Annals of Internal Medicine | Review

Systematic Review: A Century of Inhalational Anthrax Cases from 1900 to 2005

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Background: Mortality from inhalational anthrax during the 2001 U.S. attack was substantially lower than that reported historically.

Purpose: To systematically review all published inhalational anthrax case reports to evaluate the predictors of disease progression and mortality.

Data Sources: MEDLINE (1966–2005), 14 selected journal indexes (1900–1966), and bibliographies of all retrieved articles.

Study Selection: Case reports (in any language) between 1900 and 2005 that met predefined criteria.

Data Extraction: Two authors (1 author for non–English-language reports) independently abstracted patient data.

Data Synthesis: The authors found 106 reports of 82 cases of inhalational anthrax. Mortality was statistically significantly lower for patients receiving antibiotics or anthrax antiserum during the prodromal phase of disease, multidrug antibiotic regimens, or pleural fluid drainage. Patients in the 2001 U.S. attack were less likely to die than historical anthrax case-patients (45% vs. 92%; $P < 0.001$) and were more likely to receive antibiotics during the prodromal phase (64% vs. 13%; $P < 0.001$), multidrug regimens (91% vs. 50%; $P = 0.027$), or pleural fluid drainage (73% vs. 11%; $P < 0.001$). Patients who progressed to the fulminant phase had a mortality rate of 97% (regardless of the treatment they received), and all patients with anthrax meningoencephalitis died.

Limitations: This was a retrospective case review of previously published heterogeneous reports.

Conclusions: Despite advances in supportive care, fulminant-phase inhalational anthrax is usually fatal. Initiation of antibiotic or anthrax antiserum therapy during the prodromal phase is associated with markedly improved survival, although other aspects of care, differences in clinical circumstances, or unreported factors may contribute to this observed reduction in mortality. Efforts to improve early diagnosis and timely initiation of appropriate antibiotics are critical to reducing mortality.

Ann Intern Med. 2006;144:270-280. www.annals.org
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The 2001 anthrax attack demonstrated the vulnerability of the United States to anthrax bioterrorism. The mortality rate observed during the 2001 U.S. attack (45%) was considerably lower than that historically reported for inhalational anthrax (89% to 96%) (1, 2). This reduction generally is attributed to the rapid provision of antibiotics and supportive care in modern intensive care units (3). However, no comprehensive reviews of reports of inhalational anthrax cases (including those from 2001) that evaluate how patient factors and therapeutic interventions affect disease progression and mortality have been published.

Before the introduction of antibiotics, anthrax infection was primarily treated with antiserum (4). Anthrax antiserum reportedly decreased mortality by 75% compared with no treatment (5–8), and its efficacy is supported by recent animal data (9). Later, effective antibiotics, such as penicillin and chloramphenicol, were added to anthrax treatment strategies (10, 11). Currently, combination antibiotic therapy with ciprofloxacin (or doxycycline), rifampin, and clindamycin is recommended on the basis of anecdotal evidence from the U.S. 2001 experience (1, 12, 13). Historically, the clinical course of untreated inhalational anthrax has been described as biphasic, with an initial benign prodromal latent phase, characterized by a nonspecific flu-like syndrome, followed by a severe fulminant acute phase, characterized by respiratory distress and shock that usually culminates in death (2, 14). The duration of the prodromal phase has been reported to range from 1 to 6 days (14, 15), whereas that of the fulminant phase has been described as less than 24 hours (14, 16). A 1957 study confirmed these estimates of disease progression but was based on only 6 patients (17). Because a report synthesizing the data from all reported cases of inhalational anthrax (including those from 2001) has not been published, we do not have accurate estimates of the time course associated with disease progression or a clear understanding of the extent to which patient characteristics and treatment factors affect disease progression and mortality. This information is important for developing appropriate treatment and prophylaxis protocols and for accurately simulating anthrax-related illness to inform planning efforts for bioterrorism preparedness.

We systematically reviewed published cases of inhalational anthrax between 1900 and 2005 to evaluate the effects of patient factors (for example, age and sex) and ther-

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apeutic factors (for example, time to onset of treatment) on disease progression and mortality.

Key Summary Points

Initiation of antibiotic or anthrax antiserum therapy during the prodromal phase of inhalational anthrax is associated with an improved short-term survival.

Multidrug antibiotic regimens are associated with decreased mortality, especially when they are administered during the prodromal phase.

Most surviving patients will probably require drainage of reaccumulating pleural effusions.

Despite modern intensive care, fulminant-phase anthrax is rarely survivable.

Methods

Literature Sources and Search Terms

We searched MEDLINE to identify case reports of inhalational anthrax (January 1966 to June 2005) by using the Medical Subject Heading (MeSH) terms *anthrax* and *case reports*. Because many reports were published before 1966 (the earliest publication date referenced in MEDLINE), we performed additional comprehensive searches of retrieved bibliographies and the indexes of 14 selected journals from 1900 to 1966 (for example, *New England Journal of Medicine*, *The Lancet*, *La Presse Médicale*, *Deutsche Medizinische Wochenschrift*, and *La Semana Médica*) to obtain additional citations. We considered all case reports of inhalational anthrax to be potentially eligible for inclusion, regardless of language.

Study Selection

We considered a case report to be eligible for inclusion if its authors established a definitive diagnosis of inhalational anthrax. **Appendix Table 1** (available at www.annals.org) presents the details of our inclusion criteria. We excluded articles that described cases presenting before 1900 because *Bacillus anthracis* was not identified as the causative agent of clinical inhalational anthrax until 1877 (18) and because the use of reliable microscopic (19) and culture examination techniques (20) to confirm the diagnosis were not developed until the late 19th century.

Data Abstraction

One author screened potentially relevant articles to determine whether they met inclusion criteria. Two authors independently abstracted data from each included English-language article and reviewed bibliographies for additional potentially relevant studies. One author abstracted data from non–English-language articles. We resolved abstraction discrepancies by repeated review and discussion. If 2 or more studies presented the same data from 1 patient, we included these data only once in our analyses.

We abstracted 4 types of data from each included article: year of disease onset, patient information (that is, age, sex, and nationality), symptom and disease progression information (for example, time of onset of symptoms, fulminant phase, and recovery or death and whether the patient developed meningitis), and treatment information (for example, time and disease stage of the initiation of appropriate treatment and hospitalization).

We based our criteria for determining whether a patient had progressed from the prodromal phase to the fulminant phase on distinguishing clinical features of five 2001 (3, 21, 22) and five 1957 (17) cases of fulminant inhalational anthrax. The fulminant phase is described historically as a severe symptomatic disease characterized by abrupt respiratory distress (for example, dyspnea, stridor, and cyanosis) and shock. Meningoencephalitis has been reported to occur in up to 50% of cases of fulminant inhalational anthrax (23). We considered any patient who had marked cyanosis with respiratory failure, who needed mechanical ventilation, who had meningoencephalitis, or who died as having been in the fulminant phase of disease. We used the reported time of an acute change in symptoms or deteriorating clinical picture to estimate when a confirmed fulminant case had progressed from the prodromal phase.

We considered therapy for inhalational anthrax to be appropriate if either an antibiotic to which anthrax is susceptible was given (by oral, intramuscular, or intravenous routes) (24–27) or anthrax antiserum therapy was initiated. We classified patients who received antibiotics that are resistant to strains of *B. anthracis* (<70% susceptibility) as having received no antibiotics. If treatment with antibiotics or antiserum was given, we assumed that the treatment was appropriately dosed and administered.

Statistical Analyses

We used univariate analyses with SAS software, version 9.1 (SAS Institute Inc., Cary, North Carolina), to summarize the key patient and treatment characteristics. We compared categorical variables with the Fisher exact test and continuous variables with a 2-tailed Wilcoxon–Mann–Whitney test. For single comparisons, we considered a P value less than 0.05 to be statistically significant. When comparing U.S. 2001 with pre-2001 cases (or comparing patients who lived with those who died), we applied a Bonferroni correction to account for multiple comparisons (we considered $P < 0.025$ to be statistically significant: $0.05/2 = 0.025$). We computed correlations for pairs of predictors available for each case at the beginning of the course of disease.

Adjustments for Censored Data

Infectious disease data are subject to incomplete observations of event times (that is, to censoring), particularly in

the presence of therapeutic interventions. This can lead to invalid estimation of relevant event time distributions. For example, patients with longer prodromal stage durations are more likely to receive antibiotics than patients with shorter prodromal stage durations, and they may be, therefore, less likely to progress to fulminant stage or death. To account for censoring of our time data, we used maximum likelihood estimates by using both Weibull and log-normal distributions (28). The Appendix (available at www.annals.org) provides a detailed description of these analyses.

Evaluating Predictors of Disease Progression and Mortality

We used a multivariate Cox proportional hazards model to evaluate the prognostic effects of the following features on survival: providing antibiotics or antiserum (a time-dependent covariate in 3 categories: none, single-drug regimen, or multidrug regimen); the stage during which treatment with antibiotics or antiserum was initiated (prodromal stage vs. fulminant stage or no therapy); age (continuous variable); sex; if therapy was given, whether patients received a multidrug regimen (for example, ≥2 appropriate antibiotics or combination antibiotic–anthrax antiserum therapy); the use of pleural fluid drainage (a time-dependent covariate); development of anthrax meningoencephalitis (a time-dependent covariate); and whether the case was from the 2001 U.S. attack. We assessed each variable by stepwise backward regression using a P value cutoff of 0.100 or less. We excluded 8 adult patients for whom age was not reported. Although we did not perform extensive goodness-of-fit tests of our models, we did at least fit models in which we entered time not only linearly but also quadratically. Improvement in fit, as judged by conventional Wald and other tests, did not result, nor did including quadratic time variables further explain the data.

