cost effectiveness
Study Designs	Health technology assessment (HTA), systematic review, meta-analysis, randomized controlled trial (RCT), non-randomized study, economic evaluation

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications, or were published prior to 2002.

Critical Appraisal of Individual Studies

Since the included studies were non-comparative and/or provided limited information, no formal critical appraisal was completed. Methodological issues that may have affected the validity of the findings were discussed in the limitations section.

SUMMARY OF EVIDENCE:

Quantity of Research Available

From the literature search 176 articles were screened, of which three observational studies and two economic evaluations met the inclusion criteria.[2-6] Two articles of potential interest are listed in Appendix 5.

Observational Studies

Summary of Study Characteristics

The three observational studies examined adverse events and adherence to antibiotics provided to persons potentially exposed to anthrax during the US 2001 bioterrorist attack.[2,5,6] Approximately 10,000 persons in the US were offered 60 days of post exposure prophylaxis with doxycycline, ciprofloxacin or amoxicillin to prevent inhalational anthrax (phase 1 prophylaxis). In December 2001, the anthrax vaccine became available, and persons with significant exposure were offered an additional 40 days of antibiotic therapy with or without three doses of vaccine (phase 2 prophylaxis). The antibiotic therapy offered initially was ciprofloxacin, unless contraindications were present. Once susceptibility tests were performed, many persons who were taking ciprofloxacin were switched to doxycycline. Adverse event data were collected through passive and active surveillance.[2,5,6]

In the report by Shepard et al. (2002),[2] adverse events during the first 60 days of antibiotic prophylaxis were described. Adults recommended for prophylaxis were surveyed for adverse events using self- or health provider-administered questionnaires and telephone interviews. Those who sought medical attention for an adverse event potentially related to prophylaxis were investigated further and information was gathered through interviews with health care providers or medical chart reviews.[2] Of the approximately 10,000 people who were recommended for at least 60 days of antibiotic prophylaxis, 6,178 completed the interviews.[2] The majority of responders were between 40 and 64 years old and 60% were male. Of these participants, 5,343 (86%) took at least one dose of antibiotic. Most participants (56%) took ciprofloxacin for the initial treatment course and doxycycline for the rest of the therapy.[2]

Two reports, based on one original study, examined adverse events among persons who were given an additional 40 days of antibiotic prophylaxis with or without vaccine (n=1727, phase 2 prophylaxis).[5,6] Among these participants, 199 received an antibiotic plus vaccine, and 1,528 received antibiotic alone. A total of 1,194 participants (69%) took doxycycline, 332 (19%) received ciprofloxacin, and 201 (12%) received amoxicillin. The median age was 50 years (range 3 to 75) and 69% were male. Martin et al. (2005)[5] reviewed adverse event data from patient diaries and two month follow up interviews. Tierney et al. (2003)[6] screened all adverse events reported through active and passive surveillance as potential serious adverse events. A serious adverse event was defined as death, life-threatening event, inpatient hospitalization or prolongation of hospitalization, persistent or substantial disability or incapacity, congenital anomaly, or an important medical event that required intervention to avert one of these outcomes.

Summary of Findings

Overall, 57% of participants (3,032/5,343) who took at least one dose of antibiotic reported an adverse event during the first 60 days of prophylaxis, and of these, 26% reported missing at least one day of work due to due symptoms.[2] Seven of 2,135 participants (0.3%) with 30 day follow-up data had a serious adverse event and four cases were definitely or probably related to prophylaxis (diffuse rash and systemic symptoms [two cases], swelling of face and neck [two cases]). All four recovered fully. At the day 60 evaluation, 16% of respondents reported seeking medical attention for possible prophylaxis-related adverse effects during the course of therapy.[2] The antibiotic these participants received was not reported by the study's authors.

