Emerging Infectious Diseases Volume 3 Number 2 April - June 1997

Perspective

The Economic Impact of a Bioterrorist Attack: Are Prevention and Postattack Intervention Programs Justifiable?

Arnold F. Kaufmann, Martin I. Meltzer, and George P. Schmid
Centers for Disease Control and Prevention, Atlanta, Georgia, USA

DOWNLOAD article

Understanding and quantifying the impact of a bioterrorist attack are essential in developing public health preparedness for such an attack. We constructed a model that compares the impact of three classic agents of biologic warfare (*Bacillus anthracis*, *Brucella melitensis*, and *Francisella tularensis*) when released as aerosols in the suburb of a major city. The model shows that the economic impact of a bioterrorist attack can range from an estimated $477.7 million per 100,000 persons exposed (brucellosis scenario) to $26.2 billion per 100,000 persons exposed (anthrax scenario). Rapid implementation of a postattack prophylaxis program is the single most important means of reducing these losses. By using an insurance analogy, our model provides economic justification for preparedness measures.

Bioterrorism and its potential for mass destruction have been subjects of increasing international concern. Approximately 17 countries (including five implicated as sponsors of international terrorism) may have active research and development programs for biologic weapons (1). Moreover, groups and individuals with grievances against the government or society have been known to use or plan to use biologic weapons to further personal causes.

Only modest microbiologic skills are needed to produce and effectively use biologic weapons. The greatest, but not insurmountable, hurdle in such an endeavor may be gaining access to a virulent strain of the desired agent. Production costs are low, and aerosol dispersal equipment from commercial sources can be adapted for biologic weapon dissemination. Bioterrorists operating in a civilian environment have relative freedom of movement, which could allow them to use freshly grown microbial suspensions (storage reduces viability and virulence). Moreover, bioterrorists may not be constrained by the need for precise targeting or predictable results.

The impact of a bioterrorist attack depends on the specific agent or toxin used, the method and efficiency of dispersal, the population exposed, the level of immunity in the population, the availability of effective postexposure and/or therapeutic regimens, and the potential for secondary transmission. Understanding and quantifying the impact of a bioterrorist attack are essential to developing an effective response. Therefore, we have analyzed the comparative impact of three classic biologic warfare agents (*Bacillus anthracis, Brucella melitensis,* and *Francisella tularensis*) when released as aerosols in the suburbs of a major city and compared the benefits of systematic intervention with the costs of increased disease incidence (from the economic point of view used in society).

Analytic Approach

Scenario Assumptions

We compared the impact of a theoretical bioterrorist attack on a suburb of a major city, with 100,000 population exposed in the target area. The attack was made by generating an aerosol of an agent (*B. anthracis* spores, *B. melitensis*, or *F. tularensis*) along a line across the direction of the prevailing wind. The meteorologic conditions (thermal stability, relative humidity, wind direction and speed) were assumed to be optimal (2), and the aerosol cloud passed over the target area within 2 hours. We projected impact on the basis of 10% and 100% of the target population being exposed to the aerosol cloud.

We assumed that, when inhaled, the infectious dose$_{50}$ (ID_{50}) was 20,000 spores for *B. anthracis* and 1,000 vegetative cells for *B. melitensis* and *F. tularensis*. The rate of physical decay for airborne particles 5 mm or less in diameter was estimated to be negligible during the 2-hour transit time. The rate of biologic decay of the particulate agents was estimated to be negligible for the *B. anthracis* spores and 2% per minute for the *B. melitensis* and *F. tularensis* vegetative cells. Viability and virulence did not dissociate. Persons who were exposed to the *B. anthracis* cloud at any point during the 2-hour transit time inhaled one ID_{50} dose, and persons who were exposed to either the *B. melitensis* or *F. tularensis* cloud inhaled one to 10 ID_{50} doses, depending on their proximity to the origination point of the aerosol cloud.

The epidemic curve for anthrax by days after exposure was assumed to be <1 day, 0% of cases; 1 day, 5%; 2 days, 20%; 3 days,

35%; 4 days, 20%; 5 days, 10%; 6 days, 5%; and 7 or more days, 5% (3-5). Case-fatality rates were also assumed to vary by the day symptoms were first noted. The case-fatality rate was estimated as 85% for patients with symptoms on day 1; 80% for patients with symptoms on day 2; 70% for those with symptoms on day 3; 50% for those with symptoms on days 4, 5, and 6; and 70% for those with symptoms on and after day 7. The increased death rate in persons with an incubation period of 7 or more days is calculated on an assumption of delayed diagnosis, with resultant delayed therapy.

When estimating days in hospital and outpatient visits due to infection, we assumed that 95% of anthrax patients were hospitalized, with a mean stay of 7 days. Patients not admitted to a hospital had an average of seven outpatient visits, and surviving hospitalized patients had two outpatient visits after discharge from the hospital. Persons who received only outpatient care were treated for 28 days with either oral ciprofloxacin or doxycycline. No significant long-term sequelae resulted from the primary infection, and no relapses occurred.

The epidemic curve for brucellosis by days after exposure was assumed to be 0 to 7 days, 4% of cases; 8 to 14 days, 6%; 15 to 28 days, 14%; 29 to 56 days, 40%; 57 to 112 days, 26%, and 113 or more days, 10% (4, 6-9). The case-fatality rate was estimated to be 0.5%. Fifty percent of patients were hospitalized, with an average stay of 7 days. Nonhospitalized patients had an average of 14 outpatient visits, and hospitalized patients had seven outpatient visits after discharge from the hospital. Outpatients received a combination of oral doxycycline for 42 days and parenteral gentamicin for the first 7 days of therapy. Five percent of patients had a relapse or long-term sequelae, and required 14 outpatient visits within 1 year.

The epidemic curve for tularemia by days after exposure was assumed to be: <1 day, 0% of cases; 1 day, 1%; 2 days, 15%; 3 days, 45%; 4 days, 25%; 5 days, 10%; 6 days, 3%; and 7 or more days, 1% (4,10-11). The estimated case-fatality rate was 7.5%; and 95% of patients were hospitalized, with an average stay of 10 days. Nonhospitalized patients had an average of 12 outpatient visits, and hospitalized patients who survived the acute illness had two outpatient visits after discharge from the hospital. Outpatients received oral doxycycline for 14 days and parenteral gentamicin for 7 days. Five percent of patients had a relapse or long-term sequelae and required an average of 12 outpatient visits.

The efficacy of intervention strategies is unknown; our projections are our best estimates based on published clinical and experimental data (4,12-14). For anthrax, the projected intervention program was either a 28-day course of oral ciprofloxacin or doxycycline (assumed to be 90% effective), or a 28-day course of oral ciprofloxacin or doxycycline plus three doses of the human anthrax vaccine (assumed to be 95% effective); for brucellosis, a 42-day course of oral doxycycline and rifampin (assumed to be 80% effective), or a 42-day course of oral doxycycline, plus 7 days of parenteral gentamicin (assumed to be 95% effective); for tularemia, the intervention program was a 14-day course of oral doxycycline (assumed to be 80% effective), or a 14-day course of oral doxycycline plus 7 days of parenteral gentamicin (assumed to be 95% effective). Only 90% of persons exposed in the target area were assumed to effectively participate in any intervention program. Because the target area cannot be precisely defined, we estimated that for every exposed person participating in the intervention program, an additional 5, 10, or 15 nonexposed persons would also participate.

Economic Analyses of Postattack Intervention

To analyze the economic factors involved in establishing an intervention program, we compared the costs to the potential savings from such an intervention. Following the recommendation of the Panel of Cost-Effectiveness in Health and Medicine (PCEHM), we used estimates of actual costs rather than financial charges or market prices, which usually incorporate profit (15). We calculated the net savings (cost reductions) by using the following formula: Net savings = (number of deaths averted x present value of expected future earnings) + (number of days of hospitalization averted x cost of hospitalization) + (number of outpatient visits averted x cost of outpatient visits) - cost of intervention.

When we calculated the costs of hospitalization and outpatient visits, we assumed that only persons with symptoms (i.e., case-patients) would use medical facilities. The remainder of the exposed and potentially exposed populace would receive postexposure prophylaxis.

Present Value of Expected Future Earnings

The cost of a premature human death was nominally valued at the present value of expected future earnings and housekeeping services, weighted by the age and sex composition of the work force in the United States (16). The undiscounted average of future earnings is $1,688,595. As recommended by PCEHM (17), the stream of future earnings was discounted at 3% and 5%, to give values of $790,440 and $544,160, respectively. The present value of expected future earnings was estimated with 1990 dollars, adjusted for a 1% annual growth in productivity (16). However, in constant terms (1982 dollars), the average hourly earnings in private industry fell from $7.52 in 1990 to $7.40 in 1994 (18); therefore, the estimate of future earnings was not adjusted upwards.

Cost of Hospitalization

In 1993, the average charge for a single day of hospitalization was $875 (19). To derive true cost, we multiplied the average

charge by the cost-to-charge ratio of 0.635, (the April 1994 statewide average cost-to-charge ratio for urban hospitals in New York state) (16). On this basis, we estimated true hospitalization costs at $556/day (Table 1). Hospital costs included all professional services, drugs, x-rays, and laboratory tests. Lost productivity during hospital stay was valued at $65/day (the value of an "unspecified" day's earnings, weighted for age and sex composition of the U.S. work force) (16).