To estimate mortality as a function of duration from symptom onset to antibiotic initiation, we first calculated a disease progression curve describing the time from symptom onset to fulminant phase among untreated patients by using the Weibull maximum likelihood estimates from the 71 cases for which time estimates were known. We then assigned a mortality rate to patients who had treatment initiated during the prodromal phase derived from a linear regression of U.S. 2001 patients who had treatment with antibiotics initiated during the prodromal stage (conditional probability of mortality given time to antibiotic treatment initiation = $0.012 \times$ [time to antibiotic treatment measured in days] + 0.1) and a mortality rate of 100% to patients who had treatment initiated during the fulminant phase (on the basis of the U.S. 2001 experience). For example, on day 4 after symptom onset (where 51% of patients are predicted to have progressed to the fulminant phase on the basis of our Weibull model), the mortality rate was estimated at 58%: $([\{0.012 \times 4\} + 0.1] \times 0.49) + (1.0 \times 0.51)$. We then developed a curve that estimated mortality as a function of the delay between symptom onset and antibiotic initiation.

Role of the Funding Source

This work was performed under contract to the Agency for Healthcare Research and Quality (contract no. 290-02-0017) and was also supported in part by the U.S. Department of Veterans Affairs. The funding sources had no role in the design, conduct, or reporting of the study or in the decision to submit the manuscript for publication.

RESULTS

We identified 246 titles of potentially relevant articles from our MEDLINE search and 2253 additional references from our manual search of the bibliographies of retrieved articles and the indexes of the 14 selected journals. From a previous review of the 2001 U.S. anthrax attack (29), we included 1 case described in a newspaper article (30) with clinical information that was not reported in the peer-reviewed literature. Of the 2500 potentially relevant articles, 66 English-language reports (2, 3, 17, 21, 22, 30–90) and 40 non–English-language reports (91–130) describing 82 cases met our inclusion criteria (**Figure 1**). **Appendix Table 2** (available at www.annals.org) presents detailed information about each case.

Description of Excluded Cases

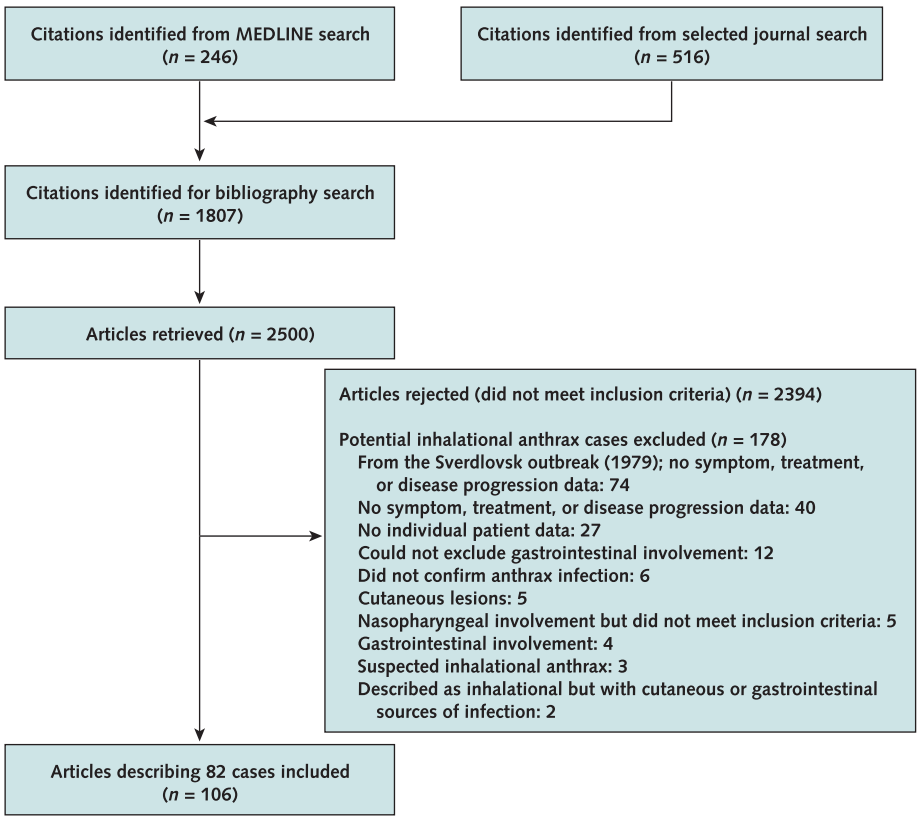
We excluded 74 cases from the 1979 Sverdlovsk outbreak because symptoms, treatment, and disease progression variables were not reported (131–137). An additional 45 reports (7, 68, 78, 122, 138–178) describing 104 additional potential cases of inhalational anthrax did not meet our inclusion or exclusion criteria (**Figure 1**).

Patient Characteristics

Table 1 presents patient characteristics, clinical symptoms, and treatment information for the 12 included patients who survived and the 70 included patients who died. Cases were highly heterogeneous with respect to age, year of disease onset, nationality, and treatment regimen. Most patients were men (73%) with a mean age of 43 years. The most common symptoms or findings at admission were abnormal temperature (81%), abnormal lung findings (80%), fever or chills (67%), tachycardia (66%), fatigue or malaise (64%), cough (62%), or dyspnea (52%). All 26 patients who underwent chest radiography had abnormal findings, including pleural effusions (69%) or widened mediastinum (54%). Thirty-one patients (38%) developed anthrax meningoencephalitis.

Thirty-seven patients (45%) received either an antibiotic to which anthrax was susceptible or anthrax antiserum (**Appendix Table 2**, available at www.annals.org). Treatment was highly heterogeneous and included single-drug antibiotic therapy (8 of 37 patients), anthrax antiserum alone (5 of 37 patients), multidrug antibiotic therapy (23 of 37 patients), and combination antibiotic and antiserum therapy (1 of 37 patients). Of the 32 patients who received

Figure 1. **Literature search and selection.**



antibiotics, 3 patients received intramuscular drugs alone, 2 patients were given oral drugs alone, and 2 patients were given combination oral and intravenous drug regimens. This heterogeneity limited our ability to investigate the greater efficacy of specific antibiotic regimens. However, both anthrax antiserum alone ($P = 0.021$) and multidrug antibiotic regimens ($P = 0.003$) were associated with a decreased mortality compared with patients who did not receive these treatments (**Table 1**). Of the 7 patients who received antibiotics or antiserum during the prodromal stage but died, 6 patients received single-drug therapy (penicillin, tetracycline, anthrax antiserum, amoxicillin, or amoxicillin–clavulanate), 4 patients received oral antibiotics, 3 patients were relatively immunocompromised (advanced age or cirrhosis), and 2 patients had underlying lung disease (chronic obstructive pulmonary disease or berylliosis).

Duration of Disease Phase in Treated and Untreated Patients

The duration of the prodromal and fulminant phases was 4.1 days and 1.1 days, respectively. Treatment with antibiotics or anthrax antiserum trended toward an association of prolonged mean prodromal stage duration (5.8 days) compared with untreated patients (4.1 days). **Appendix Table 3**, **Appendix Table 4**, **Appendix Figure 1**, and **Appendix Figure 2** (available at www.annals.org) provide detailed data that summarize the analysis of time in each disease phase with and without treatment.

Association of Treatment and Patient Characteristics and Time to Death

The hazard ratios for time to death statistically significantly decreased in patients who had treatment with antibiotics or anthrax antiserum initiated during the prodromal phase (compared with treatment initiated during the fulminant phase or no therapy) (hazard ratio, 0.09; $P < 0.001$), who were given several antibiotics or combination antiserum–antibiotic therapy (hazard ratio, 0.02; $P < 0.001$), or who were among the U.S. 2001 cases (hazard ratio, 0.3; $P = 0.034$). Increasing time to the initiation of antibiotic or antiserum therapy (hazard ratio, 4.5; $P = 0.002$), increasing time to pleural fluid drainage (hazard ratio, 4.5; $P = 0.010$), advancing age (hazard ratio, 1.04; $P = 0.003$), and the development of meningoencephalitis (hazard ratio, 7.5; $P < 0.001$) were associated with statistically significantly higher hazard ratios for death. (Note that these P values are not corrected for multiple comparisons.)

We found that the variables that were not time-dependent (for example, age, whether a patient received antibiotics or antiserum during the prodromal stage, or whether

Table 1. **Patient Characteristics and Clinical Signs at Admission**

Variable	Patients Who Lived (n = 12)*	Patients Who Died (n = 70)*	P Value†
Characteristic			
Mean age, *y*	44 (12)	43 (62)	0.47
Men, %	75 (12)	74 (70)	1.00
U.S. 2001 case, %	50 (12)	7 (70)	<0.001
Symptoms at presentation, %			
Fever or chills	92 (12)	62 (61)	0.089
Cough	100 (12)	54 (61)	0.002
Dyspnea	83 (12)	46 (61)	0.026
Chest pain	58 (12)	41 (61)	0.34
Fatigue or malaise	75 (12)	62 (61)	0.52
Myalgia or arthralgia	33 (12)	26 (61)	0.73
Diaphoresis	50 (12)	23 (61)	0.077
Nausea or emesis	67 (12)	38 (61)	0.108
Abdominal pain or tenderness	17 (12)	28 (61)	0.72
Headache	58 (12)	47 (61)	0.54
Nonheadache neurologic symptoms	50 (12)	51 (61)	1.00
Altered mental status	33 (12)	43 (61)	0.75
Focal neurologic deficits	25 (12)	30 (61)	1.00
Meningeal signs	0 (12)	11 (61)	0.59
Odynophagia	33 (12)	10 (61)	0.053
Any nasal symptom	33 (12)	10 (61)	0.053
Rhinorrhea	8 (12)	5 (61)	0.52
Clinical signs at presentation, %			
Abnormal temperature (>37.5 °C or <36.5 °C)	92 (12)	78 (50)	0.43
Abnormal lung findings on examination (any)	100 (12)	74 (43)	0.967
Tachycardia (heart rate ≥ 100 beats/min)	83 (12)	61 (49)	0.190
Hypotension (systolic blood pressure ≤ 110 mm Hg)	17 (12)	41 (49)	0.182
Tachypnea (respiratory rate ≥ 25 breaths/min)	17 (12)	26 (50)	0.71
Abnormal chest radiograph (any)	100 (8)	100 (18)	1.00
Widened mediastinum	50 (8)	56 (18)	1.00
Pleural effusion	75 (8)	67 (18)	1.00
Treatments, %			
Any antibiotic‡ or anthrax antiserum therapy	92 (12)	37 (70)	<0.001
Single-drug antibiotic regimen (no anthrax antiserum)‡	0 (12)	13 (70)	0.34
Anthrax antiserum therapy (no antibiotics)	25 (12)	3 (70)	0.021
Multidrug antibiotic regimen (no antiserum)‡	67 (12)	21 (70)	0.003
Therapy started in prodromal phase§	75 (12)	10 (70)	<0.001
Single-drug antibiotic regimen (no anthrax antiserum)‡	0 (12)	6 (70)	1.00
Anthrax antiserum therapy (no antibiotics)	25 (12)	1 (70)	0.009
Multidrug antibiotic regimen (no antiserum)‡	50 (12)	3 (70)	<0.001
Intubation or tracheotomy performed	0 (12)	13 (70)	0.34
Pleural fluid drainage	83 (12)	9 (70)	<0.001
Outcomes, %			
Developed meningoencephalitis	0 (12)	44 (70)	0.003