There were no statistically significant differences in the incidence of adverse events at day 10 among those who received ciprofloxacin compared with doxycycline (data not shown).[2] At day 30, persons who received ciprofloxacin reported experiencing one or more adverse events, nervous systems adverse events or joint problems more frequently than those who received doxycycline (Table 2). Gastrointestinal symptoms, including nausea, vomiting, diarrhea, abdominal pain or heartburn, were more commonly reported among those receiving doxycycline at day 30 than ciprofloxacin.[2]

A total of 2,631 participants (56%) discontinued antibiotic therapy before 60 days.[2] Of these, 43% reported adverse events, 25% reported low perception of risk for anthrax, and 7% reported fear of long term side effects as the most important reason for discontinuation.[2] A total of 172 persons never obtained their prophylaxis, the main reason being low perception of risk for anthrax.[2]

Table 2. Adverse event reported during phase I prophylaxis[2]

Outcome (day 30)	Ciprofloxacin* % (n=737)	Doxycycline* % (n=2,050)	P value
≥1 adverse event	77	71	<0.01
Gastrointestinal symptoms	42	49	<0.01
Fainting, dizziness, light-headedness, seizures	23	18	0.01
Rash, hives, itchy skin	14	14	0.60
Joint problems	25	16	<0.01

*Most recent antibiotic taken at day 30.

Among participants who received an additional 40 days of antibiotic therapy with or without anthrax vaccine (phase 2 prophylaxis), the incidence of adverse events ranged from 18% to 77% in those who received ciprofloxacin, and from 21% to 71% in those who received doxycycline (Appendix 2). In general, the incidence of specific adverse events was similar in those who received ciprofloxacin compared to doxycycline. Diarrhea, dizziness, fatigue, headache insomnia, myalgia, and pruritis were the most common adverse events reported.[5]

Among the 1,727 persons who opted for an additional 40 days of prophylaxis (phase 2), a total of 12 people (0.7%) had a serious adverse event. Of these patients, one person was taking ciprofloxacin, eight were taking doxycycline, and three were receiving amoxicillin as prophylaxis (Table 3). No deaths were reported.[6]

Table 3. Serious adverse events reported during phase 2 prophylaxis[6]

Prophylaxis*	Age (years), sex	Primary complaint	Causality assessment
Ciprofloxacin	44 F	Nausea, allergic interstitial nephritis	probable
Doxycycline	56 F	Abdominal pain, extended work absence	possible
Doxycycline	53 F	Diarrhea, chest pain	possible
Doxycycline	46 M	Nausea, back pain, anxiety, extended work absence	unlikely
Doxycycline	59 F	Fatigue, malaise, hypertension, extended work absence	unlikely
Doxycycline	46 M	Liver problems	not related
Doxycycline	40 M	Depression, extended work absence	not related
Doxycycline	49 M	Allergic reaction to ciprofloxacin	not related
Doxycycline	58 F	Bowel obstruction	not related

*Among the 1727 receiving prophylaxis, 1194 (69%) took doxycycline and 332 (19%) received ciprofloxacin. None of the persons treated with ciprofloxacin or doxycycline received and who experienced a serious adverse event had received the anthrax vaccine.
F=female; M=male

Economic Evaluations

Summary of Study Characteristics

Two US economic evaluations published in 2005 and 2007, examined the cost-effectiveness of antibiotic for post-exposure prophylaxis to anthrax (Appendix 3).[3,4]

Fowler et al. (2005)[3] developed a decision analytic model evaluating the cost-effectiveness of strategies in response to a large scale anthrax bioterrorism attack on a US city. Pre-attack vaccination and no vaccination strategies, and four post-attack strategies were compared (no prophylaxis, antibiotic alone, vaccination alone, or antibiotic plus vaccination). In the model, antibiotic prophylaxis consisted of 60 days of oral doxycycline or ciprofloxacin, and possibly amoxicillin, depending on age, allergy, comorbid conditions, drug supply or susceptibility of the *B. anthracis* strain. In the base case analysis, the least costly appropriate oral antibiotic was used. The model assumed a rapid distribution of prophylaxis following the attack and 100% adherence to therapy. The model took a societal perspective and a life-time time horizon. It assumed a 1% annual risk of a bioterrorist attack. The cost estimates in the model included vaccination or antibiotic prophylaxis and management of adverse effects, inpatient and outpatient medical care of inhalational anthrax infections, lost earnings, death costs, and age-specific medical care. The published literature and expert opinion were used to provide model data on treatment efficacy and safety, the probability of exposure, and utilities. The Centers for Medicare & Medicaid was the source for health care costs. Deterministic and probabilistic sensitivity analyses were conducted to test the robustness of the model to changes in the model parameters.