Table 1. Costs of hospitalization and outpatient visits (OPVs) following a bioterrorist attack

	Anthrax		Tularemia		Brucellosis	
	Base	Upper	Base	Upper	Base	Upper
Hospitalized patient						
Days in hospital	7	7	10	10	7	7
Cost per day ($)[a]	556	669	556	669	556	669
Lost productivity ($/day)	65	65	65	65	65	65
Follow-up OPVs (no.)	2	2	2	2	7	7
Cost 1st OPV ($)	28	44	28	44	28	44
Cost other OPVs, ea. ($)	13	24	13	24	13	24
OPV laboratory ($)[b,c]	87	174	87	174	131	261
OPV x-rays costs ($)[d]	66	66	0	0	0	0
Lost productivity ($/OPV)[e]	16	16	16	16	16	16
Total costs ($)	4,541	5,380	6,338	7,582	4,584	5,587
Avg. costs/day ($/day)	649	769	634	758	655	798
% increase: Base to upper estimate		*18*		*20*		*22*
Nonhospitalized patient						
Number of OPVs	7	7	12	12	14	14
Cost 1st OPV ($)	28	44	28	44	28	44
Cost other OPVs, ea. ($)	13	24	13	24	13	24
Lost productivity ($/OPV)[e]	16	16	16	16	16	16
Laboratory costs ($)[b,f]	131	174	261	522	261	522
X-ray costs ($)[d]	66	66	66	66	66	66
Drugs used[g]	D	C	D+G	D+G	D+R	D+R+G
Cost of drugs ($)	6	181	29	29	220	246
Total costs ($)	422	810	722	1,120	972	1,418
Avg. costs/day ($/day)	60	116	60	93	69	101
% increase: Base to upper estimate		*93*		*55*		*46*

Notes: All costs rounded to the nearest whole dollar.
[a]Hospital costs assumed to include all costs such as drugs, laboratory tests, and x-rays.
[b]Laboratory tests consists of general health panel (CPT code 80050) and an antigen or antibody test (modeled on the cost of a *Streptococcus* screen, CPT code 86588).
[c]Follow-up OPVs for hospitalized patients included two laboratory test sets for anthrax and tularemia patients and three laboratory test sets for brucellosis patients.
[d]X-ray costs (CPT code 71021), included two sets taken at different OPVs.
[e]Productivity lost due to an OPV was assumed to be one-quarter of an unspecified day's value.
[f]For OPVs of nonhospitalized patients, one set of laboratory tests is assumed for every two visits.
[g]Drugs used: D = doxycycline; C = ciprofloxacin; R = rifampin.
Sources: See text for explanation of sources of cost estimates.

Cost of Posthospitalization Outpatient Visits

After discharge from the hospital, a patient was assumed to have follow-up outpatient visits, the number of which varied by disease (Table 1). Outpatient visit costs were valued by using the Medicare National Average Allowance (20), which was chosen to represent the equivalent of bulk purchase discounted costs (i.e., actual costs) (Table 1). The first visit has a Current Procedural Terminology (CPT) code of 99201, which is classified as a "level 1" visit, requiring a physician to spend an average of 10 minutes

with a patient (20). Subsequent level 1 visits, with the physician spending an average of 5 minutes with each patient, have a CPT code of 99211 (20). During outpatient visits, a general health panel test incorporating clinical chemistry tests and complete blood counts (CPT code 80050) and a single antigen or antibody detection test (e.g., CPT code 86558) were assumed to be ordered (20). Although data on Medicare allowances for office visits and many other procedures were available, data on Medicare allowances for laboratory tests were not. Thus, to establish the costs of the tests, we arbitrarily divided the lowest allowable charge for each test in half. X-rays (CPT code 71021) were valued according to the Medicare National Average Allowance (Table 1). In terms of lost productivity, we assumed that each outpatient visit cost the equivalent of 2 hours, or one-quarter, of the value of an unspecified day (16).

Cost of Outpatient Visits of Nonhospitalized Patients

For nonhospitalized outpatients, the cost of each visit, laboratory test, x-ray, and lost productivity was the same as an outpatient visit for discharged hospital patients and varied by disease (Table 1). We assumed that one set of laboratory tests would be ordered every other visit and that two sets of x-rays (CPT code 71021) would be ordered during the therapeutic course. Drug costs are discussed below.

Cost of an Intervention

The costs of an intervention can be expressed as follows: Cost of intervention = (cost of drugs used) x ([number of people exposed x multiplication factor] - number killed - number hospitalized - number of persons who require outpatient visits).

The intervention costs per person depend directly on the costs of the antimicrobial agents and vaccines used in a prophylaxis program (Table 2). We obtained drug prices from the 1996 Drug Topics Red Book and used the lowest cost available for each drug (21). The cost of doxycycline ($0.22 per 200 mg total daily dose) was the Health Care Financing Administration cost, whereas the cost of gentamicin ($3.76 per 160 mg total daily dose), ciprofloxacin ($3.70 per 1,000 mg total daily dose), and rifampin ($5.01 per 900 mg total daily dose) were wholesale costs from pharmaceutical companies. The cost of anthrax vaccine was $3.70 per dose (Helen Miller-Scott, pers. comm., 1996). The cost of administering one vaccine dose or gentamicin injection was estimated at $10.00, on the basis of the 1992 cost of administering a vaccine in a clinical setting (Valerie Kokor, pers. comm., 1996). In estimating the cost of administering oral antimicrobial agents, we assumed weekly visits, during which the drug would be distributed and counseling would be given ($15.00 for the first visit and $10.00 for each subsequent visit).

Table 2. Costs of prophylaxis following a bioterrorist attack

Level of effectiveness	Anthrax	Tularemia	Brucellosis
Lower			
Effectiveness (%)	90	80	80
Drugs used[a]	D or C	D	D+R
Cost of drugs ($)[b]	6 or 181	3	220
No. of visits[c]	4	2	6
Total cost/ person ($)	51 or 226	28	285
Upper Effectiveness (%)	95	95	95
Drugs used[a]	D+V or C+V	D+G	D+G
Cost of drugs ($)[b]	17 or 193	29	36
No. of visits[c]	4	7	12
Total cost/ person ($)	62 or 238	104	161
Minimum No. participants[d]	451,912	418,094	423,440
Maximum No. participants[e]	1,492,750	1,488,037	1,488,037

Notes: All costs are rounded to the nearest whole dollar.

[a]Drugs used: D = doxycycline; C = ciprofloxacin; V = anthrax vaccine; G = gentamicin; R = rifampin.

[b]See text for explanation of drug costs.
[c]Cost of visit to drug-dispensing site: 1st visit = $15/person; follow-up visits = $10/person/visit.
[d]Estimate assumed that the prophylaxis program was initiated on postattack day 6 for anthrax and tularemia and postattack day 113 for brucellosis, that the prophylaxis program had the lower effectiveness level, and that the multiplication factor for unnecessary prophylaxis given to unexposed persons was 5.
[e]Estimate assumed that prophylaxis was initiated on postattack day 0 (day of release), that prophylaxis had the upper effectiveness level, and that the multiplication factor for unnecessary prophylaxis given to unexposed persons was 15.

We assumed that more people would receive prophylaxis than were actually exposed because of general anxiety and uncertainty about the boundaries of the attack, the timing of the attack, and the time it would take nonresidents to travel through the attack area. Three different multiplication factors (5, 10, and 15) were used to construct within the population. Finally, ongoing intelligence gathering would detect possible bioterrorist threats. The cost of these prerequisite activities can be calculated if they are seen as a form of insurance, the goal of which is to "purchase" the maximum net savings through preparedness to manage the consequences of an attack and reduce the probability of an attack. The "actuarially fair premium" for the "insurance" can be defined as follows (22): Actuarially fair premium = reduction of loss probability x value of avoidable loss.

The term "reduction of loss probability" indicates that, although increased surveillance and related activities can reduce the odds of an attack, they cannot guarantee absolute protection. The term "avoidable loss" refers to the fact that, even if a postexposure prophylaxis program were implemented on the day of release (day zero), some deaths, hospitalizations, and outpatient visits would be unavoidable.

Various reductions of attack probability illustrated the impact of these estimates on the calculation of actuarially fair premiums. Such reductions included reducing the probability from 1 in 100 years (0.01) to 1 in 1,000 years (0.001), a reduction of 0.009, and reducing a probability from 1 in a 100 years (0.01) to 1 in 10,000 years (0.0001), and from 1 in 100 years (0.01) to 1 in 100,000 years (0.00001). The attack probability of 0.01 in the absence of enhanced preventive actions was selected for illustrative purposes and does not represent an official estimate.

A range of minimum and maximum values of avoidable loss was derived from the net savings calculations. The values reflect differences in effectiveness of the various prophylaxis regimens, the reduced impact of delayed prophylaxis on illness and death, and the two discount rates used to calculate the present value of earnings lost because of death.

Sensitivity Analyses

In addition to the scenarios discussed above, three sensitivity analyses were conducted. First, the impact of increasing the cost of hospitalization and outpatient visits was assessed by using a set of upper estimates (Table 1). The cost of a hospital day was increased to $669 by increasing the cost-to-charge ratio from 0.634 to 0.764 (the ratio for Maryland) (16). The costs of outpatient visits (first and follow-up) were increased by assuming each visit was a "level 2" visit, doubling the average time a physician spends with each patient. The alternative cost-of-intervention scenarios that take into account persons who were not at risk but participated in the prophylaxis program. Thus, if 100,000 people were exposed, we assumed that the maximum number seeking prophylaxis was 500,000, 1,000,000, or 1,500,000.

Economic Analysis of Preparedness: Insurance

The analyses outlined above consider only the economics of an intervention after an attack and include several assumptions: First, stockpiles of drugs, vaccines, and other medical supplies would be available and could be rapidly moved to points of need. Second, civil, military, and other organizations would be in place and have the capability to rapidly identify the agent, dispense drugs, treat patients, and keep order costs of laboratory tests were increased to the full amount of the allowable charge (20).