* The number of patients used in each analysis is shown in parentheses.
† P value is for the comparison between patients who lived and died.
‡ Received appropriate antibiotics (≥70% of *Bacillus anthracis* strains were susceptible). The 70% cutoff was chosen a priori as a minimal standard for having received an acceptable antibiotic. Reanalysis using a ≥90% susceptibility cutoff had no effect on the analysis.
§ Received appropriate antibiotics or anthrax antiserum.

a patient was a U.S. 2001 case) were highly correlated with each other and negatively correlated with death. The development of meningoencephalitis was highly positively correlated with death.

Comparison of U.S. 2001 Cases with Pre-2001 Cases

Our analysis of the 82 included cases demonstrated differences between the U.S. 2001 cases and the pre-2001 cases (**Table 2**). The U.S. 2001 patients were older and were more likely to have had therapy initiated during the prodromal phase of the disease, to have received several antibiotics or combination antiserum–antibiotic therapy, and to have had pleural fluid drainage. However, they were less likely to have progressed from the prodromal to the fulminant phase of the disease or to have died. Of the 32 patients who received antibiotics, U.S. 2001 patients were more likely to receive fluoroquinolone (91% vs. 0%; $P < 0.001$), rifampin (55% vs. 0%; $P < 0.001$), or clindamycin (46% vs. 0%; $P = 0.002$) than pre-2001 cases.

Analysis of all 82 patients demonstrated that, with the exception of 1 patient, those who were not given antibiot-

ics or anthrax antiserum during the prodromal phase progressed to the fulminant phase (97). This patient, a veterinarian, was thought to have partial immunity from previous anthrax exposures. Antibiotic or anthrax antiserum therapy was associated with decreased disease progression among the U.S. 2001 cases (14% vs. 100% progression; $P = 0.015$) and pre-2001 cases (67% vs. 98% progression; $P = 0.006$). Regardless of antibiotic or antiserum therapy or other medical intervention, such as mechanical ventilation, only 2 patients survived after progressing to the fulminant phase (overall mortality rate in fulminant phase, 97%) (17, 35–39, 97, 98). Both surviving patients received multidrug antibiotic regimens and pleural fluid drainage. None of the 5 patients during the response to the 2001 U.S. attack or the 4 pre-2001 patients who received mechanical ventilation or a tracheotomy survived. Most surviving patients ($n = 10$ [83%]) received pleural fluid drainage. The 2 patients who did not receive pleural fluid drainage did not have clinically significant pleural effusions.

Predicting Mortality from Delays in Treatment Initiation

We estimated mortality as a function of duration between symptom onset and antibiotic treatment initiation (**Figure 2**). The U.S. 2001 median time from symptom onset to antibiotics was 4.7 days. The U.S. 2001 patients who received antibiotics in 4.7 days or sooner (median, 3.3 days) had a 40% mortality rate (**Figure 2**), similar to the predicted mortality rate of 45%. If antibiotic therapies were initiated after 4.7 days (median, 4.9 days), then the U.S. 2001 mortality rate was 75% (**Figure 2**), similar to the predicted mortality rate of 74%. If antibiotics had been initiated 2 days earlier (on average) during the 2001 U.S. attack, our model predicts that the mortality rate would have decreased by 53% (relative risk reduction).

Sensitivity Analyses

We performed several sensitivity analyses to explore further the differences in mortality between U.S. 2001 cases and pre-2001 cases. To assess whether differences in mortality between U.S. 2001 cases and pre-2001 cases were due to publication bias (for example, the possibility that deaths were more likely to be reported before 2001), we reanalyzed the Cox proportional hazards analysis, excluding the 11 U.S. 2001 cases, and found no significant effect on our findings, except that pleural fluid drainage was no longer statistically significant ($P = 0.093$). To assess whether modern methods of supportive and intensive care for patients, other than antibiotics, were a key determinant of the differences between U.S. 2001 cases and pre-2001 cases, we analyzed patients who received care before and after 1970 (a surrogate marker for the introduction of modern intensive care). Univariate analysis that excluded U.S. 2001 cases demonstrated no difference in mortality between cases presenting before 1970 ($n = 60$) or after 1970 ($n = 11$) (91% vs. 92%). Analysis of the 60 cases before 1970 demonstrated a significant association between reduced mortality and patients who received antibiotics or antiserum during the prodromal phase (60% vs. 7%; $P = 0.009$) or pleural fluid drainage (60% vs. 2%; $P = 0.001$).

Discussion

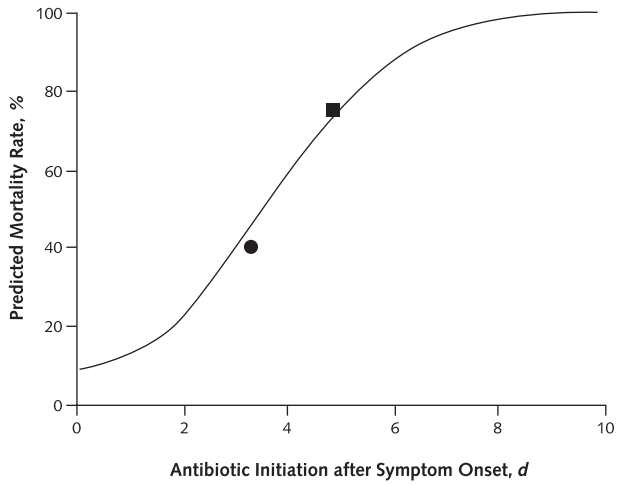
Our systematic review of 82 cases of inhalational anthrax had several key findings. First, initiation of antibiotic

Table 2. **Comparison of U.S. 2001 and Pre-2001 Patient and Disease Progression Characteristics**

Variable	U.S. 2001 Cases* ($n = 11$)	Pre-2001 Cases* ($n = 71$)	*P* Value†
Characteristic			
Mean age, *y*	60 (11)	40 (63)	<0.001
Men, %	64 (11)	75 (71)	0.47
Disease progression, %			
Mortality	45 (11)	92 (71)	<0.001
Progression from prodromal to fulminant phase for all cases	45 (11)	94 (71)	<0.001
Progression from fulminant phase to death	100 (5)	97 (67)	1.00
Meningitis	9 (11)	42 (71)	0.045
Treatment			
Mean time from symptom onset to antibiotics or anthrax antiserum, *d*‡§	4.1 (11)	4.3 (26)	0.80
Therapy (antibiotics or antiserum) started in prodromal phase, %‡	64 (11)	13 (71)	<0.001
Mortality if antibiotics or antiserum initiated during prodromal phase, %‡	14 (7)	67 (9)	0.060
Mortality if antibiotics or antiserum initiated during fulminant phase, %‡	100 (4)	88 (17)	1.0
Multidrug regimen (≥2 antibiotics or combined antiserum–antibiotic therapy) if therapy given, %‡§	91 (11)	50 (26)	0.027
Pleural fluid drainage, %	73 (11)	11 (71)	<0.001
Survivors who received pleural fluid drainage, %	100 (6)	67 (6)	0.45

* Pre-2001 cases represent cases from 1900 to 2000. The number of patients used in each analysis is shown in parentheses.
† *P* value is for the comparison between U.S. 2001 cases and pre-2001 cases.
‡ Received appropriate antibiotics (≥70% of *Bacillus anthracis* strains were susceptible) or anthrax antiserum.
§ Excluding cases for which antibiotics or anthrax antiserum was not given.

Figure 2. **Predicted mortality rate on the basis of time of antibiotic initiation.**



This graph predicts mortality rate as a function between symptom onset and antibiotic initiation. On day 4 after symptom onset (where 51% of patients are predicted to have progressed to the fulminant phase), the mortality rate was estimated at 58%: ([{0.012 × 4} + 0.1] × 0.49) + (1.0 × 0.51). See text for details. This curve closely matches the observed mortality during the 2001 U.S. attack. The median time from symptom onset to antibiotic treatment for U.S. 2001 cases was 4.7 days. The U.S. 2001 patients who received antibiotics in less than 4.7 days (median, 3.3 days) had an observed mortality rate of 40% (*circle*; predicted mortality rate, 45%). Antibiotic treatment initiation of 4.7 days or more (median, 4.9 days) during the U.S. 2001 attack resulted in an observed mortality rate of 75% (*square*; predicted mortality rate, 74%). This graph assumes that multidrug regimens, pleural fluid drainage, and intensive care support are provided, as observed during the 2001 U.S. attack.

or anthrax antiserum therapy during the prodromal phase of disease was associated with a substantial improvement in short-term survival. Second, both multidrug antibiotic regimens and pleural fluid drainage were associated with decreased mortality. Although these findings are clinically reasonable, we caution that, because our analysis was retrospective and the cases were highly heterogeneous, we cannot determine definitively whether the observed improvement in survival was due to time of initiation of antibiotic therapy, type of antibiotic therapy, the use of pleural fluid drainage, or other observed or unobserved factors. Third, even in the era of modern intensive care, fulminant-phase anthrax is rarely survivable. Finally, the duration of the prodromal phase is longer than that reported historically. The duration of the fulminant phase is extremely short, as reported previously.