In the report by Schmitt et al. (2007),[4] a Markov model was developed to evaluate the cost-effectiveness of different strategies in response to a small scale bioterrorist attack on US postal centers. The model tested a pre-attack vaccination strategy, and two post-attack strategies: antibiotic prophylaxis (60 days ciprofloxacin), or antibiotic plus vaccination. The model used a societal perspective over a 10 year time horizon and assumed that one attack would occur during the 10 year time frame, exposing 2,000 workers. The model included medical costs for

prophylaxis, inpatient and outpatient treatment of inhalational and cutaneous anthrax infections, and adverse effects from prophylaxis. Clinical data to populate the model were obtained from the published literature, or expert opinion.[4] The model parameters were varied in sensitivity analyses. Different incremental cost-effectiveness ratio (ICER) estimates were calculated by varying the speed of response to the attack, adherence to prophylaxis, and the proportion of exposed person who, without intervention, would become infected (i.e., infectious dose).

Summary of Findings

The cost-effectiveness evaluation by Fowler et al. (2005)[3] found that vaccination plus antibiotics was the most effective post-attack strategy, as it had the highest life-years and quality-adjusted life-years (QALY), and was the least costly (Appendix 4). Antibiotic prophylaxis alone had a similar cost to vaccination plus antibiotic prophylaxis but was less effective. Antibiotic prophylaxis alone was more effective and less costly than vaccination alone. All three prophylaxis strategies were more effective and less costly than the no prophylaxis strategy. In the sensitivity analyses on the cost of antibiotic prophylaxis, doxycycline was always the dominant treatment strategy (lowest cost, most effective). In the probabilistic sensitivity analysis, post-attack antibiotic plus vaccination was the preferred strategy in 77% of simulations versus vaccination alone, if the cost-effectiveness threshold was $50,000 per QALY.

In response to a small scale anthrax attack of US Postal Service, the post-attack ciprofloxacin plus vaccination strategy was the cost-effective option, with an ICER of US$59,600 per QALY gained versus ciprofloxacin therapy alone.[4] These results were consistent across most of the model parameters tested in the sensitivity analyses. Post-attack ciprofloxacin therapy alone was the most cost effective option when the risk of dying from anthrax was low (<1.4%). Pre-attack vaccination had the highest costs and was least effective.[4]

Limitations

No systematic review, meta-analyses, randomized or non-randomized controlled studies were found that evaluated the effectiveness of ciprofloxacin or doxycycline for the treatment or prevention of anthrax infections. Safety data were available from surveillance studies only. In these surveillance studies there was incomplete data on adverse events because some participants did not complete surveys, diaries or interviews. The percent of non-participation ranged from 5% to 96% for participant diaries[5] and was approximately 35% for interviews.[2,5] The interviews, which were done several weeks after completing therapy, may have been limited by recall bias.[5] The short-term evaluation of serious adverse events was more rigorous in that it included follow up with health care professionals and medical records to verify events.[2,6] Because patients may have received more than one antibiotic for prophylaxis, the adverse events reported cannot necessarily be attributed to a specific antibiotic. Although there were some children who received prophylaxis in 2001, the adverse event data reported were limited to adults.[2]