The second sensitivity analysis considered a reduced impact, in which only 10% of the original 100,000 target population were considered exposed. All other estimates were held constant. The third sensitivity analysis considered the threshold cost of an intervention, given differences due to the effectiveness of various drug regimens, and discount rates used to calculate the present value of expected lifetime earnings lost to a death. The threshold cost occurs when net savings equal $0. Thus, the threshold value represents the maximum that could be spent per person on an intervention without having the intervention cost more than the loss from no intervention.

Findings

Postattack Illness and Death

In our model, all three biologic agents would cause high rates of illness and death. In the absence of an intervention program for the 100,000 persons exposed, the *B. anthracis* cloud would result in 50,000 cases of inhalation anthrax, with 32,875 deaths; the *F. tularensis* cloud in 82,500 cases of pneumonic or typhoidal tularemia, with 6,188 deaths; and the *B. melitensis* cloud in 82,500

cases of brucellosis requiring extended therapy, with 413 deaths.

The speed with which a postattack intervention program can be effectively implemented is critical to its success (Figure 1). For diseases with short incubation periods such as anthrax and tularemia, a prophylaxis program must be instituted within 72 hours of exposure to prevent the maximum number of deaths, hospital days, and outpatient visits (Figure 1). Some benefit, however, can be obtained even if prophylaxis is begun as late as day 6 after exposure. The relative clinical efficacy of the intervention regimen has a lesser but definite impact on observed illness and death rates (Figure 1).

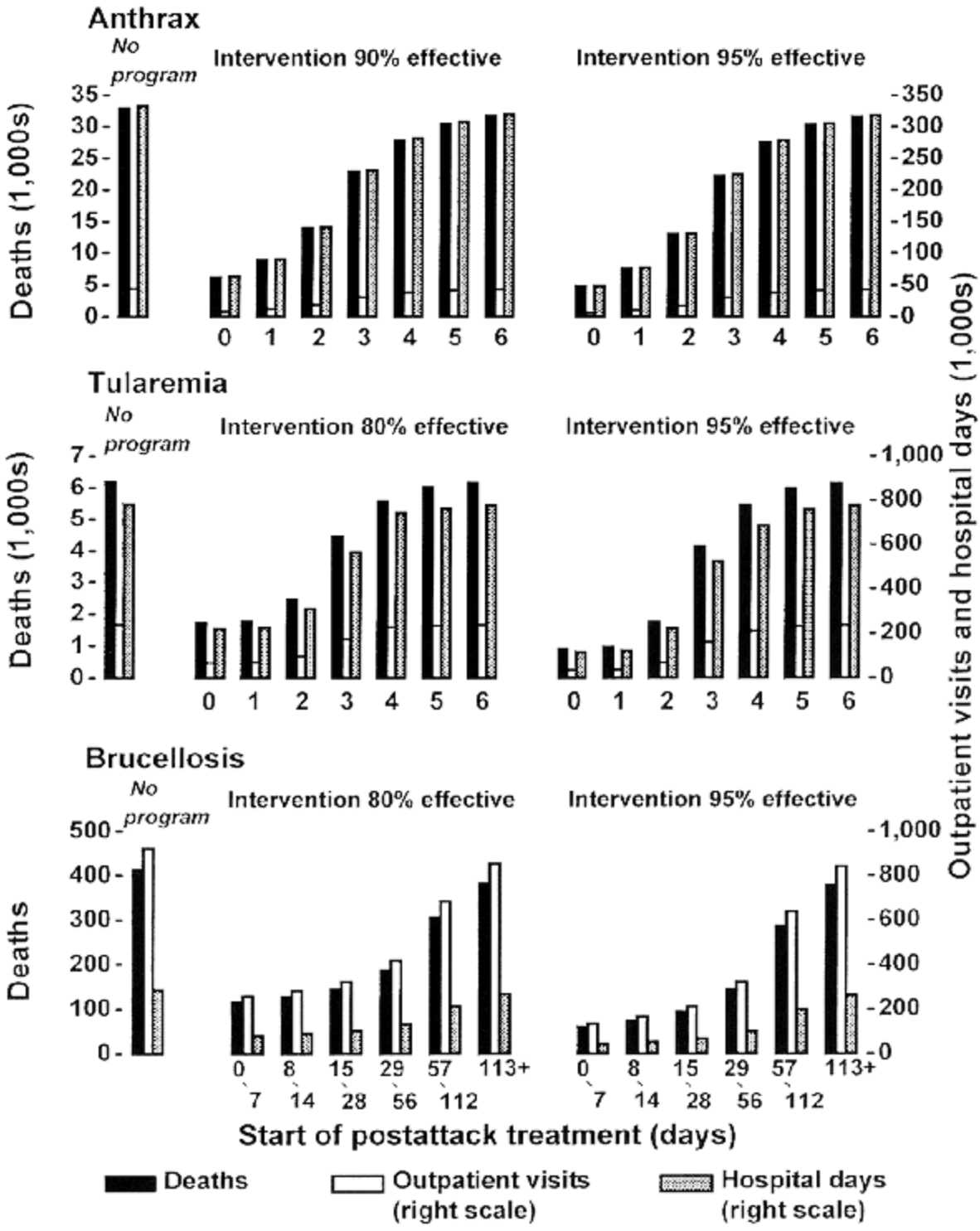

Figure 1. Total deaths, hospital days, and outpatient visits associated with aerosol releases of *B. anthracis*, *B. melitensis*, and *F. tularensis* by the postattack day of prophylaxis initiation and level of prophylaxis effectiveness.

A disease with a long incubation period such as brucellosis has a similar pattern (Figure 1); an important difference is the time

available to implement an intervention program. Having more time available to implement an intervention program can make a marked difference in its effectiveness. However, the prolonged incubation period creates a greater potential for panic in potentially exposed persons because of the uncertainty about their health status.

Economic Analyses of Postattack Intervention: No Program

Without a postexposure prophylaxis program, an attack with *B. anthracis* is far costlier than attacks with *F. tularensis* or *B. melitensis* (Table 3). The differences between agents in medical costs as a percentage of total estimated costs are due to the large differences in death rates attributed to each agent (Figure 1).

Table 3. Costs[a] ($ millions) of a bioterrorist attack with no postexposure prophylaxis program

	Anthrax	Tularemia	Brucellosis
Direct costs			
Medical: Base estimates[b]			
Hospital	194.1	445.8	170.3
OPV[c]	2.0	10.5	48.9
Medical: Upper estimates[d]			
Hospital	237.1	543.3	211.7
OPV[c]	4.4	18.5	78.3
Lost productivity			
Illness[e]			
Hospital	21.6	50.9	18.8
OPV[c]	0.7	3.9	15.0
Death			
3% discount[f]	25,985.7	4,891.2	326.5
5% discount[f]	17,889.3	3,367.3	224.7
Total costs			
Base estimates			
3% discount[f]	26,204.1	5,402.4	579.4
5% discount[f]	18,107.7	3,878.4	477.7
Upper estimates			
3% discount[f]	26,249.7	5,507.9	650.1
5% discount[f]	18,153.1	3,983.9	548.4

[a]Assuming 100,000 exposed.
[b]Medical costs are the costs of hospitalization (which include follow-up outpatient visits) and outpatient visits (Table 1).
[c]OPV = outpatient visits.
[d]Upper estimates calculated with data in Table 1.
[e]Lost productivity due to illness is the value of time spent in hospital and during OPVs (Table 1).
[f]Discount rate applied to calculate the present value of expected future earnings and housekeeping services, weighted by age and sex composition of the United States workforce (16), lost due to premature death.

Net Savings Due to a Postexposure Prophylaxis Program

If the postexposure prophylaxis program is initiated early, it reduces the economic impact of all three diseases, especially anthrax (Figure 2). Regardless of drug costs, the largest cost reductions are obtained through a combination of the most effective prophylaxis regimen (i.e., 95% effective, Table 2), the smallest multiplication factor to adjust for persons who unnecessarily receive prophylaxis, and a 3% discount rate to calculate the present value of the expected value of lifetime earnings.

In the case of anthrax, either doxycycline or ciprofloxacin could be used in the intervention program (Table 2), but the use of

doxycycline generated the largest savings. The largest difference in net savings between the two drugs was approximately $261.6 million. This difference occurred when it was assumed that the program began on day zero (day of release), each drug was used in combination with the anthrax vaccine, a 3% discount rate was used, and a multiplication factor of 15 for unnecessary prophylaxis was used. This amount is equal to approximately 1.2% of the maximum total net savings generated by using a regimen of doxycycline plus the anthrax vaccine.

Some scenarios, particularly those in which prophylaxis programs were started late, generated negative net savings (i.e., net losses). In the case of tularemia, at a 5% discount rate, net losses of $10.7 to $115.1 million occurred when a post-exposure program was delayed until day 6 after exposure, and a prophylaxis regimen of doxycycline and gentamicin (estimated 95% efficacy) was used. For the same scenario, but with a 3% discount, a net savings of $1,513.3 million was observed when a multiplication factor of five for unnecessary prophylaxis was used. However, multiplication factors of 10 and 15 generated net losses of $49.8 and $102.0 million, respectively. With the same drug combination, beginning the program 1 day earlier (day 5 after exposure) resulted in net savings in all scenarios except when a multiplication factor of 15 and a discount rate of 5% were used. Under the latter two assumptions, net savings result only for prophylaxis initiated by day 4 after exposure.

In the case of brucellosis, the use of a doxycycline-rifampin regimen (estimated 80% efficacy), a multiplication factor of 15 for unnecessary prophylaxis, and a discount rate of either 3% or 5% generated net losses regardless of when intervention began (Figure 2). The doxycycline-gentamicin regimen (estimated 95% efficacy) generated net losses only when it was assumed that the start of a program was delayed until 113 or more days after exposure.