Our analysis also indicates that mortality was reduced in patients who received antibiotics during the prodromal phase of the disease during the 2001 U.S. anthrax attack compared with pre-2001 patients who received antibiotic or antiserum therapy during the prodromal phase. Both multidrug regimens (≥2 antibiotics or combination antiserum–antibiotic therapy) and pleural fluid drainage were used in most U.S. 2001 cases (91% and 73%, respectively) but were used in relatively few historical cases (50% and 11%, respectively). Thus, differences in patient characteristics, anthrax exposure, supportive care, antibiotic efficacy, or other confounding factors may contribute to observed differences.

Despite these limitations, our findings support the early initiation of multidrug antibiotic therapy during the prodromal phase of the disease and the drainage of pleural effusions as important components of anthrax treatment strategies. Previous investigators have noted that of the first 10 cases during the 2001 U.S. attack, all 4 patients who had antibiotic therapy initiated during the fulminant phase died, while the 6 surviving patients had antibiotic therapy initiated during the prodromal phase (3). In addition, 10 of 12 survivors of inhalational anthrax (6 from the 2001 U.S. cases and 4 from the pre-2001 cases) required pleural fluid drainage. Of the 11 U.S. 2001 cases, 4 patients required serial therapeutic thoracenteses and 4 other patients required chest tubes to relieve respiratory distress from reaccumulating pleural effusions. Bioterrorism response plans should consider the capacity to perform this invasive but potentially important procedure.

We found that the most common symptoms of inhalational anthrax were fever (or chills), fatigue, cough, or dyspnea. These findings are consistent with 2 recent reviews, 1 review with 28 cases (179) and another review with 47 cases (180) of inhalational anthrax, which found fever (75% to 90%) and cough (79% to 94%) to be common presenting clinical features. In addition, we found that all patients who underwent chest radiography had abnormal radiologic findings.

Our analyses demonstrate that the durations of both prodromal and fulminant phases were longer than those historically reported and that antibiotics were associated with a prolongation of these stage durations. Limited data from the 1979 Sverdlovsk anthrax outbreak suggest that the overall mortality rate was 88% with a mean time from symptom onset to death of 3.9 days (131, 132, 134, 136). Our analyses found an overall mortality rate of 85% (95% CI, 75% to 93%) with a mean time from symptom onset to death of 4.8 days (CI, 4.3 to 5.3 days). We suspect possible key differences in patient characteristics, type and quality of therapeutic interventions, virulence in *B. anthracis* strains, or inhalation doses between cases in the Sverdlovsk outbreak and the anthrax cases included in our analyses. The reported mean time of 4.6 days from symptom onset to death during the U.S. 1957 outbreak (5 cases) (17) is similar to our finding from the complete set of 82 patients.

Our analyses had several potential limitations. First, because we did not have access to the original hospital and medical records, our analyses depended on the completeness and accuracy of the reporting physicians. Of the 82 included cases, 8 did not provide the age of the patient and 14 provided insufficient case descriptions to abstract time data. Second, cases were highly heterogeneous with respect

to age, year of disease onset, nationality, and treatment regimen. Thus, our findings may be attributed to patient characteristics, supportive measures and care (other than antibiotics), antibiotic efficacy, or other confounding factors that we could not assess or control. Although supportive measures and care for patients, other than antibiotics, probably varied substantially among cases, antibiotic (or antiserum) therapy during the prodromal stage and pleural fluid drainage were statistically significantly associated with decreased mortality in patients presenting before 1970 (who probably did not receive modern intensive care). Third, despite an exhaustive search, we may not have identified all cases of inhalational anthrax. The observed decreased mortality rates between U.S. 2001 and pre-2001 anthrax cases could be attributed to overreporting of anthrax-associated deaths before the 2001 U.S. attack (publication bias). However, excluding U.S. 2001 cases demonstrated no statistically significant effect on our multivariate analyses except for pleural fluid drainage. Fourth, because of the limited number of cases, our regression analysis was underpowered, and we could not include all potential interaction terms. Fifth, inhalational anthrax from bioterrorism may present and progress differently than infection from an occupational exposure. Because most pre-2001 case-patients are presumed to have contracted anthrax from an occupational exposure and because the 2001 U.S. attack was via postal exposures, our results may not be generalizable to an aerosolized attack. Finally, differences between the U.S. 2001 and historical cases may have been due to underlying patient characteristics, such as smoking status and the presence of lung disorders, that we could not include given the lack of reporting in the included articles. Of interest, no patient from the 2001 U.S. anthrax attack was a smoker and only 2 patients had a history of underlying lung disease (asthma and chronic obstructive pulmonary disease) (3, 21). We also could not evaluate whether patients were infected with different strains and received different inhalation doses of *B. anthracis* that led to differences in virulence of infection.

The U.S. Commission on National Security in the 21st Century noted that the United States is increasingly vulnerable to attack and cited the use of biological weapons, such as anthrax, "as the most likely choice of means for disaffected states and groups in the 21st century" (181). We believe that our review of 82 cases of inhalational anthrax is the first to provide a comprehensive estimate of the time course of the disease, as well as the potential effect of patient and therapeutic interventions on mortality. This information is important for developing guidelines for the timely diagnosis and appropriate management of patients presenting with inhalational anthrax. It will also be useful for developing realistic simulations that are needed to inform planning efforts for bioterrorism preparedness, such as those directed at addressing gaps in distribution systems for antibiotics, vaccines, and other necessary resources for treating and preventing inhalational anthrax.

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Acknowledgments: The authors thank Corinna Haberland, MD, MS; Veronika Sharp, MD; Pavel Strnad, MD; Kelvin Tan, MS; Suzana Tulac, PhD; and Irina Worthey for their assistance in translating non–English-language articles. The authors also thank Ingram Olkin, PhD, for statistical assistance; Nathaniel Hupert, MD, MPH, for comments on the manuscript; and Rebecca Kim and Emilee Wilhelm for retrieving articles.

Grant Support: This work was performed by the Stanford University–University of California, San Francisco, Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (contract no. 290-02-0017). This project was also supported in part by the U.S. Department of Veterans Affairs. Dr. Olshen was supported in part by National Institutes of Health/National Institute of Biomedical Imaging and Bioengineering grant 2-R01-EB-002784-30.

Potential Financial Conflicts of Interest: None disclosed.

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Appendix

Adjusting Data for Time Censoring By Using Maximum Likelihood Estimators

The clinical courses for many diseases, such as anthrax, are described in a series of multistage progressions involving transient states (for example, incubation, prodromal stage, and fulminant stage) and absorbing states (for example, death). Data describing this progression are termed "chain-of-events data" because longitudinally observed events occur in a succession in a prescribed order (182).

Data from retrospective or surveillance sources that describe this disease progression are often censored or truncated (that is, partially observed) because of underreporting caused by delays in reporting to the surveillance system (183–185) or prevention of disease progression because of public health interventions, such as antibiotic therapy (186, 187). For example, early estimates of the AIDS incubation period were inaccurate because of both right censoring (for example, exclusion of patients with HIV infection who had not yet developed AIDS) and left censoring (for example, exclusion of undiagnosed patients during the early years of the epidemic) (188). Data obtained from the 1979 Sverdlovsk outbreak are right-censored because of the interventions that prevented exposed patients from developing symptoms (186).

Censoring is particularly relevant to anthrax disease progression states in the presence of therapeutic interventions. For example, patients with longer prodromal stages have more time to seek medical care and are thus more likely to receive antibiotics or other therapy (compared with patients with shorter prodromal stage durations) during this earlier disease state and may be less likely to progress to the fulminant stage or to death.

Turnbull (28) and Dempster and colleagues (189) first proposed a maximum likelihood estimator for the analysis of censored or truncated data. It works by developing a likelihood function based on the available data and finding values of the variable estimates (for a given distribution) that maximize the likelihood function through an interactive process. The maximum likelihood estimator is highly consistent when assessing censored data (190) and is particularly useful in the analysis of chain-of-events data (191). Maximum likelihood estimators have been used to

derive time estimates of censored data for AIDS survival and incubation distributions (182, 184, 188, 191–195), the severe acute respiratory syndrome mortality and incubation times (196–199), the incubation period and disease frequency for Creutzfeldt–Jakob disease (200–204), and anthrax incubation periods (186, 205, 206).

To estimate disease progression variables, we assumed that inhalational anthrax disease progression follows a chain of events (that is, patients who died had progressed from the prodromal to fulminant stage and patients who did not progress to the fulminant stage did not die). We also assumed that antibiotic or antiserum therapy may prolong stage duration and may prevent disease progression. We performed maximum likelihood analyses by using the Reliability procedure in SAS software, version 9.1. We considered the data to be right-censored if antibiotic or antiserum therapy was given and the patient did not have disease progression or interval-censored if the patient had disease progression despite antibiotic or antiserum therapy.