We identified two cost-effectiveness studies that modeled different strategies in response to a small scale[4] or large scale[3] bioterrorist release of anthrax in the US. Overall, the methods used in these studies appear robust and included multiple sensitivity analyses to explore uncertainty in the model parameters. Although both studies took a societal perspective, only the report by Fowler et al. (2005)[3] included potential lost wages among the costs. The small scale model only included ciprofloxacin and did not test if the choice of antibiotic altered the cost-effectiveness.[4] Both were US studies and their findings may not be generalizable to the Canadian context.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

No studies were found that evaluated the effectiveness of ciprofloxacin or doxycycline for the treatment or prevention of anthrax infections. Three surveillance studies were found that reported on the safety of 60 to 100 days of post-exposure antibiotic prophylaxis when used during the 2001 US bioterrorist attack. Short-term serious adverse events were infrequent, with an incidence of 0.3% to 0.7%. The proportion of adults who experienced an adverse event ranged from 18% to 77% among those who received ciprofloxacin, and from 21% to 71% among those given doxycycline. Adverse events were reported as the most common reason for stopping prophylaxis before the 60 day therapy was complete. Gastrointestinal, neurologic, joint problems or myalgia, and rashes or itchy skin were the most common adverse events reported. The frequency of these adverse events were similar for ciprofloxacin and doxycycline however since most participants had received more than one antibiotic it is not possible to attribute these events to a specific antibiotic.

Two US economic studies evaluated the cost-effectiveness of vaccination and/or antibiotic prophylaxis in response to a small scale, or large scale anthrax bioterrorist attack. In both models, the post-attack strategy of antibiotics plus vaccination was the most cost-effective option however the generalizability of these findings to Canada is unclear.

Overall, clinical and economic evidence on the use of ciprofloxacin and doxycycline for anthrax is sparse.

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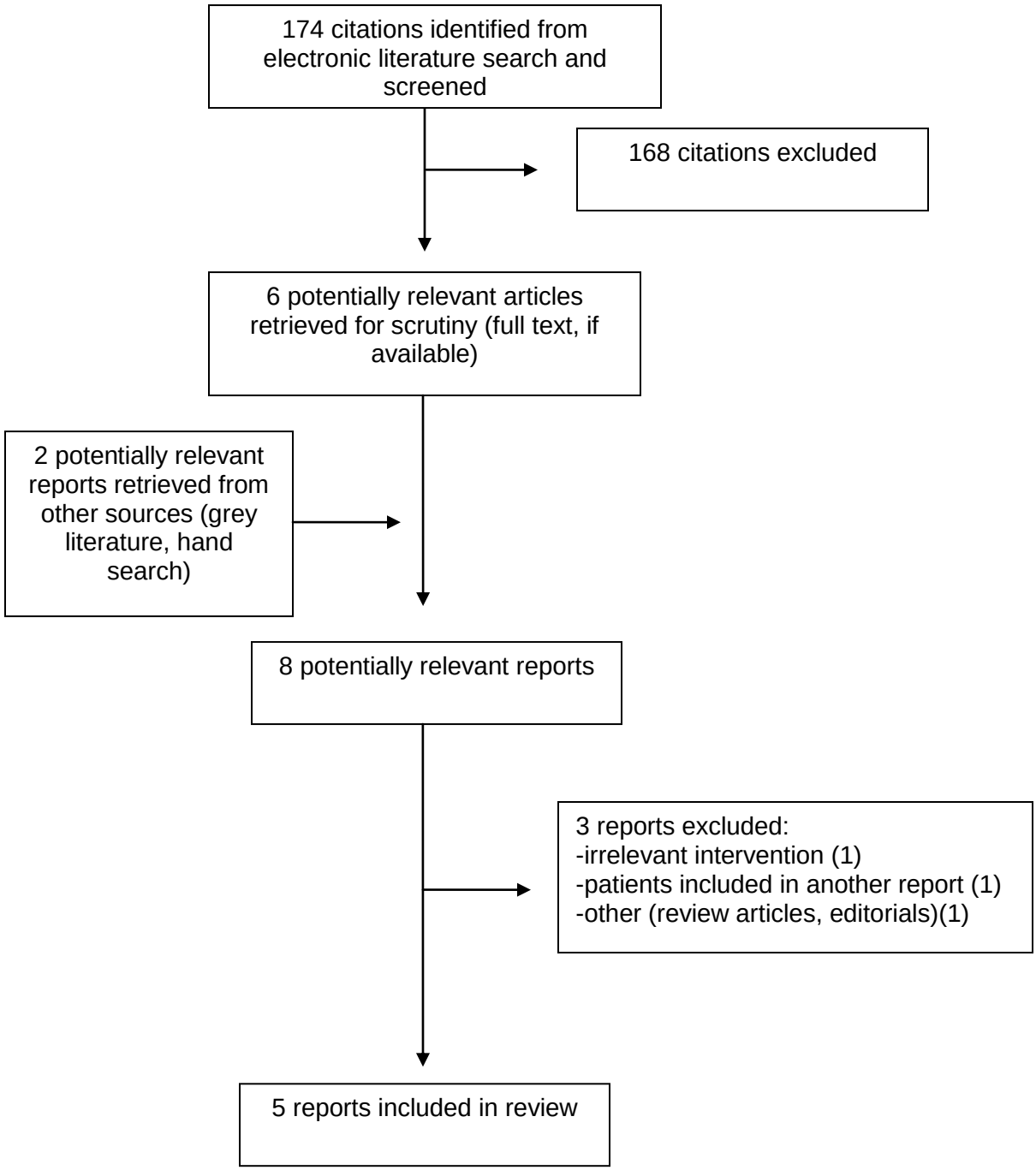
APPENDIX 1: Selection of Included Studies