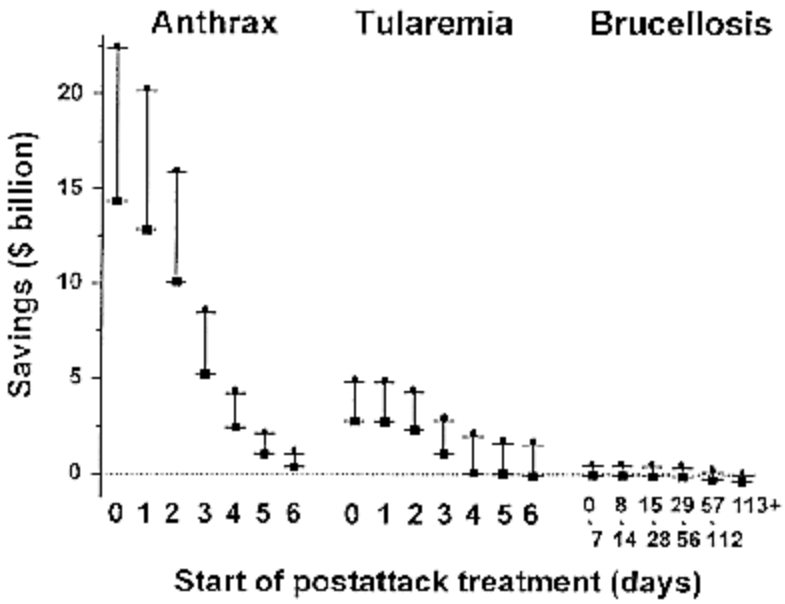

Figure 2. Ranges[a] of net savings due to postattack prophylaxis by disease and day of prophylaxis program initiation.

[a]Maximum savings (l) were calculated by assuming a 95% effectiveness prophylaxis regimen and a 3% discount rate in determining the present value of expected lifetime earnings lost due to premature death (16) and a multiplication factor of 5 to adjust for unnecessary prophylaxis. Minimum savings (n) were calculated by assuming an 80% to 90% effectiveness regimen and a 5% discount rate and a multiplication factor of 15. In tularemia prophylaxis programs initiated on days 4-7 postattack, the minimum savings were calculated by assuming a 95% prophylaxis regimen effectiveness rather than an effectiveness of 80% to 90%.

Preparedness: Insurance

The annual actuarially fair premium that can be justifiably spent on intelligence gathering and other attack prevention measures increases with the probability that a bioterrorist attack can be decreased by such measures (Table 4). However, the potential net savings attributed to reduced probability are minor compared with the potential net savings from implementing a prophylaxis program. Depending on the level of protection that can be achieved, the annual actuarially fair premium in an anthrax scenario would be $3.2 million to $223.5 million (Table 4). The lower premium would be justifiable for measures that could reduce the risk for an attack from 0.01 to 0.001 and provide the ability to mount an intervention program within 6 days of the attack. The higher premium would be justifiable for measures that could reduce the risk from 0.01 to 0.00001 and allow immediate intervention if an

attack occurred.

Table 4. The maximum annual actuarially fair premium[a] by reduction in probability of event and size of avoided loss: Anthrax

Days post-attack[b]	Preventable loss ($millions)	Actuarially fair annual premium ($ millions)		
		0.01 tp 0.001	0.01 to 0.0001	0.01 to 0.00001
Maximum loss estimate[c]				
0	22,370.5	201.3	221.5	223.5
1	20,129.4	181.2	199.3	201.1
2	15,881.5	142.9	157.2	158.7
3	8,448.0	76.0	83.6	84.4
4	4,200.1	37.8	41.6	42.0
5	2,076.1	18.7	20.6	20.7
6	1,013.8	9.1	10.0	10.1
Minimum loss estimate[d]				
0	14,372.4	128.9	141.8	143.1
1	12,820.1	115.4	126.9	128.1
2	10,049.1	90.4	99.5	100.4
3	5,200.1	46.8	51.5	51.9
4	2,429.7	21.9	24.1	24.3
5	1,004.2	9.4	10.3	10.4
6	351.2	3.2	3.5	3.5

[a]See text for definition.

[b]No. of days from attack to effective initiation of prophylaxis.

[c]Maximum loss preventable (potential net savings) occurs with the doxycycline-anthrax vaccine prophylaxis regimen, a multiplication factor of 5 for unnecessary prophylaxis, and a discount rate of 3% (Table 2).

[d]Minimum loss preventable (potential net savings) occurs with the ciprofloxacin prophylaxis regimen, a multiplication factor of 15 for unnecessary prophylaxis, and a discount rate of 5% (Table 2).

Sensitivity Analyses

The upper estimates of the cost of hospitalization increased average costs per day by 18% to 22%, and upper estimates of the cost of outpatient visits increased average costs per day by 46% to 93% (Table 1). However, the upper estimates only increased medical costs by 1% to 6% of the total medical costs associated with a bioterrorist attack (Table 3). The largest increase was for brucellosis, for which upper estimates increased medical costs from 38% to 44% of total costs (Table 3).

When the number of persons infected during an attack was reduced tenfold, the patient-related costs were reduced proportionately (Table 3). In most cases, however, the net savings in total costs are less than 10% of the net savings when 100% of the target population was presumed infected. The shortfall in savings is caused by an increase in the number of unexposed persons receiving prophylaxis. In the case of anthrax, when intervention programs are initiated within 3 days of exposure, savings are 4.1% to 10% of those in the original scenario (Figure 2). Delaying initiation of prophylaxis until days 4, 5, or 6 after exposure, however, results in net losses of $13.4 to $283.1 million. Losses occur regardless of prophylaxis regimen, discount rate, or multiplication factor used to adjust for unnecessary prophylaxis by unexposed persons.

In scenarios in which a multiplication factor of 15 was used to adjust for unnecessary prophylaxis, the threshold value of intervention was always above the prophylaxis cost for anthrax but not above the prophylaxis costs for tularemia and brucellosis (Table 5). For tularemia, the threshold intervention costs exceeded disease costs up to day 5 in the scenario with 95% effectiveness and a 5% discount, and for brucellosis, at all levels in the scenarios with 80% effectiveness and up to day 56 in the scenarios with 95% effectiveness. This is consistent with the lower range of estimated net savings (net losses) given in Figure 2. Reducing the number of unexposed persons receiving prophylaxis increases the cost thresholds, making the program cost

beneficial. For example, changing the multiplication factors for unnecessary prophylaxis to 5 and 10 increases the cost thresholds to $659 and $319, respectively, for a brucellosis prophylaxis program initiated 15 to 28 days after exposure, with a 5% discount rate. If a discount rate of 3% is used instead of 5%, the cost thresholds increase to $799 and $387. All these cost thresholds are above the estimated prophylaxis cost of $285 per person for the doxycycline-rifampin regimen and $161 per person for the doxycycline-gentamicin regimen (Table 2).

Table 5. Cost thresholds[a] of interventions ($/person) by day of intervention initiation, prophylaxis effectiveness, and discount rates.

	Threshold costs for intervention ($/person, multiplication factor of 15[b])								
	Anthrax			Tularemia			Brucellosis		
Post-attack day[d]	Disc. rate[c] 5%	3%	Post-attack day	Disc. rate 5%	3%	Post-attack day	Disc. rate 5%	3%
	90% effectiveness[e]			*80% effectiveness[e]*			*80% effectiveness[e]*		
0	9,838	14,238	0	1,891	2,633	0-7	233*	282*
1	8,851	12,809	1	1,873	2,609	8-14	224*	272*
2	7,022	10,162	2	1,599	2,227	15-28	211*	255*
3	3,775	5,463	3	756	1,053	29-56	179*	217*
4	1,893	2,739	4	258	366	57-112	86*	104*
5	944	1,366	5	79	110	113+	24*	30*
6	468	677	6	20*	28			
Prophylaxis cost[c]		*$226*			*$28*			*$285*
	95% effectiveness[e]			*95% effectiveness[e]*			*95% effectiveness[e]*		
0	10,370	15,007	0	2,229	3,104	0-7	274	333
1	9,359	13,544	1	2,207	3,074	8-14	264	320
2	7,427	10,948	2	1,898	2,644	15-28	248	301
3	3,995	5,782	3	898	1,251	29-56	211	256
4	2,004	2,900	4	328	457	57-112	102*	124*
5	1,000	1,447	5	93*	131	113+	29*	35*
6	496	718	6	23*	32*			
Prophylaxis cost[e]		*$238*			*$104*			*$161*

*Threshold value is below estimated cost of prophylaxis.

[a]Cost threshold is the point where cost of intervention and net savings due to the intervention are equal.

[b]Multiplication factor to adjust for persons who participated in the prophylaxis program but were unexposed.

[c]Applied to present value of expected future earnings and housekeeping services (weighted average for age and sex).

[d]Postattack day on which prophylaxis was effecively implemented.

[e]See Table 2 for prophylaxis regimens assumed to give the stated levels of effectiveness and cost/person of prophylaxis.

Conclusions

The economic impact of a bioterrorist attack can range from $477.7 million per 100,000 persons exposed in the brucellosis scenario to $26.2 billion per 100,000 persons exposed in the anthrax scenario (Table 3). These are minimum estimates. In our analyses, we consistently used low estimates for all factors directly affecting costs. The ID_{50} estimates for the three agents are twofold to 50-fold higher than previously published estimates (5,6,10,11), resulting in a possible understatement of attack rates. Also, in our analyses we did not include a number of other factors (e.g., long-term human illness or animal illnesses) (Table 6) whose cumulative effect would likely increase the economic impact of an attack.