Appendix Table 1. **Inclusion Criteria***

1. Cultures† and symptoms or autopsy findings‡
2. Symptoms‡ and Gram stain§ and improvement with appropriate therapy or autopsy findings‡
3. During an ongoing anthrax outbreak‖ with confirmed cases (meeting criterion 1 or 2): symptoms‡ and autopsy findings‡ or improvement with appropriate therapy¶
4. For patients with high-risk inhalational anthrax exposure (e.g., wool mill worker): symptoms‡ and improvement with anthrax antiserum (and did not receive antibiotics)

* Patients who met any 1 of the criteria were included.
† Culture (any source) or immunologic evidence of recent *Bacillus anthracis* infection (an increase in IgM antibodies or confirmed seroconversion with IgG antibodies to anthrax-protective antigen or capsule [16]). Immunologic criteria were included because of the rapidity of sterilization of blood cultures after the initiation of antibiotic treatment (13).
‡ Clinical symptoms of inhalational anthrax included flu-like symptoms, fever, cough, dyspnea, chest pain, abnormal findings on lung examination, or mediastinal widening or pleural effusions on chest radiography. Autopsy findings of inhalational anthrax included excessive pleural fluid (particularly if hemorrhagic), enlarged or hemorrhagic mediastinum, mediastinal lymphadenopathy, or subpleural congestion (40, 132, 134).
§ Gram stain evidence (any source) of *B. anthracis*: gram-positive, spore-forming, nonmotile, hemolytic, and spore-forming bacilli measuring 1 to 1.3 × 3 to 10 μm (14).
‖ An anthrax outbreak was defined as ≥2 cases of anthrax infection from a suspected common source (e.g., wool mill) presenting within a close temporal relationship (e.g., days to weeks).
¶ Received appropriate antibiotics (≥70% of *B. anthracis* strains were susceptible) or antiserum. The 70% cutoff was chosen a priori as a minimal standard for having received an acceptable antibiotic. Reanalysis using a ≥90% susceptibility cutoff had no effect on the included case reports.

Appendix Table 2. **Individual Inhalational Anthrax Case Reports***

Case Number (Reference)	Year	Country	Age, *y*	Sex	Exposure Risk†	Prodromal Symptoms‡
1 (3, 41–45)	2001	US	63	Male	Presumed bioterrorism	Malaise, myalgia, fatigue, fever, chills, anorexia, diaphoresis, nausea, emesis
2 (3, 41, 42)	2001	US	73	Male	Presumed bioterrorism	Fatigue, cough, lethargy, dyspnea, fever, rhinorrhea, diaphoresis, abdominal pain, emesis, conjunctivitis, confusion
3 (3, 30, 41, 46–48)	2001	US	56	Male	Bioterrorism	Fever, chills, odynophagia, headache, malaise, cough, dyspnea, pleurisy, myalgia, arthralgia, anorexia, diaphoresis, nausea, emesis, hemoptysis
4 (3, 41, 46–48)	2001	US	56	Male	Bioterrorism	Headache, fever, chills, odynophagia, myalgia, nausea, malaise, diaphoresis, cough, pleurisy, dyspnea, blurred vision, photophobia
5 (3, 41, 42, 47, 49)	2001	US	55	Male	Bioterrorism	Fever, diaphoresis, myalgia, cough, fatigue, dyspnea, chills, chest pain, nausea, emesis
6 (3, 41, 42, 47, 49–52)	2001	US	47	Male	Bioterrorism	Cough, nausea, emesis, abdominal colic, syncope, diaphoresis, fatigue, lightheadness, flu-like symptoms, myalgia, chills, dyspnea
7 (3, 41)	2001	US	59	Male	Bioterrorism	Diaphoresis, fatigue, myalgia, fever, chills, headache, nausea, emesis, abdominal pain, cough, chest pain
8 (3, 41, 42, 52, 53)	2001	US	56	Female	Bioterrorism	Emesis, diarrhea, fever, chills, headache, fatigue, cough, dyspnea, pleurisy
9 (3, 41, 42, 53)	2001	US	43	Female	Bioterrorism	Fever, chills, cough, chest pain, dyspnea, myalgia, fatigue, nausea, emesis, headache, stuffy head, mild confusion
10 (3, 22, 40–42, 54, 55)	2001	US	61	Female	Presumed bioterrorism	Malaise, fatigue, myalgia, chills, chest pain, dyspnea, cough, hemoptysis
11 (21, 41, 42, 56, 57)	2001	US	94	Female	Presumed bioterrorism	Fever, fatigue, myalgia, cough, dyspnea, anorexia, confusion
12 (58, 59)	1997	Turkey	64	Male	Wool	Malaise, fever, headache, abdominal pain, dyspnea
13 (91)	1992	France	33	Male	Unknown	Myalgia, asthenia, dyspnea, cough, diarrhea
14 (99)	1986	Switzerland	54	Female	Unknown	Fever, generalized weakness, nausea, back pain
15 (97, 98)	1980	Switzerland	37	Male	Textile mill	Cough, fever, dyspnea, hematemesis, melena, head cold symptoms
16 (60)	1977	India	63	Male	Unknown	Cough, fever, dizziness, headache, restlessness, urinary incontinence
17 (2, 39, 61, 62)	1976	US	32	Male	Imported yarn	Fever, odynophagia, chest pain, headache, nausea, anorexia
18 (63)	1976	Great Britain	53	Male	Unknown, bone meal?	Odynophagia, fever, chest pain, cough
19 (64)	1975	Iran	16	Female	Unknown	Dyspnea, axilla swelling
20 (64)	1975	Iran	34	Male	Unknown	Cough, dyspnea, hemoptysis
21 (100, 101)	1972	Switzerland	44	Male	Imported wool, carpet factory	Headache, emesis
22 (93–95)	1971	France	39	Male	Fertilizer factory (bone dust)	Fatigue, insomnia, emesis, diarrhea, confusion
23 (2, 39, 65)	1966	US	46	Male	Nearby goat hair factory	Fatigue, cough, diaphoresis
24 (66, 67)	1965	Great Britain	54	Male	Contaminated bone dust	Backache, abdominal pain, fever

Appendix Table 2—**Continued**

Clinical Signs at Presentation§	Treatment‖	Medical Complications¶	Died	Time to Care, *d***	Time to Antibiotic Therapy, *d*††	Time to Death, *d*‡‡
Delirium, febrile, tachycardia, abnormal findings on lung examination, abnormal chest radiogram	Cefotaxime, ceftazidime, gentamicin, metronidazole, doxycycline, ampicillin, trimethoprim–sulfamethoxazole, vancomycin	Meningitis, MV, PE	Yes	4.8	4.9	8.4
Febrile, tachycardia, hypotension, abnormal findings on lung examination, abnormal chest radiogram	Azithromycin, cefotaxime, ciprofloxacin	PE, PFD	No	5.9	6.0	–
Tachycardia, abnormal findings on lung examination, afebrile, abnormal chest radiogram	Ciprofloxacin, rifampin, clindamycin	PE, PFD	No	3.0	3.5	–
Tachycardia, abnormal findings on lung examination, afebrile, abnormal chest radiogram	Ciprofloxacin, rifampin, clindamycin	PE, PFD	No	4.0	4.7	–
Febrile	Levofloxacin	MV, PE	Yes	2.0	4.8	5.3
Hypothermic, hypotensive, abnormal chest radiogram	Penicillin, ceftriaxone, rifampin, levofloxacin	MV, PE	Yes	4.9	5.2	6.3
Febrile, tachycardia, abnormal chest radiogram	Ciprofloxacin, penicillin, rifampin, vancomycin	PE, PFD	No	1.9	2.0	–
Febrile, tachycardia, abnormal findings on lung examination, hypoxia, respiratory distress, abnormal chest radiogram	Levofloxacin, rifampin, ciprofloxacin, vancomycin	PE, PFD	No	5.0	5.2	–
Febrile	Levofloxacin, azithromycin, ciprofloxacin, doxycycline, clindamycin, ceftriaxone	PE, PFD	No	1.0	1.1	–
Hypothermic, tachycardia, tachypnea, hypoxia, abnormal findings on lung examination, abnormal chest radiogram	Levofloxacin, rifampin, ciprofloxacin, gentamicin, nafcillin, clindamycin, ceftazidime	MV, PE, PFD	Yes	3.0	3.3	5.6
Febrile, tachycardia, hypotension, abnormal chest radiogram	Ceftazidime, vancomycin, ciprofloxacin, ampicillin–sulbactam, erythromycin, clindamycin	MV, PE, PFD	Yes	2.0	4.0	6.9
Comatose, febrile, tachypnea, tachycardia, hypotension, neck swelling, neurologic deficits, abnormal chest radiogram	Penicillin, chloramphenicol	Meningitis	Yes	3.1	3.1	3.9
Febrile, hypotension, abnormal findings on lung examination, abnormal chest radiogram	Penicillin, amoxicillin–clavulanate	PE, PFD	Yes	3.0	3.1	7.1
Comatose, hypothermic, cyanosis, abnormal findings on lung examination, hypotensive, abnormal chest radiogram	Amoxicillin, chloramphenicol, flucloxacillin	Meningitis, PE, cyanosis, MV	Yes	2.0	4.4	6.3
Febrile, tachycardia, hypotension, abnormal findings on lung examination, abnormal chest radiogram	Ampicillin, gentamicin, cefamandole, rolitetracycline	PE, PFD	No	6.1	6.1	–
Tachycardia, hypotension, delirium, neurologic deficits	Penicillin, chloramphenicol	Meningitis	Yes	2.0	2.2	2.8
Abnormal findings on lung examination, neurologic deficits, tachycardia, abnormal chest radiogram	Penicillin, streptomycin	Meningitis, PE	Yes	5.0	5.3	6.2
Abdominal tenderness	Ambramycin	Meningitis, cyanosis, PE	Yes	3.1	3.1	3.8
Abnormal findings on lung examination, afebrile, abnormal chest radiogram	Penicillin, chloramphenicol	–	Yes	2.0	2.1	5.0
Abnormal findings on lung examination, restlessness, labored breathing, clammy skin, abnormal chest radiogram	None	Cyanosis, PE, PFD	Yes	3.0	–	3.8
Febrile, delirium, meningeal signs	None	Meningitis	Yes	3.0	–	4.0
Agitated, coma, diaphoretic, tachycardia, neurologic deficits, afebrile, hypotension	None	Meningitis, tracheotomy, PE	Yes	3.5	–	3.7
Delirium, lethargy, diaphoresis, abnormal findings on lung examination, febrile, tachycardia, neurologic deficits, abnormal chest radiogram	Penicillin, chloramphenicol	Meningitis, PE	Yes	5.3	5.4	5.6
Normal findings on lung examination	None	PE	Yes	0.2	–	2.3