Appendix 2: Adverse events reported during phase 2 prophylaxis[5]

Any adverse events reported[5]

Outcome / subgroup	Ciprofloxacin n (%)	Doxycycline n (%)	Total* n (%)
Patient diaries†			N=1727‡
≥ 1 adverse event			
Antibiotic alone	43 (18)	230 (21)	312 (20)
Antibiotic + vaccine	60 (83)	93 (85)	168 (84)
≥ 1 adverse event rated moderate or severe			
Antibiotic alone	25 (10)	110 (10)	156 (10)
Antibiotic + vaccine	28 (39)	48 (44)	85 (43)
Two month telephone interview			N=1113
≥ 1 adverse event			
Antibiotic alone	67 (46)	315 (45)	440 (46)
Antibiotic + vaccine	25 (40)	39 (45)	71 (43)

† Patients were asked to complete 3 diaries of adverse events that occurred during each 2 week period during treatment;
*includes persons who received amoxicillin or penicillin prophylaxis;
‡Percentages were calculated using the total number of patients enrolled in phase 2 in the denominator however, not all patients returned the diaries. The percentage of participants returning diaries 1, 2 and 3 ranged from 47 % to 4%, and 95% to 41%, in the antibiotic, and antibiotic plus vaccine groups, respectively.
n=number; NR=not reported

Specific adverse events reported[5]

Adverse event	Ciprofloxacin % (n=146)	Doxycycline % (n=702)	P value
Depression	8	8	0.88
Diarrhea or abdominal pain, upper	17	16	0.66
Dizziness	14	10	0.15
Dyspepsia	10	10	0.83
Dyspnea	8	5	0.19
Face edema or tongue edema	1	2	0.61
Fatigue	16	12	0.15
Fungal infection	10	8	0.43
Hallucinations	0	0.7	0.31
Headache	19	18	0.79
Increased tendency to bruise	2	1	0.47
Insomnia or nightmare	14	15	0.93
Joint swelling or arthralgia	10	10	0.79
Myalgia	16	15	0.65
Nausea or vomiting	13	14	0.70
Odynophagia	3	2	0.49
Pruritus	16	12	0.84
Psychometric seizures	0	0.1	0.65
Pyrexia	4	3	0.27
Rash or urticarial	9	7	0.50
Rigors	10	4	0.0011
Syncope	0.7	0.4	0.68
Vaginosis, fungal	6	6	0.81