Our model shows that early implementation of a prophylaxis program after an attack is essential. Although the savings achieved by initiating a prophylaxis program on any given day after exposure has a wide range, a clear trend of markedly reduced savings is associated with delay in starting prophylaxis (Figure 2). This trend was found in the analysis of all three agents studied.

Table 6. Potential factors affecting the economic impact of a bioterrorist attack

Potential impact on Factor	Relative magnitude net savings	of impact
Higher than projected case-fatality rate	Increase	++++
Long term illness (physical and psychological)	Increase	++
Decontamination and disposal of biohazardous waste	Increase	++
Disruptions in commerce (local, national, and international)	Increase	++
Animal illness and death	Increase	+
Lower than projected effectiveness of prophylaxis	Decrease	- - -
Adverse drug reactions due to prophylaxis	Decrease	-
Postattack prophylaxis distribution costs, including crowd control and security	Decrease	-
Training and other skill maintenance costs	Decrease	-
Procurement and storage of antimicrobial drugs and vaccines before attack	Decrease	-
Criminal investigations and court costs	Variable	+/-

Delay in starting a prophylaxis program is the single most important factor for increased losses (reduced net savings). This observation was supported by the actuarially fair premium for preparedness analysis (Table 4). Reductions in preventable loss due to early intervention had significantly greater impact on the amount of an actuarially fair premium than reductions in probability of an attack through intelligence gathering and related activities.

Although implemented at different times in a threat-attack continuum, both attack prevention measures and prophylaxis programs are forms of preventive medicine. Attack prevention measures seek to prevent infection, while prophylaxis programs prevent disease after infection has occurred.

Using an actuarially fair premium analogy in which cost and benefit are required to be equal, we find that the incremental rate of increasing prevention effectiveness (the marginal increase) declines rapidly as probability reduction targets go from 0.001 to 0.0001 to 0.00001. Because the loss probability is decreasing on a logarithmic scale, the potential increment in marginal benefit drops comparably, resulting in ever smaller increments in the protection above the preceding base level.

Conversely, delaying a prophylaxis program for anthrax, a disease with a short incubation period and a high death rate, increases the risk for loss in a manner akin to a semilogarithmic scale. Arithmetic increases in response time buy disproportionate increases in benefit (prevented losses.) The potential for reducing loss is great because an attack is assumed, thus increasing the actuarially fair premium available to prepare for and implement a rapid response.

Large differences between prophylaxis costs and the threshold costs for most scenarios, particularly if prophylaxis is early (Table 5), suggest that the estimates of savings from prophylaxis programs are robust. Even with large increases in prophylaxis cost, net savings would still be achieved.

The ability to rapidly identify persons at risk would also have significant impact on costs. For example, the threshold costs for brucellosis prophylaxis are often lower than intervention costs when the ratio of unexposed to exposed persons in the prophylaxis

program is 15:1 (Table 5). This finding provides an economic rationale for preparedness to rapidly and accurately identify the population at risk and reduce unnecessary prophylaxis costs.

The maximum amount of the annual actuarially fair premium varies directly with the level of risk reduction and the rapidity of postattack response (Table 4). The calculated amount of actuarially fair premiums, however, should be considered a lower bound estimate. A higher estimate (called the certainty equivalent) can also be calculated; however, this requires the determination of a social welfare function (22), and such complexity is beyond the scope of this study.

Our model provides an economic rationale for preparedness measures to both reduce the probability of an attack and increase the capability to rapidly respond in the event of an attack. The larger portion of this preparedness budget (insurance premium) should be allocated to measures that enhance rapid response to an attack. These measures would include developing and maintaining laboratory capabilities for both clinical diagnostic testing and environmental sampling, developing and maintaining drug stockpiles, and developing and practicing response plans at the local level. These measures should be developed with a value-added approach. For example, the laboratory capability could be used for other public health activities in addition to preparedness, and drugs nearing their potency expiration date could be used in government-funded health care programs. However, these secondary uses should not undermine the preparedness program's effectiveness.

Arnold Kaufmann is a retired Public Health Service officer, formerly assigned to the National Center for Infectious Diseases.

Address for correspondence: Martin I. Meltzer, Mail Stop C-12, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA 30333; fax: 404-639-3039; e-mail: qzm4@cdc.gov.

References

1. Cole LA. The specter of biological weapons. Sci Am 1996;275:60-5.
2. Gochenour WS. Aerobiology. Mil Med 1963;128:86-9.
3. Abramova FAN, Grinberg LM, Yampolskaya OV, Walker DH. Pathology of inhalational anthrax in 42 cases from the Sverdlovsk outbreak of 1979. Proc Natl Acad Sci 1993;90:2291-4.
4. Benenson AS, editor. Control of communicable diseases manual. 16th ed. Washington (DC): American Public Health Association, 1995.
5. Messelson M, Guillemin J, Hugh-Jones M, Langmuir A, Popova I, Shelokov A, et al. The Sverdlosvsk anthrax outbreak of 1979. Science 1994;266:1202-8.
6. Kaufmann AF, Fox MD, Boyce JM, Anderson DC, Potter ME, Martone WJ, et al. Airborne spread of brucellosis. Ann NY Acad Sci 1980;335:105-14.
7. Olle-Goig JE, Canela-Soler J. An outbreak of *Brucella melitensis* infection by airborne transmission among laboratory workers. Am J Public Health 1987;77:335-8.
8. Staszkiewicz J, Lewis CM, Colville J, Zervos M, Band J. Outbreak of *Brucella melitensis* among microbiology laboratory workers in a community hospital. J Clin Microbiol 1991;29:287-90.
9. Trever RW, Cluff LE, Peeler RN, Bennett IL. Brucellosis I. laboratory-acquired acute infection. Arch Intern Med 1959;103:381-97.
10. McCrumb FR. Aerosol infection of man with *Pasteurella tularensis*. Bacteriolical Reviews 1961;25:262-7.
11. Saslaw S, Eigelsbach HT, Wilson HR, Prior JA, Carhart S. Tularemia vaccine study II. respiratory challenge. Arch Intern Med 1961;107:689-701.
12. Friedlander AM, Welkos SL, Pitt MLM, Ezzell JW, Worsham PL, Rose, KJ, et al. Postexposure prophylaxis against experimental inhalation anthrax. J Infect Dis 1993;167:1239-42.
13. Sawyer WD, Dangerfield HG, Hogge AL, Crozier D. Antibiotic prophylaxis and therapy of airborne tularemia. Bacteriolical Reviews 1966;30:542-8.
14. Solera J, Rodriguez-Zapata M, Geijo P, Largo J, Paulino J, Saez L, et al. Doxycycline-rifampin versus doxycycline-streptomycin in treatment of human brucellosis due to *Brucella melitensis*. Antimicrob Agents Chemother 1995;39:2061-7.
15. Luce BR, Manning WG, Siegel JE, Lipscomb J. Estimating costs in cost-effectiveness analysis. In: Gold MR, Siegel JE, Russell LB, Weinstein MC, editors. Cost-effectiveness in health and medicine. New York: Oxford University Press, 1966:176-213.
16. Haddix AC, Teutsch SM, Shaffer PA, Dunet DO, editors. Prevention effectiveness: a guide to decision analysis and economic evaluation. New York: Oxford University Press, 1996.
17. Lipscomb J, Weinstein MC, Torrance GW. Time preference. In: Gold MR, Siegel JE, Russell LB, Weinstein MC, editors. Cost-effectiveness in health and medicine. New York: Oxford University Press, 1966:214-35.
18. U.S. Bureau of the Census. Statistical abstract of the United States: 1995. 115th ed. Washington (DC): U.S. Government Printing Office, 1996.
19. National Center for Health Statistics. Health, United States, 1995. Hyattsville (MD):U.S.Departmentof Health and Human Services, Public Health Service, 1996.
20. HealthCare Consultants of America, Inc. HealthCare Consultants' 1996 physicians fee and coding guide. 6th ed. Augusta (GA): HealthCare Consultants of America, Inc. 1996.
21. Cardinale V, editor. 1996 Drug Topics Red Book. Montvale (NJ): Medical Economics Company, Inc., 1996.
22. Robison LJ, Barry PJ. The competitive firm's response to risk. New York: Macmillan, 1987.

Emerging Infectious Diseases
National Center for Infectious Diseases
Centers for Disease Control and Prevention
Atlanta, GA

URL: http://www.cdc.gov/ncidod/EID/vol3no2/kaufman.htm
Updated: 97/05/14

Emerging Infectious Diseases Volume 3 Number 2 April - June 1997

Commentary

Biologic Terrorism — Responding to the Threat

DOWNLOAD article

The growing awareness of the possibility that a terrorist organization might use a biologic agent in an attack on a civilian target in the United States raises important questions about our capability as a nation to respond effectively to the threat and to deal with the consequences of an attack. The article by Kaufmann et al. in this issue of *Emerging Infectious Diseases* describes three possible biologic attack scenarios and uses an economic analysis to describe the benefits of a rapid medical response and early intervention. The authors conclude that major reductions in morbidity and mortality and consequent cost savings can be achieved by early intervention. The effectiveness of postattack intervention depends on a rapid response which requires prior planning, preparation, and training. Achieving the level of preparedness implied by the assumptions stated in the article will require a major national effort. This discussion of possible bioterrorist attack scenarios adds to a growing concern about our willingness as a nation to commit the effort and resources necessary to protect our citizens.

Biologic warfare and use of biologic weapons by terrorists have only recently been discussed openly and realistically. The fall of the Soviet Union and the defeat of Iraq uncovered extensive biologic weapons programs of surprising sophistication and diversity. The threat to the nation from biologic weapons is no longer a debate issue. Now the questions are how immediate and serious is the threat and how do we respond effectively?