Continued on following page

Appendix Table 2—**Continued**

Case Number (Reference)	Year	Country	Age, *y*	Sex	Exposure Risk†	Prodromal Symptoms‡
25 (68)	1965	Croatia	54	Female	Wool	Fever, chills, cough, chest pain, headache, nausea, constipation, emesis, hemoptysis, anorexia, flu-like symptoms, urticaria
26 (69)	1964	Iran	30	Male	Farmer	Fever, cough, headache, malaise, hemoptysis
27 (102)	1963	France	39	Male	Unknown	Malaise, emesis, fever
28 (2, 39, 70)	1961	US	51	Female	Goat hair, textile mill	Weakness, chills, cough, chest pain, myalgia, abdominal pain, fever, back pain, diaphoresis
29 (2, 71)	1958	US	53	Male	Laboratory	Fever, headache, myalgia
30 (17, 35–39, 72, 73)	1957	US	60	Male	Goat hair, textile mill	Headache, cough, back pain, malaise, fever
31 (17, 35–39, 72)	1957	US	65	Female	Goat hair, textile mill	Cough, chest pain, malaise, fatigue, abdominal pain, chills, fever, cold symptoms
32 (17, 35–39, 72, 73)	1957	US	49	Male	Goat hair, textile mill	Cough, chest pain, anorexia, emesis, abdominal pain, fever
33 (17, 35–39, 72)	1957	US	46	Male	Goat hair, textile mill	Malaise, fever, chills, cough, dyspnea, diaphoresis, cold symptoms
34 (17, 37–39, 72, 73)	1957	US	33	Male	Goat hair, textile mill	Fever, chills, cough, malaise, myalgia, coryza, diaphoresis, chest pain, dyspnea, emesis, dysphagia, odynophagia, anorexia
35 (2, 39, 74, 75)	1957	US	28	Male	Nearby tannery and goat hair mill	Dyspnea, cough, anorexia, chest pain, nausea
36 (103)	1955	Russia	NR	Female	Unknown	Respiratory congestion (catarrh), flu-like symptoms
37 (104, 105)	1954	France	NR	Female	Horse hair	Flu-like symptoms, headache
38 (106, 107)	1954	Russia	13	Male	Dust from infected sheep and calf	–
39 (76)	1953	Nairobi	30	Male	Tannery	Headache, hematuria, painful axilla swelling
40 (2, 77)	1951	US	37	Female	Tannery, wool mill dust	Malaise, fever, leg pain, headache, backache, anorexia, emesis, restlessness
41 (2, 74)	1948	US	50	Female	Tannery, mill dust	Cold symptoms, emesis, headache, rhinorrhea
42 (78)	1947	US	46	Male	Unknown	Cough, malaise, dyspnea, fever, headache, chest pain, hemoptysis
43 (34)	1946	US	29	Female	Unknown	Headache, upset stomach, dizziness, anorexia
44 (79)	1942	US	42	Male	Textile mill	Nausea, emesis, dyspnea, fever, chills, chest pain, abdominal pain, back pain, cough
45 (108)	1941	US	71	Male	Leather factory	Fatigue, headache, rhinorrhea, dyspnea, odynophagia
46 (109)	1929	Germany	17	Male	Wool	Fever, chills, pleurisy, cough, dyspnea, hemoptysis
47 (80)	1928	US	2.5	Female	Unknown	Choking spell, cough, restlessness
48 (110)	1928	Czech Republic	38	Male	Unknown	Chest pain, emesis, headache, cough, insomnia, fatigue, anorexia, hoarseness

Appendix Table 2—**Continued**

Clinical Signs at Presentation§	Treatment‖	Medical Complications¶	Died	Time to Care, *d***	Time to Antibiotic Therapy, *d*††	Time to Death, *d*‡‡
Febrile, tachycardia, abnormal findings on lung examination	Ambramycin, rolitetracycline	PE, cyanosis	Yes	3.1	2.4	5.1
Febrile, stuporous, hypotension, tachycardia, tachypnea, abnormal findings on lung examination, neurologic deficits, meningeal signs, abnormal chest radiogram	Penicillin, chloramphenicol, streptomycin	–	Yes	5.0	5.4	8.2
Febrile, comatose, abnormal findings on lung examination, neurologic deficits, convulsions, meningeal signs	Penicillin, tetracycline, streptomycin	Meningitis, tracheotomy	Yes	7.0	7.1	7.6
Abnormal findings on lung examination, afebrile, abnormal chest radiogram	None	Cyanosis, PE	Yes	1.0	–	3.8
Febrile, abnormal chest radiogram	Tetracycline	Cyanosis, PE	Yes	1.1	2.0	6.3
Febrile, tachycardia, hypotension, diaphoresis, respiratory stridor, abnormal findings on lung examination	None	Cyanosis, PE	Yes	0.3	–	2.9
Hypothermic, tachycardia, hypotension, abnormal findings on lung examination, abnormal chest radiogram	Penicillin	Cyanosis, PE	Yes	3.0	5.5	5.9
Delirium, febrile, tachypnea, abnormal findings on lung examination	Penicillin, streptomycin	Meningitis, PE	Yes	4.0	4.0	4.8
Febrile, tachycardia, tachypnea, abnormal findings on lung examination, cyanotic, delirium, ulcerated erythematous pharynx or tonsil, injected conjunctiva	Penicillin, streptomycin	Cyanosis, PE, PFD	No	2.9	2.9	–
Febrile, abnormal findings on lung examination, diaphoretic, pharyngeal erythema	Penicillin	Meningitis, cyanosis, PE	Yes	2.3	2.5	4.2
Tachycardia, tachypnea, afebrile	Penicillin	Cyanosis, PE	Yes	7.0	7.5	7.6
Prostration, "sepsis"	None	–	Yes	4.6	–	5.3
–	None	Meningitis	Yes	1.5	–	1.6
–	None	Meningitis	Yes	–	–	–
Febrile	Penicillin, anthrax antiserum	Meningitis	Yes	4.0	4.2	6.3
Comatose, febrile, tachycardia, neurologic deficits, meningeal signs	None	Meningitis, PE	Yes	5.0	–	5.1
Comatose, febrile, hypotension, abnormal findings on lung examination, meningeal signs, cyanosis, tachycardia, neurologic deficits, cold and clammy skin	Penicillin	Meningitis, cyanosis, PE	Yes	2.9	2.9	3.2
Tachycardia, tachypnea, hypotension, diaphoretic, abnormal findings on lung examination, cyanosis, neurologic deficits, delirium	None	Cyanosis, PE	Yes	2.9	–	3.0
Comatose, febrile, tachypnea, tachycardia, neurologic deficits, convulsions, abnormal findings on lung examination, meningeal signs	Chlortetracycline	Meningitis, PE	Yes	5.3	5.4	6.6
Febrile, cyanosis, tachycardia, tachypnea, hypotension, abnormal findings on lung examination, diaphoretic, abnormal chest radiogram	Sulfathiazole, sulfadiazine	Cyanosis, PE	Yes	0.3	–§§	4.6
Febrile, tachycardia, neck swelling, nasal obstruction, nasal turbinate edema, respiratory distress	Sulfathiazole, anthrax antiserum, sulfanilamide	PE	Yes	2.5	4.0	6.4
Febrile, tachycardia, abnormal findings on lung examination	Anthrax antiserum	–	No	3.0	3.5	–
Febrile, abnormal findings on lung examination, neurologic deficits, cyanosis, pharyngeal erythema and edema, abdominal distention, mottled skin, erythematous bulging tympanic membranes	Anthrax antiserum, horse antiserum	PE, PFD, cyanosis‖‖	No	2.0	6.0	–
Febrile, abnormal findings on lung examination, neurologic deficits, delirium, cyanosis, tachycardia, tachypnea	None	Meningitis, cyanosis	Yes	4.9	–	5.3