†Based on data collected from 2 month follow up telephone interview among those who received antibiotic prophylaxis only (i.e., no vaccine)

Appendix 3: Summary of economic evaluations

Study, Location, Funding	Study design, Outcomes	Perspective, Time Horizon, Discounting, Dollar	Population	Comparators	Key assumptions in base case analysis
Schmitt 2007[4] US Funding: Veterans Affairs	Markov model Incremental costs and health benefits (QALY), ICER	societal perspective 10 year time horizon 3% discount rate 2005 US dollars	US postal workers exposed to anthrax through a small scale bioterror attack N=350,000 aged 18 to 65 years	Pre-attack: vaccination (6 doses) Post-attack: antibiotic prophylaxis (60 days ciprofloxacin), or antibiotic prophylaxis plus vaccination (3 doses)	-Probability of attack: 10%/year -Number exposed: 2000 -Probability of exposure given attack: 57% -Rapid response after attack with partial adherence to prophylaxis -Infection rate: 56%, 34% and 29% for pre-attack, antibiotic, and combination strategies respectively. -Mortality: inhalation 45%; cutaneous anthrax 0%
Fowler 2005[3] US Funding: academic and charitable grants, AHRQ	decision-analytic model Incremental costs and health benefits (QALY LY), ICER	societal perspective life- time horizon 3% discount rate 2004 US dollars	Residents of a large metropolitan US city, exposed to aerosolized anthrax through a bioterror attack mean age 36 years, 53% female	Pre-attack: vaccination (6 doses) vs. no vaccination Post-attack: no prophylaxis, vaccination alone (3 doses), antibiotic prophylaxis alone (60 days), or antibiotic prophylaxis plus vaccination	-Probability of attack: 1% /year -Probability of exposure given attack: 10% -Rapid response after attack with complete adherence to prophylaxis -Probability of inhalational anthrax infection given exposure: no prophylaxis 95%; antibiotic 20%; vaccination 7%; antibiotic plus vaccination 2% -Mortality from inhalational anthrax: 45%

AHRQ=Agency for Healthcare Research and Quality; ICER=incremental cost effectiveness ratio; LY=life-years; QALY=quality adjusted life year

Appendix 4: Results of economic evaluations

Author	Fowler 2005[3]				Schmitt 2007[4]				
Strategy	**Costs, $**	**LY**	**QALY**	**ICER**	**Expected number of anthrax infections**	**Expected number of anthrax deaths**	**Costs, $**	**QALY**	**ICER ($/QALY)**
Post-attack									
No prophylaxis	46,958	22.40	20.61	Dominated†	--	--	--	--	--
Vaccination	46,434	22.89	21.05	--	--	--	--	--	--
Antibiotic	46,102	23.09	21.24	--	6.22	1.70	1,568,455	14,801,486	Reference
Vaccination and antibiotic	46,099	23.23	21.36	Dominant*	5.73	1.45	1,954,188	14,801,492	59,558‡
Pre-attack									
No vaccination	45,579	23.39	21.51	Dominant*	--	--	--	--	--
Vaccination	45,742	23.38	21.50	Dominated†	11.06	2.80	105 million	14,801,456	Dominated†

ICER=incremental cost-effectiveness ratio; LY=life=years; QALY=quality adjusted life year
*Dominant strategy is the most effective and least costly option
†Dominated strategy is least effective and most costly option
‡ICER is calculated by dividing the difference in costs by the difference in QALYs for the reference (least costly) compared to the next best option.

Appendix 5: Additional articles of interest (Uncontrolled studies)

1. Powell AG, Crozier JE, Hodgson H, Galloway DJ. A case of septicaemic anthrax in an intravenous drug user. BMC Infect Dis [Internet]. 2011 [cited 2012 Oct 30];11:21. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3033829

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