Protecting the armed forces against biologic weapons, although complex and difficult, is less challenging than protecting the civilian population. The armed forces are relatively small populations that can be vaccinated against the major threat agents. Aerosols containing biologic materials can be detected at a distance, and protective masks and suits are effective. Military medical personnel are trained to recognize and treat casualties, and antibiotics, antiviral drugs, and antitoxins can be stockpiled for military contingencies. The preponderance of scientific expertise for many of the threat agents is within the military medical research laboratories, although this capability is now being seriously compromised by budget cuts and personnel reductions.

The civilian population cannot be protected in the same manner as the armed forces. We must rely heavily on our intelligence and criminal investigation agencies and on international efforts to identify specific threats and deter terrorists. We must also recognize the possibility that a determined terrorist organization may not be deterred, may evade detection, and may succeed in releasing an aerosol of a virulent bacterium, virus, or toxin in a susceptible target area such as an airport or stadium. Our current capability to effectively respond to such a scenario and minimize the impact is far less than needed.

The U.S. Armed Forces and the Department of Defense have the greatest capability in biologic defense, but the responsibility for dealing with the threat of biologic weapon use by a terrorist falls on multiple federal, state, and municipal agencies and the civilian health care community. Most of the organizations are inadequately prepared to deal effectively with the problem.

The organizational aspects of dealing with an attack on our civilian population are daunting. Responsibility for recognizing an unusual outbreak of illness that may be the result of the deliberate release of a biologic warfare agent will fall on the health care community. Early recognition will be an important factor in determining the overall outcome and will depend on the level of suspicion and knowledge of the health care providers that see the initial cases. Rapid, precise, and reliable diagnosis will be the responsibility of the federal and state public health laboratory system with help from their military colleagues. Organizing and managing the care of patients and mounting the appropriate public health response will involve local health care and municipal agencies and authorities and state public health authorities. The effectiveness of coordination, support, and leadership at the federal level may make huge differences in reducing death rates and containing the possible secondary spread of a communicable disease. The Federal Emergency Management Agency has the major responsibility for planning and coordinating the consequences phase of a federal response, but the level of preparedness at all levels will ultimately determine the outcome.

If we take the biologic warfare threat seriously, a major effort will be needed to develop contingency plans and initiate coordinated and mutually supportive programs in all involved agencies. Training and education of the health care community will require a major effort involving several major professional organizations. Developing and improving diagnostic and identification capability is essential for medical care, public health, intelligence, and law enforcement agencies and should be a national priority.

The science base needed to deal with the broad spectrum of agents on the threat list, bacteria, viruses, toxins, and parasites, is widely distributed among several federal laboratories in the Department of Health and Human Services, the Department of Defense, and the Department of Energy, as well as in universities and state public health laboratories. In addition, since many of

the biologic agents are not normally large public health problems or popular subjects of scientific research, critical areas have inadequate research capability and limited expert personnel. Deficiencies in our scientific knowledge and a paucity of experts will ultimately limit our capability to rapidly and precisely identify agents and respond effectively in a crisis. For example, the global molecular epidemiology of the agents at the top of the threat list is critically important for identifying the organisms accurately and differentiating local from exotic strains. Current databases are inadequate, and no organized effort is being made to fill in the gaps.

The current public discussion of the threat of biologic terrorism is an opportunity to evaluate our collective capabilities and to assess weaknesses and vulnerabilities. Raising the level of national preparedness will require leadership and action by responsible federal agencies. A thoughtful analysis of the consequences of unpreparedness provides a mandate for action.

Philip K. Russell
Johns Hopkins University, Baltimore, Maryland, USA

Emerging Infectious Diseases
National Center for Infectious Diseases
Centers for Disease Control and Prevention
Atlanta, GA

URL: http://www.cdc.gov/ncidod/EID/vol3no2/russell.htm
Updated: 97/05/14

EMERGING INFECTIOUS DISEASES Volume 4 Number 3
Past Issues | Current Issue | Upcoming Issue | Past Issues | Search | Home | July–September 1998
Download | ASCII Text | Adobe PDF | Postscript |

Special Issue

Bioterrorism as a Public Health Threat

D.A. Henderson
The Johns Hopkins University, Baltimore, Maryland, USA

The threat of bioterrorism, long ignored and denied, has heightened over the past few years. Recent events in Iraq, Japan, and Russia cast an ominous shadow. Two candidate agents are of special concern: smallpox and anthrax. The magnitude of the problems and the gravity of the scenarios associated with release of these organisms have been vividly portrayed by two epidemics of smallpox in Europe during the 1970s and by an accidental release of aerosolized anthrax from a Russian bioweapons facility in 1979. Efforts in the United States to deal with possible incidents involving bioweapons in the civilian sector have only recently begun and have made only limited progress. Only with substantial additional resources at the federal, state, and local levels can a credible and meaningful response be mounted. For longer-term solutions, the medical community must educate both the public and policy makers about bioterrorism and build a global consensus condemning its use.

Until recently, biological terrorism had been little discussed or written about. Until recently, I had doubts about publicizing the subject because of concern that it might entice some to undertake dangerous, perhaps catastrophic experiments. However, events of the past 12 to 18 months have made it clear that likely perpetrators already envisage every possible scenario.

Four points of view prevalent among national policy circles and the academic community at various times have served to dismiss biological terrorism as nothing more than a theoretical possibility. l) Biological weapons have so seldom been deployed that precedent would suggest they will not be used. 2) Their use is so morally repugnant that no one would deign to use them. 3) The science of producing enough organisms and dispersing them is so difficult that it is within the reach of only the most sophisticated laboratories. 4) Like the concept of a "nuclear winter," the potential destructiveness of bioweapons is essentially unthinkable and so to be dismissed. Each of these arguments is without validity.

Nations and dissident groups exist that have both the motivation and access to skills to selectively cultivate some of the most dangerous pathogens and to deploy them as agents in acts of terrorism or war. After the Gulf War, Iraq was discovered to have a large biological weapons program. In 1995, Iraq confirmed that it had produced, filled, and deployed bombs, rockets, and aircraft spray tanks containing *Bacillus anthracis* and botulinum toxin (1,2); its work force and technologic infrastructure are still wholly intact. Also in 1995, the Japanese cult, Aum Shinrikyo, released the nerve gas Sarin in the Tokyo subway. The cult also had plans for biological terrorism (3); included in its arsenal were large quantities of nutrient media, botulinum toxin, anthrax cultures, and drone aircraft equipped with spray tanks. Members of this group had traveled to Zaire in 1992 to obtain samples of Ebola virus for weapons development.

Of more recent concern is the status of one of Russia's largest and most sophisticated former bioweapons facilities, called Vector, in Koltsovo, Novosibirsk. Through the early 1990s, this was a 4,000-person, 30-building facility with ample biosafety level 4 laboratory facilities, used for the isolation of both specimens and human cases. Situated on an open plain surrounded by electric fences and protected by an elite guard, the facility housed the smallpox virus as well as work on Ebola, Marburg, and the hemorrhagic fever viruses (e.g., Machupo and Crimean-Congo). A visit in the autumn of 1997 found a half-empty facility protected by a handful of guards who had not been paid for months (P. Jahrling, pers. comm., 1998). No one can say where the scientists have gone, nor is there confidence now that this is the only storage site for smallpox virus outside the Centers for Disease Control and Prevention.

The number of countries engaged in biological weapons experimentation has grown from 4 in the 1960s to 11 in the 1990s (4). Meanwhile, the bombing of the World Trade Center and the Oklahoma City Federal Building have dramatized the serious problems even small dissident groups can cause.

A comprehensive review of the problems posed by biological terrorism and warfare has been published (5). Four observations deserve special note. First, biological terrorism is more likely than ever before and far more threatening than either explosives or chemicals. Second, official actions directed at the threat to the civilian population (less than 2 years in the making) have been only marginally funded and minimally supported (6). Third, preventing or countering bioterrorism will be extremely difficult. Recipes for making biological weapons are now available on the Internet, and even groups with modest finances and basic training in biology and engineering could develop, should they wish, an effective weapon (7) at little cost. Fourth, detection or interdiction of those

intending to use biological weapons is next to impossible. Thus, the first evidence of such weapons will almost certainly be cases in hospital emergency rooms. Specialists in infectious diseases thus constitute the front line of defense. The rapidity with which they and emergency room personnel reach a proper diagnosis and the speed with which they apply preventive and therapeutic measures could spell the difference between thousands and perhaps tens of thousands of casualties. Indeed, the survival of physicians and health-care staff caring for the patients may be at stake. However, today few have ever seen so much as a single case of smallpox, plague, or anthrax, or, for that matter, would recall the characteristics of such cases. Few, if any, diagnostic laboratories are prepared to confirm promptly such diagnoses.

Of a long list of potential pathogens, only a handful are reasonably easy to prepare and disperse and can inflict sufficiently severe disease to paralyze a city and perhaps a nation. In April 1994, Anatoliy Vorobyov, a Russian bioweapons expert, presented to a working group of the National Academy of Sciences the conclusions of Russian experts as to the agents most likely to be used (8). Smallpox headed the list followed closely by anthrax and plague. None of these agents has so far effectively been deployed as a biological weapon, and thus no real world events exist to provide likely scenarios. However, we have had several well-documented smallpox importations into Europe over recent decades; two bear recounting.

Smallpox is caused by a virus spread from person to person; infected persons have a characteristic fever and rash. Virus infection invariably results in symptomatic disease. There are no mild, subclinical infections among unvaccinated persons. After an incubation period of 10 to 12 days, the patient has high fever and pain. Then a rash begins with small papules developing into pustules on day 7 to 8 and finally changing to scabs around day 12. Between 25% and 30% of all unvaccinated patients die of the disease. There was, and is, no specific treatment.