Continued on following page

Appendix Table 2—**Continued**

Case Number (Reference)	Year	Country	Age, *y*	Sex	Exposure Risk†	Prodromal Symptoms‡
49 (81)	1924	US	45	Female	Unknown	Dyspnea, nervousness, cough, indigestion
50 (111)	1924	Germany	34	Male	Animal fur and skins	"Not feeling well"
51 (82)	1920	US	36	Male	Tannery	Odynophagia, chest pain, cough, dyspnea
52 (83)	1917	US	50	Male	Hides, bone dust	Headache, "taken ill"
53 (84)	1917	Uganda	NR	Male	Unknown	Cough, chills, chest pain
54 (85)	1916	Great Britain	22	Male	Unknown	Chills, chest pain, headache, emesis
55 (111)	1914	Germany	59	Male	Unknown	Headache, nausea, fatigue, malaise
56 (112, 113)	1914	Germany	NR	Male	Unknown	Headache, malaise, leg weakness
57 (114, 115)	1913	Russia	42	Male	Laboratory	Felt "ill", myalgia, fatigue
58 (111)	1910	Germany	35	Male	Unknown	Cough, dyspnea, malaise
59 (116)	1910	Germany	NR	Male	Unknown	Fever
60 (86)	1909	Great Britain	42	Male	Unknown	Cold symptoms, emesis, chills, cough, wheezing, insomnia, dyspnea, headache, abdominal pain, pleurisy, malaise, syncope
61 (96)	1909	Switzerland	26	Male	Veterinarian	Chest pain, diaphoresis, chills, cough, dyspnea, headache
62 (92)	1908	Germany	31	Male	Textile mill	Chest pain, dyspnea, fatigue, abdominal pain, chills
63 (117)	1908	Russia	56	Female	Infected wool	Headache, fever, cough, fatigue
64 (117)	1908	Russia	56	Female	Infected wool	Chills, cough, chest pain, fever, fatigue, dyspnea, headache
65 (117)	1908	Russia	29	Female	Infected wool	Headache, abdominal pain, emesis, fever, fatigue, cough, dyspnea, chest pain
66 (117)	1908	Russia	NR	Female	Infected wool	Headache, chills, cough, fever, fatigue, dyspnea, chest pain
67 (117)	1908	Russia	42	Male	Infected wool	Fever, fatigue, dyspnea, chest pain, headache
68 (117)	1908	Russia	NR	Male	Infected wool	Headache, cough, stabbing flank pain, fever, fatigue, dyspnea, chest pain
69 (87)	1907	US	28	Male	Hair and wool mill	Malaise, myalgia, headache, emesis, fever, cough, dyspnea, abdominal pain
70 (88)	1907	Great Britain	32	Male	Wool mill	Headache, abdominal pain
71 (118)	1907	Germany	37	Female	Horsehair	Fever, laryngitis, cough, hemoptysis, dyspnea
72 (89)	1906	Great Britain	53	Male	Wool mill	Cough, dyspnea, shivering, nausea, headache, vertigo, malaise, emesis
73 (31–33)	1905	Great Britain	36	Male	Unknown	Headache, dizziness, anorexia
74 (119)	1904	Germany	20	Male	Horsehair	Fever, exhaustion, neck swelling
75 (120)	1904	Germany	42	Male	Dock worker	Chest pain, chills, exhaustion
76 (121, 122)	1902	Germany	54	Female	Animal hides	Chest pain, dyspnea, malaise, arthralgias
77 (123)	1902	Germany	42	Male	Unknown	–
78 (90)	1901	Great Britain	33	Male	Wool mill	Chills, myalgia, nausea
79 (124, 125)	1901	Poland	16	Female	Unknown	–
80 (126, 127)	1900	Germany	32	Male	Unknown	Chills, fever, myalgia
81 (128)	1900	Austria	NR	Male	Unknown	–
82 (129, 130)	1900	Germany	35	Male	Unknown	–

* Three patients (31–33, 91, 92) who received a diagnosis of gastrointestinal anthrax by the treating physicians met our inclusion criteria. The first patient initially received a diagnosis of community-acquired pneumonia and had pleural effusions with mediastinal lymphadenopathy but no ascites (91). Although this patient had diarrhea, this patient had no clear history of eating contaminated meat and gastrointestinal symptoms were similar to those in the US 2001 inhalational cases. The second patient had no gastrointestinal symptoms except for mild abdominal tenderness and was found to have pleural effusions with hemorrhagic mediastinitis and mediastinal lymphadenopathy at autopsy (31–33). The treating physicians could not exclude an inhalational port of entry. The final patient reported chest pain with dyspnea, and the treating physicians suspected either an inhalational or gastrointestinal source of infection (92). Two additional case-patients who met our inclusion criteria (34, 93–95) received a diagnosis of primary anthrax meningoencephalitis. In 1 case, the treating physicians suspected an inhalational port of entry (transethmoidal), and this patient had large bilateral pleural effusions at autopsy (93–95). The second case had lung disease at autopsy and was included in previous reviews of inhalational anthrax (34). Excluding these 5 patients did not statistically significantly affect the Cox proportional hazards analysis. MV = mechanical ventilation; NR = not reported; PE = pleural effusion; PFD = pleural fluid drainage; US = United States.
† Exposure to anthrax-contaminated mail in 4 of 11 US 2001 cases is unproven (e.g., presumed bioterrorism).
‡ A dash indicates not reported or inability to determine.
§ A dash indicates no additional findings compared with prodromal symptoms column, patient did not present to health care provider before death, not reported, or inability to determine.
‖ Antibiotics or anthrax antiserum. Of the 37 patients who received an anthrax-susceptible antibiotic or anthrax antiserum, 24 were given penicillins, 10 were given fluoroquinolones, 7 were given chloramphenicol, 7 were given tetracyclines, 6 were given anthrax antiserum, 6 were given rifampin, 5 were given cephalosporins, 5 were given clindamycin, 4 were given vancomycin, 3 were given macrolides, and 3 were given aminoglycosides.
¶ A dash represents cases either not seen before death or no additional signs or symptoms noted in case report at presentation.
** Time from symptom onset to initial health care contact. A dash represents cases not seen before death or inability to calculate.
†† Time from symptom onset to antibiotic (or antiserum) therapy. A dash represents no treatment given or inability to calculate.
‡‡ Time from symptom onset to death. A dash represents no death or inability to calculate.
§§ Sulfa-based antibiotics have little or no efficacy for treating anthrax (see text).
‖‖ Mild cyanosis without respiratory distress.

Appendix Table 2—**Continued**

Clinical Signs at Presentation§	Treatment‖	Medical Complications¶	Died	Time to Care, *d***	Time to Antibiotic Therapy, *d*††	Time to Death, *d*‡‡
Fever, tachycardia, tachypnea	None	–	Yes	–	–	–
Delirium	None	PE	Yes	2.6	–	2.7
Febrile, abnormal findings on lung examination, diaphoretic, cyanosis, pharyngeal congestion	Anthrax antiserum	Cyanosis	Yes	7.0	8.3	10.0
Moribund	None	–	Yes	3.9	–	4.0
Febrile, tachycardia, tachypnea, abnormal findings on lung examination	None	–	Yes	4.1	–	10.3
Comatose	None	Meningitis, PE	Yes	1.7	–	2.4
Comatose, febrile, tachycardia	None	PE, meningitis	Yes	1.0	–	1.6
Febrile, neurologic deficits, delirium	None	Meningitis	Yes	1.3	–	1.5
Afebrile, tachycardia, orthostatic dizziness	None	Cyanosis	Yes	3.5	–	3.9
Cyanosis, tachycardia, afebrile, abnormal findings on lung examination	None	Cyanosis, PE, meningitis	Yes	2.7	–	3.4
Abnormal findings on lung examination	None	PE	Yes	–	–	–
Hypothermic, hypotensive, abnormal findings on lung examination	None	PE	Yes	4.1	–	4.3
Febrile, abnormal findings on lung examination, tachycardia, slight cyanosis‡‡	None	Cyanosis‡‡	No	29.3	40.1	–
–	None	PE	Yes	4.4	–	5.0
–	None	–	Yes	–	–	5.0
Wheezing, afebrile, cyanosis, delirium, weak pulse	None	Cyanosis	Yes	2.0	–	3.0
–	None	–	Yes	–	–	2.1
–	None	–	Yes	–	–	2.0
–	None	–	Yes	–	–	3.0
Cardiovascular collapse	None	–	Yes	–	–	4.0
Febrile, tachycardia, abnormal findings on lung examination, diaphoresis	None	PE, PFD	Yes	7.0	–	7.2
–	None	-	Yes	8.0	–	8.0
Laryngeal obstruction	None	Meningitis, PE, tracheotomy	Yes	3.0	–	3.2
Febrile, abnormal findings on lung examination, tachypnea	Anthrax antiserum	Cyanosis, PE, PFD	No	2.5	3.0	–
Delirium, afebrile, neurologic deficits, abdominal tenderness	None	Meningitis, PE	Yes	0.8	–	1.5
Febrile, delirium	None	PE	Yes	8.1	–	8.6
Febrile, tachycardia, cyanosis, abnormal findings on lung examination	None	Cyanosis, PE	Yes	4.0	–	5.0
Tachycardia, cyanosis, abnormal findings on lung examination, hypothermic	None	PE, cyanosis	Yes	2.3	–	2.6
–	None	PE, meningitis	Yes	–	–	–
Febrile, tachycardia	None	Meningitis, PE	Yes	1.1	–	4.5
"In agony"	None	Meningitis, PE	Yes	–	–	–
Unconsciousness, convulsions, trismus, opisthotonos	None	Meningitis, PE	Yes	2.0	–	2.4
Unconsciousness, cyanosis, neurologic deficits	None	Cyanosis, PE, meningitis	Yes	–	–	–
Delirium, cyanosis, hypothermic	None	Cyanosis	Yes	5.0	–	6.1

Appendix Table 3. Summary of Time Analysis*

Variable	Patients, *n*	Mean Duration (95% CI), *d*	Median Duration (IQR), *d*
Overall			
Prodromal to fulminant phase	62	3.9 (3.5–4.4)	3.8 (2.7–4.9)
Fulminant phase to death	60	1.1 (0.8–1.3)	0.7 (0.3–1.5)
No antibiotics†			
Prodromal to fulminant phase	55	3.8 (3.3–4.2)	3.7 (2.6–4.8)
Fulminant phase to death	34	0.8 (0.5–1.0)	0.5 (0.3–1.2)
Antibiotic treatment started in prodromal phase†			
Prodromal to fulminant phase	8	5.0 (3.7–6.3)	4.6 (3.7–5.3)
Fulminant phase to death	8	1.3 (0.6–2.0)	1.2 (0.5–2.1)
Antibiotic treatment started in fulminant phase†			
Fulminant phase to death	18	1.5 (1.0–2.0)	1.0 (0.7–2.2)
Symptom onset to antibiotic treatment‡			
Overall	37	4.2 (3.7–4.8)	4.0 (3.0–5.4)
Lived	11	4.0 (3.0–5.0)	3.5 (2.9–5.6)
Died	26	4.3 (3.7–5.0)	4.1 (3.1–5.3)
Time in hospital			
Overall§	69	3.5 (1.9–5.1)	0.8 (0.3–3.0)
Lived§	9	18.2 (11.9–24.5)	17.0 (12.0–22.0)
Died	60	1.3 (0.9–1.6)	0.7 (0.3–1.6)
Symptom onset to recovery§	9	22.1 (15.1–29.2)	22.0 (14.0–27.0)
Symptom onset to death	64	4.8 (4.3–5.3)	4.7 (3.1–6.3)