Until 1980, essentially all countries conducted vaccination programs of some sort, whether or not they had endemic disease (9). Until 1972, the United States mandated smallpox vaccination for all children at school entry, although the last cases had occurred in 1949, 23 years before. In the United Kingdom, four standby hospitals were to be opened only if smallpox cases were imported, and in Germany, two state-of-the-art isolation hospitals were constructed in the 1960s specifically for the isolation of smallpox cases should they occur.

In 1962, the initial response of U.S. officials to the occurrence of a single case of smallpox illustrated extreme concern. That year, a young Canadian boy returned from Brazil, traveling by air to New York and by train to Toronto by way of Albany and Buffalo (10). Shortly after arrival in Toronto, he developed a rash and was hospitalized. In response to this single case, senior U.S. government officials seriously considered a plan of action that called for the border with Canada to be closed, for mass vaccination campaigns to be conducted in all cities along the route from New York through Albany, Syracuse, Rochester, and Buffalo, and for vaccination of all who had been in Grand Central Station on the day the Canadian boy was there. Sensibly, this plan was soon scrapped for more modest measures, albeit not without considerable debate.

The potential of aerosolized smallpox to spread over a considerable distance and to infect at low doses was vividly demonstrated in an outbreak in Germany in 1970 (11). That year, a German electrician returning from Pakistan became ill with high fever and diarrhea. On January 11, he was admitted to a local hospital and was isolated in a separate room on the ground floor because it was feared he might have typhoid fever. He had contact with only two nurses over the next 3 days. On January 14 a rash developed, and on January 16 the diagnosis of smallpox was confirmed. He was immediately transported to one of Germany's special isolation hospitals, and more than 100,000 persons were promptly vaccinated. The hospital had been closed to visitors because of an influenza outbreak for several days before the patient was admitted. After the diagnosis of smallpox, other hospital patients and staff were quarantined for 4 weeks and were vaccinated; very ill patients received vaccinia-immune globulin first. However, the smallpox patient had had a cough, a symptom seldom seen with smallpox; coughing can produce a large-volume, small-particle aerosol like what might occur after its use as a terrorist weapon. Subsequently, 19 cases occurred in the hospital, including four in other rooms on the patient's floor, eight on the floor above, and nine on the third floor. Two were contact cases. One of the cases was in a visitor who had spent fewer than 15 minutes in the hospital and had only briefly opened a corridor door, easily 30 feet from the patient's room, to ask directions. Three of the patients were nurses, one of whom died. This outbreak occurred in a well-vaccinated population.

An outbreak in Yugoslavia in February 1972 also illustrates the havoc created even by a small number of cases. Yugoslavia's last case of smallpox had occurred in 1927. Nevertheless, Yugoslavia, like most countries, had continued populationwide vaccination to protect against imported cases. In 1972, a pilgrim returning from Mecca became ill with an undiagnosed febrile disease. Friends and relatives visited from a number of different areas; 2 weeks later, 11 of them became ill with high fever and rash. The patients were not aware of each other's illness, and their physicians (few of whom had ever seen a case of smallpox) failed to make a correct diagnosis.

One of the 11 patients was a 30-year-old teacher who quickly became critically ill with the hemorrhagic form, a form not readily diagnosed even by experts. The teacher was first given penicillin at a local clinic, but as he became increasingly ill, he was transferred to a dermatology ward in a city hospital, then to a similar ward in the capital city, and finally to a critical care unit because he was bleeding profusely and in shock. He died before a definitive diagnosis was made. He was buried 2 days before the first case of smallpox was recognized.

The first cases were correctly diagnosed 4 weeks after the first patient became ill, but by then, 150 persons were already infected;

of these, 38 (including two physicians, two nurses, and four other hospital staff) were infected by the young teacher. The cases occurred in widely separated areas of the country. By the time of diagnosis, the 150 secondary cases had already begun to expose yet another generation, and, inevitably, questions arose as to how many other yet undetected cases there might be.

Health authorities launched a nationwide vaccination campaign. Mass vaccination clinics were held, and checkpoints along roads were established to examine vaccination certificates. Twenty million persons were vaccinated. Hotels and residential apartments were taken over, cordoned off by the military, and all known contacts of cases were forced into these centers under military guard. Some 10,000 persons spent 2 weeks or more in isolation. Meanwhile, neighboring countries closed their borders. Nine weeks after the first patient became ill, the outbreak stopped. In all, 175 patients contracted smallpox, and 35 died.

What might happen if smallpox were released today in a U.S. city? First, routine vaccination stopped in the United States in 1972. Some travelers, many military recruits, and a handful of laboratory workers were vaccinated over the following 8 years. Overall, however, it is doubtful that more than 10% to 15% of the population today has residual smallpox immunity. If some modest volume of virus were to be released (perhaps by exploding a light bulb containing virus in a Washington subway), the event would almost certainly go unnoticed until the first cases with rash began to appear 9 or 10 days later. With patients seen by different physicians (who almost certainly had never before seen a smallpox case) in different clinics, several days would probably elapse before the diagnosis of smallpox was confirmed and an alarm was sounded.

Even if only 100 persons were infected and required hospitalization, a group of patients many times larger would become ill with fever and rash and receive an uncertain diagnosis. Some would be reported from other cities and other states. Where would all of these patients be admitted? In the Washington, D.C., metropolitan area, no more than 100 hospital beds provide adequate isolation. Who would care for the patients? Few hospital staff have any smallpox immunity. Moreover, one or two patients with severe hemorrhagic cases (which typically have very short incubation periods), who would have been hospitalized before smallpox was suspected, would have been cared for by a large, unprotected intensive care team.

What of contacts? In past outbreaks, contacts of confirmed or suspected cases numbered in the thousands, if not tens of thousands. What measures should or could be taken to deal with such numbers? Would patients be isolated as in Yugoslavia, and if so, where? Logistics could be simplified if rapid, easily used laboratory tests could confirm or rule out smallpox among suspected cases. At present, however, such tests are known only to scientists in two government laboratories.

An immediate clamor for mass vaccination (as in the outbreaks in Germany and Yugoslavia) can be predicted. U.S. stocks of smallpox vaccine are nominally listed at 15 million doses, but with packaging, the useful number of doses is perhaps half that number. How widely and quickly should this vaccine be used? Were vaccine to be limited strictly to close contacts of confirmed cases, comparatively few doses would be needed. However, the realities of dealing with even a small epidemic would almost certainly preclude such a cautious, measured vaccination effort. Vaccine reserves would rapidly disappear, and there is, at present, no manufacturing capacity to produce additional vaccine. If an emergency effort were made to produce new stocks of smallpox vaccine, many months to a year or more would be required.

What of anthrax, which has been so enthusiastically embraced by both Iraq and the Aum Shinrikyo? The organism is easy to produce in large quantity. In its dried form, it is extremely stable. The effect of aerosolized anthrax on humans once had to be inferred from animal experiments and the occasional human infection among workers in factories processing sheep and goat hides (12). It was clear that inhalation of anthrax is highly lethal. Just how lethal became evident in the 1979 Sverdlovsk epidemic (13).

In all, 77 cases were identified with certainty; 66 patients died. The actual total number of cases was probably considerably more than 100. The persons affected lived or worked somewhere within a narrow zone extending some 4 km south and east of a military bioweapons facility. An accidental airborne release of anthrax spores occurred during a single day and may well have lasted no more than minutes. Further investigations revealed anthrax deaths among sheep and cows in six different villages up to 50 km southeast of the military compound along the same axis as the human cases.

Of the 58 patients with known dates of disease onset, only 9 had symptoms within a week after exposure; some became ill as late as 6 weeks after exposure. Whether the onset of illness occurred sooner or later, death almost always followed within 1 to 4 days after onset. However, there appeared to be a somewhat higher proportion of survivors after the fourth week. This almost certainly resulted from the widespread application of penicillin prophylaxis and anthrax vaccine, both of which were distributed in mid-April throughout a population of 59,000.

Meselson and his colleagues, who documented this outbreak, calculate that the weight of spores released as an aerosol could have been as little as a few milligrams or as much as "nearly a gram." Iraq acknowledged producing at least 8,000 L of solution with an anthrax spore and cell count of 109/ml (1). The ramifications of even a modest-sized release of anthrax spores in a city are profound. Emergency rooms would begin seeing a few patients with high fever and some difficulty breathing perhaps 3 to 4 days after exposure. By the time the patients were seen, it is almost certain that it would be too late for antibiotic therapy. All patients would die within 24 to 48 hours. No emergency room physicians or infectious disease specialists have ever seen a case of inhalation anthrax; medical laboratories have had virtually no experience in its diagnosis. Thus, at least 3 to 5 days would elapse before a definitive diagnosis would be made.

Once anthrax was diagnosed, one would be faced with the prospect of what to do over the succeeding 6 to 8 weeks. Should vaccine be administered to those who might have been exposed? At present, little vaccine is available, and no plan exists to produce any for civilian use. Should antibiotics be administered prophylactically? If so, which antibiotics, and what should be the criteria for exposure? What quantity would be required to treat an exposed population of perhaps 500,000 over a 6-week period? Should one be concerned about additional infections resulting from anthrax spores subsequently resuspended and inhaled by others? Should everyone who has been anywhere near the city report to a local physician for treatment at the first occurrence of fever or cough, however mild? Undoubtedly, many would have such symptoms, especially in the winter; how can such symptoms be distinguished from the premonitory symptoms of anthrax that may proceed to death within 24 to 48 hours?