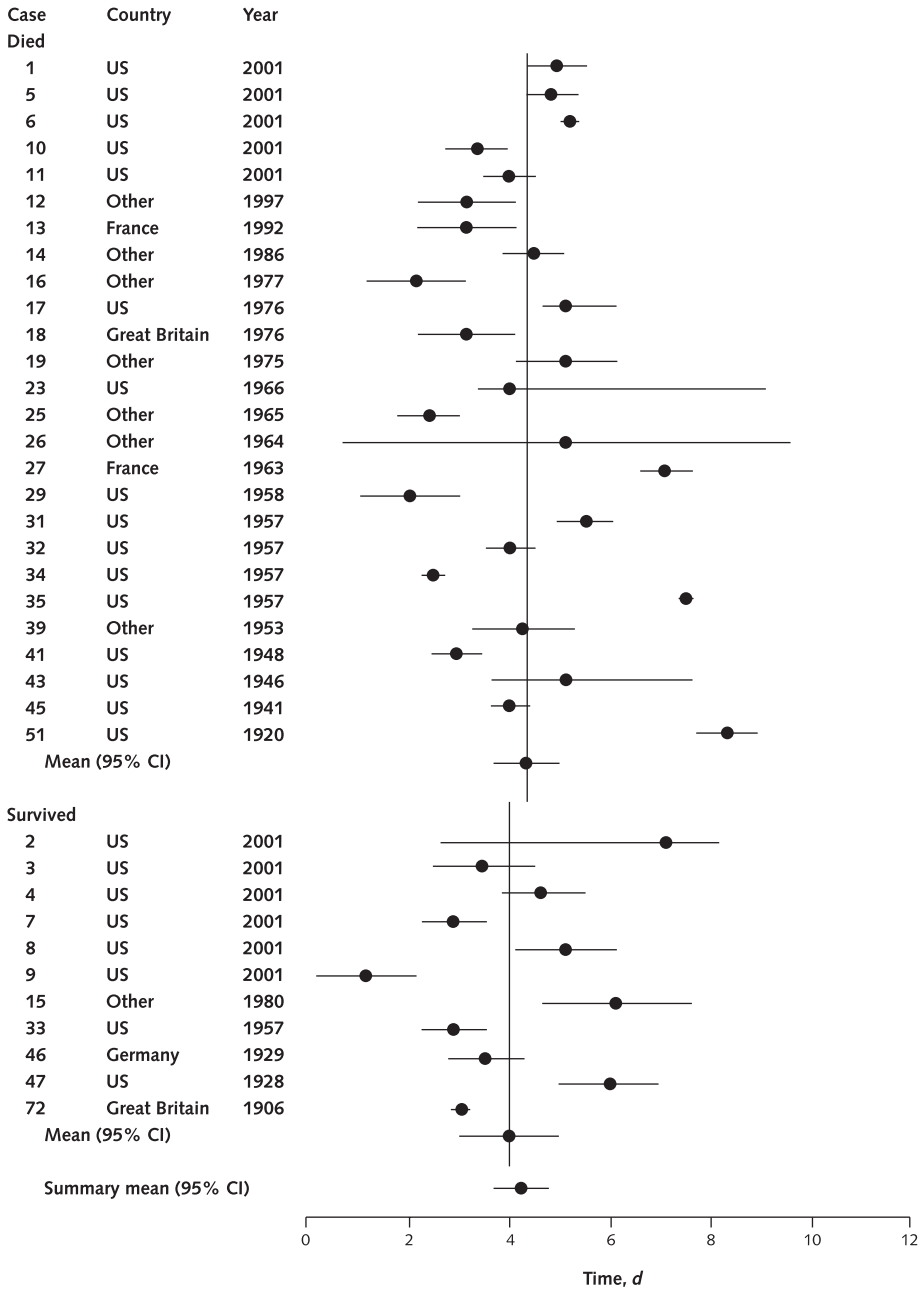
* Time calculations are uncorrected for censoring. For time estimates of onset and progression of disease, if exact times were not provided, we calculated a point estimate and range (minimum and maximum) from abstracted data and then applied a triangular distribution. IQR = interquartile range.
† Including all patients who received either appropriate antibiotics (≥70% of *Bacillus anthracis* strains were susceptible) or anthrax antiserum.
‡ Excluding patients who were not given appropriate antibiotics or anthrax antiserum.
§ Two patients were excluded because of insufficient data on the time of recovery or hospital discharge. One patient was excluded because of a prolonged hospitalization (e.g., outlier).

Appendix Table 4. Summary Maximum Likelihood Estimate Time Analysis*

Duration	Patients, *n*†	Weibull Maximum Likelihood Estimate, *d*			Log-Normal Maximum Likelihood Estimate, *d*		
		Mean Time ± SE	Mean (SD) Scale	Mean (SD) Shape	Mean Time ± SE	Mean (SD) Location	Mean (SD) Scale
Overall							
Prodromal to fulminant phase	71	4.1 ± 1.8	4.7 (0.24)	2.5 (0.24)	4.3 ± 2.4	1.3 (0.06)	0.5 (0.05)
Fulminant phase to death	61	1.1 ± 0.89	1.1 (0.12)	1.2 (0.12)	1.1 ± 1.3	–0.3 (0.12)	0.9 (0.09)
No antibiotics							
Prodromal to fulminant phase	71	4.1 ± 1.7	4.6 (0.24)	2.5 (0.24)	4.2 ± 2.3	1.3 (0.06)	0.5 (0.05)
Fulminant phase to death	48	0.7 ± 0.58	0.7 (0.10)	1.2 (0.14)	0.7 ± 0.74	–0.8 (0.14)	0.9 (0.10)
Antibiotic treatment begun in prodromal phase‡							
Prodromal to fulminant phase	17	5.8 ± 1.9	6.5 (0.69)	3.2 (0.79)	5.8 ± 2.0	1.7 (0.11)	0.3 (0.08)
Fulminant phase to death	8	1.3 ± 1.0	1.4 (0.41)	1.3 (0.38)	1.4 ± 1.8	–0.1 (0.34)	1.0 (0.24)
Antibiotic treatment begun in fulminant phase‡							
Fulminant phase to death	19	1.5 ± 1.0	1.7 (0.28)	1.5 (0.27)	1.5 ± 1.3	0.1 (0.18)	0.8 (0.13)

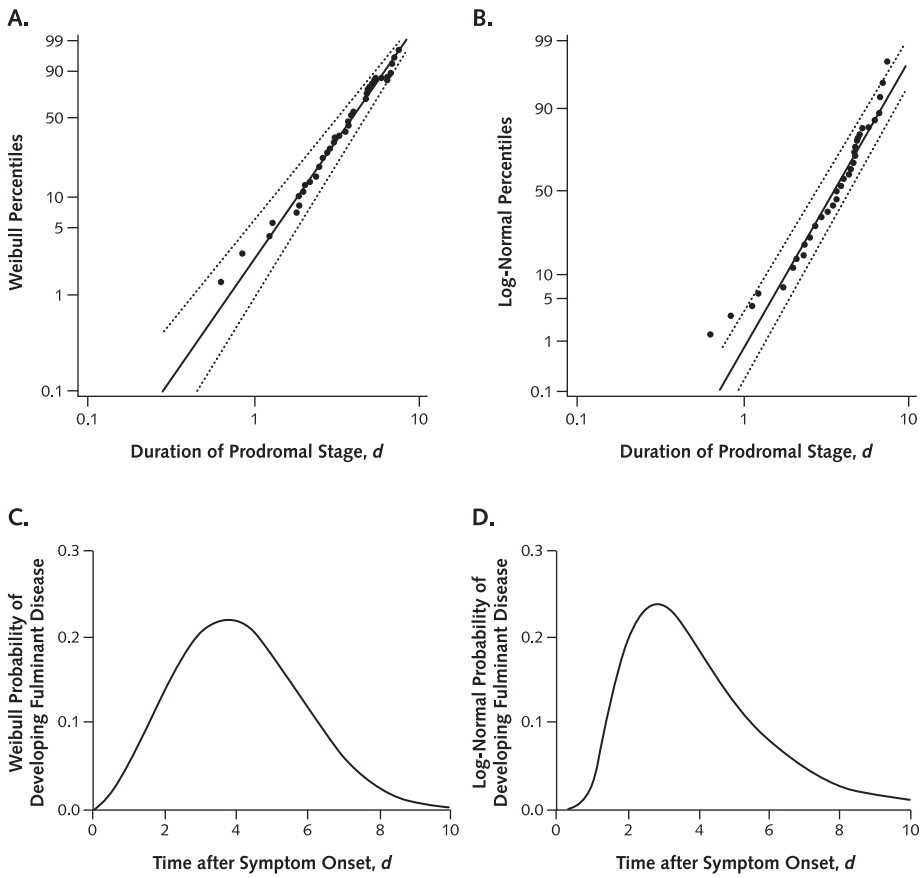
* Time calculations are corrected for censoring by using maximum likelihood estimates (see text).
† Patients used in the maximum likelihood analysis.
‡ All patients who received either appropriate antibiotics (≥70% of *Bacillus anthracis* strains were susceptible) or anthrax antiserum were included.

Appendix Figure 1. **Time duration from symptom onset to antibiotic initiation.**



This figure shows point and range time estimates (minimum and maximum) from symptom onset until antibiotic or antiserum therapy initiation for those who lived and those who died. US = United States.

Appendix Figure 2. **Weibull and log-normal maximum likelihood estimates of untreated prodromal stage duration.**



The maximum likelihood estimate of untreated (i.e., no antibiotics or antiserum), prodromal to fulminant-phase disease progression is shown by using a Weibull (*panel A*) or log-normal (*panel B*) distribution. Panels C and D show the probability of progression from prodromal to fulminant phase after symptom onset if no antibiotics or anthrax antiserum are given by using the Weibull or log-normal distribution, respectively.