We are ill-prepared to deal with a terrorist attack that employs biological weapons. In countering civilian terrorism, the focus (a modest extension of existing protocols to deal with a hazard materials incident) has been almost wholly on chemical and explosive weapons. A chemical release or a major explosion is far more manageable than the biological challenges posed by smallpox or anthrax. After an explosion or a chemical attack, the worst effects are quickly over, the dimensions of the catastrophe can be defined, the toll of injuries and deaths can be ascertained, and efforts can be directed to stabilization and recovery. Not so following the use of smallpox or anthrax. Day after relentless day, additional cases could be expected, and in new areas.

The specter of biological weapons use is an ugly one, every bit as grim and foreboding as that of a nuclear winter. As was done in response to the nuclear threat, the medical community should educate the public and policy makers about the threat. We need to build on the 1972 Biological and Toxin Weapons Convention to strengthen measures prohibiting the development and production of biological weapons and to ensure compliance with existing agreements. In a broader sense, we need a strong moral consensus condemning biological weapons.

But this is not enough. In the longer term, we need to be as prepared to detect, diagnose, characterize epidemiologically, and respond appropriately to biological weapons use as to the threat of new and reemerging infections. In fact, the needs are convergent. We need at international, state, and local levels a greater capacity for surveillance; a far better network of laboratories and better diagnostic instruments; and a more adequate cadre of trained epidemiologists, clinicians, and researchers.

On the immediate horizon, we cannot delay the development and implementation of strategic plans for coping with civilian bioterrorism. The needed stocking of vaccines and drugs as well as the training and mobilization of health workers, both public and private, at state, city, and local levels will require time. Knowing well what little has been done, I can only say that a mammoth task lies before us.

D.A. Henderson is a distinguished service professor at the Johns Hopkins University, with appointments in the Departments of Health and Epidemiology, School of Hygiene and Public Health. Dr. Henderson directed the World Health Organization's global smallpox eradication campaign (1966-1977) and helped initiate WHO's global program of immunization in 1974. He also served in the federal government as deputy assistant secretary and senior science advisor in the Department of Health and Human Services.

References

1. Ekeus R. Iraq's biological weapons programme: UNSCOM's experience. Memorandum report to the United Nations Security Council; 1996 20 Nov; New York.
2. Zalinskas RA. Iraq's biological weapons: the past as future? JAMA 1997;278:418-24.
3. Daplan E, Marchell A. The cult at the end of the world. New York: Crown Publishing Group; 1996.
4. Roberts B. New challenges and new policy priorities for the 1990s. In: Biologic weapons: weapons of the future. Washington: Center for Strategic and International Studies; 1993.
5. Bioweapons and bioterrorism. JAMA 1997;278:351-70, 389-436.
6. Tucker JB. National health and medical services response to incidents of chemical and biological terrorism. JAMA 1997;285:362-8.
7. Danzig R, Berkowsky PB. Why should we be concerned about biological warfare? JAMA 1997;285:431-2.
8. Vorobyov A. Criterion rating as a measure of probable use of bio agents as biological weapons. In: Papers presented to the Working Group on Biological Weapons Control of the Committee on International Security and Arms Control, National Academy of Sciences; 1994 Apr; Washington.
9. Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi I. Smallpox and its eradication. Geneva: World Health Organization; 1988.
10. Epidemiologic report. Smallpox, Canada. MMWR Morb Mortal Wkly Rep 1962;11:258.
11. Wehrle PF, Posch J, Richter KH, Henderson DA. An airborne outbreak of smallpox in a German hospital and its significance with respect to other recent outbreaks in Europe. Bull World Health Organ 1970;4:669-79.
12. Brachman PS, Friedlander AM. Anthrax. In: Plotkin SA, Mortimer EA, editors. Vaccines. Philadelphia: WB Saunders; 1994.
13. Meselson M, Guillemin V, Hugh-Jones M, Langmuir A, Popova I, Shelokov A, et al. The Sverdlovsk anthrax outbreak of 1979. Science 1994;266:1202-8.

Emerging Infectious Diseases
National Center for Infectious Diseases
Centers for Disease Control and Prevention
Atlanta, GA

URL: http://www.cdc.gov/ncidod/EID/vol4no3/hendrsn.htm

Updated: 11/16/1998 15:43:05

EMERGING INFECTIOUS DISEASES Volume 4 Number 3
Past Issues | Current Issue | Upcoming Issue | Past Issues | Search | Home | July–September 1998
Download | ASCII Text | Adobe PDF | Postscript |

Special Issue

Bioterrorism as a Public Health Threat

Joseph E. McDade* and David Franz‡
*Centers for Disease Control and Prevention, Atlanta, Georgia, USA; ‡U.S. Army Medical Research Institute of Infectious Diseases, Ft. Detrick, Maryland, USA

In addition to meeting the continuing threat of new and reemerging infectious diseases, public health officials must also prepare for the possible use of infectious agents as weapons by terrorists to further personal or political agendas. These were the conclusions of session panelists Scott Lillibridge, Centers for Disease Control and Prevention (CDC); Michael Skeels, Oregon State Public Health Laboratory; Marcelle Layton, New York City Department of Public Health; David Franz, U.S. Army Medical Research Institute of Infectious Diseases; and Randall Murch, Federal Bureau of Investigation (FBI).

The potential spectrum of bioterrorism ranges from hoaxes and use of nonmass casualty devices and agents by individuals and small groups to state-sponsored terrorism that employs classic biological warfare agents and can produce mass casualties. The agents of anthrax, plague, brucellosis, smallpox, viral encephalidites, and viral hemorrhagic fevers are of particular concern: they are relatively easy and inexpensive to produce, cause death or disabling disease, and can be aerosolized and distributed over large geographic areas. If released under ideal environmental circumstances, these agents can infect hundreds of thousands of persons and cause many deaths. Such scenarios would present serious challenges for patient management and for prophylaxis of exposed persons; environmental contamination could provide a continuing threat to the population (especially those exposed at the beginning of the crisis) and generate panic in the community.

Bioterrorist attacks could be covert or announced and could be caused by virtually any pathogenic microorganism. The case of the Rajneeshee religious cult in The Dalles, Oregon, is an example (1). The cult planned to infect residents with *Salmonella* on election day to influence the results of county elections. To practice for the attack, they contaminated salad bars at 10 restaurants with *S.* Typhimurium on several occasions before the election. A communitywide outbreak of salmonellosis resulted; at least 751 cases were documented in a county that typically reports fewer than five cases per year. Although bioterrorism was considered a possibility when the outbreak was being investigated by public health officials, it was considered unlikely. The source of the outbreak became known only when FBI investigated the cult for other criminal violations. A vial of *S.* Typhimurium identical to the outbreak strain was found in a clinical laboratory on the cult's compound, and members of the cult subsequently admitted to contaminating the salad bars and putting *Salmonella* into a city water supply tank. This incident, among other recent events, underscores the importance of improving preparedness at all levels.

A bioterrorist attack may be difficult to distinguish from a naturally occurring infectious disease outbreak. Investigators must first examine the etiology and epidemiology of an outbreak to identify its source, mode of transmission, and persons at risk. Certain clues may indicate whether an outbreak is the result of purposeful release of microorganisms. Naturally occurring diseases are endemic to certain areas and involve traditional cycles of transmission; some diseases occur seasonally, and sentinel cases are not uncommon. In contrast, a disease outbreak due to bioterrorism could occur in a nonendemic-disease area, at any time of year, without warning, and depending on the etiologic agent and mode of transmission, in large numbers—thousands of cases might occur abruptly. Public health officials must be appropriately sensitized to the possibility of bioterrorism when investigating disease outbreaks. Suspected bioterrorism should be reported promptly to FBI, which is responsible for coordinating interagency investigations of such episodes. FBI scientists are also well trained in forensic methods for criminal investigations and are prepared to react quickly and effectively.

Maintaining effective disease surveillance is an essential first step in preparedness and is important in helping law enforcement officials to react swiftly. Ensuring adequate epidemiologic and laboratory capacity nationwide are prerequisites to effective surveillance systems. Preparations also must include plans for rapid identification and characterization of agents involved and for emergency distribution of large quantities of medical supplies, especially antibiotics and vaccines. Coordination and communication links also need to be strengthened to minimize response time, especially at first when exposed but asymptomatic persons may still be treated prophylactically. Also, when response time is shortened, the possibility of apprehending perpetrators increases. Education and training in bioterrorism and its potential consequences must become national priorities.

Many agencies and organizations must work

collaboratively to ensure national preparedness against bioterrorist attacks. CDC is well positioned to provide leadership in several areas. In partnership with state health departments, the agency maintains infectious disease surveillance systems and provides reference laboratory diagnosis and epidemiologic support, especially during outbreak investigations; disseminates public health recommendations and other information, issues quarantine measures, and provides expert advice on worker health and safety; and is the logical bridge between the public health community and FBI's scientific and response capabilities. Enhancing the public health infrastructure will improve U.S. ability to respond to any infectious disease outbreak and provide added value in the event of a bioterrorist event.

References

1. Torok TJ, Tauxe RV, Wise RP, Livengood JR, Sokolow R, Mauvais S, et al. A large community outbreak of salmonellosis caused by intentional contamination of restaurant salad bars. JAMA 1997;278:389-95.

Joseph McDade, Centers for Disease Control and Prevention, Atlanta, Georgia, USA; Carlos Lopez, Eli Lilly and Company, Indianapolis, Indiana, USA; D.A. Henderson, The Johns Hopkins University, Baltimore, Maryland, USA

Emerging Infectious Diseases
National Center for Infectious Diseases
Centers for Disease Control and Prevention
Atlanta, GA

URL: http://www.cdc.gov/ncidod/EID/vol4no3/mcdade.htm

Updated: 11/16/1998 15:43:08