PUBLIC HEALTH

Prevention of Inhalational Anthrax in the U.S. Outbreak

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The anthrax outbreak in the United States in fall 2001 resulted from the intentional dissemination of *Bacillus anthracis* spores (*1*). In response to the outbreak, public health authorities recommended that some groups of individuals undergo a 60-day regimen of antimicrobial prophylaxis (AP) (*2*). There have been no reported cases of inhalational anthrax among persons using AP. We report the results of a statistical analysis to estimate the number of cases of inhalational anthrax that may have been prevented by AP.

The first cluster of cases occurred in two employees of a Florida media-publishing company, although neither the likely source of exposure (a contaminated letter) nor the date of exposure has been identified. A second cluster of two cases occurred among postal workers in New Jersey. A third cluster of four cases occurred among postal workers in Washington, D.C. The source of exposure for the second and third clusters was a contaminated letter(s) sent to a government official(s) in Washington, D.C., processed through several postal facilities. The dates of onset of symptoms for the cases from these three clusters have been estimated through epidemiological investigation (*3*) (Fig. 1A). Three additional cases have been reported that do not fall into these three clusters.

Public health officials recommended AP for persons presumptively exposed, which included the following three groups: (i) persons who worked at or visited the media-publishing company in Florida, (ii) workers at two postal facilities in New Jersey, (iii) and workers at a postal facility in Washington, D.C. A statistical model can be used to estimate the numbers of cases of inhalational anthrax prevented by AP among persons in these three groups using information about dates of exposure, symptom onset, AP, and the incubation period. The key idea is that the observed cases from a group are only a fraction of those that would have occurred, because they are the ones with incubation periods shorter than the time interval between exposure and use of AP. The incubation period distribution, $F(t)$, is the probability of onset of symptoms within t days of exposure if an individual received sufficient dose of spores to cause disease but did not receive AP. If N is the number of individuals who received a sufficient dose of spores to cause disease and X is the number of cases who had disease onset within T days after exposure, at which point exposed individuals began AP, the relation $X = N \cdot F(T)$ can be used to solve for N. Because the date of exposure is unknown for the Florida cases, this estimation method is modified with maximum likelihood methods (*4*). These methods require knowledge of the incubation period. The most reliable human data on the incubation period of inhalational anthrax are based on the outbreak in the city of Sverdlovsk, Russia, in April 1979, with a median of 11 days (*5*, *6*) (Fig. 1B).

Using these data (Fig. 1, A and B) and methods (*4*), we maximized the profile likelihood function for N at $N = 17$ (Fig. 1C). These results suggest that although eight cases occurred in the three groups, about nine additional cases were prevented. Thus, the epidemic in these three groups could have been about twice as large had they not undergone a timely regimen of antimicrobial therapy. The precise number of cases that would have occurred in the absence of antibiotics (N) is uncertain (95% confidence interval is 10 to 28) and depends on the incubation period. The incubation period may depend on factors such as age, numbers of inhaled spores, and host susceptibility. The estimate of N increases as the assumed (median) incubation period increases. A sensitivity analysis yielded estimates of N for 12, 17, and 26 cases for median incubation periods of 8, 11, and 15 days, respectively. Sensitivity analyses to a range of incubation distributions, including a model that was a mixture of short and long incubation distributions, all indicated that fewer than 50 cases were prevented by AP.

As of January 2002, about 10,000 persons nationwide had been recommended to undergo the 60-day regimen of AP, including about 5000 persons in the three groups considered here. The risks and benefits of treatment options beyond 60 days, such as additional antibiotics or vaccine, are important public health issues. Although we cannot be certain that the 60-day regimen eliminates all risk of delayed germination of spores, it is reassuring that no cases in the 1979 Sverdlovsk outbreak had disease onset more than 60 days after exposure. Even under the pessimistic assumption that a 60-day regimen of antibiotics only delays rather than prevents disease, our results indicate that few of the 5000 persons would be at subsequent risk of onset of inhalational anthrax. Our results also underscore the importance of disease surveillance and rapid identification of exposed persons as critical elements of any strategy to minimize mortality and morbidity from future acts of bioterrorism.

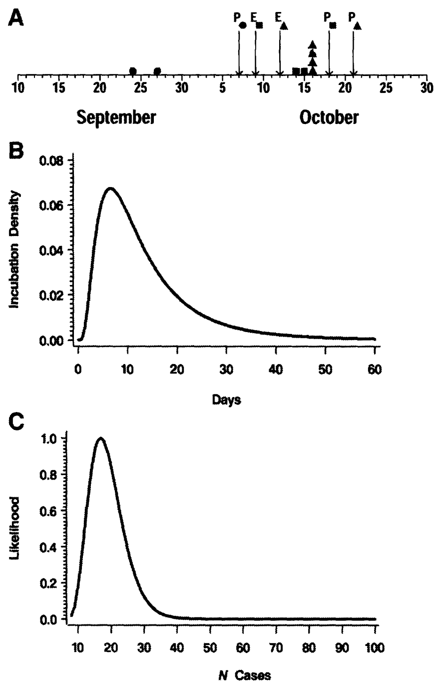

Fig. 1. **(A)** Disease onset dates for three clusters of cases of inhalational anthrax among employees of a media-publishing company in Florida (●), New Jersey postal workers (■), and District of Columbia postal workers (▲). Dates of exposure and AP in 2001 are indicated by E and P, respectively. **(B)** Incubation period density of inhalational anthrax, $f(t)$, estimated from the 1979 Sverdlovsk anthrax outbreak with lognormal model [median = 11.0 days, dispersion = $\exp(\sigma)$ = 2.04]. **(C)** Profile likelihood for the number of cases of inhalational anthrax, N, that would have occurred if there had not been AP among the Florida media-publishing company employees, New Jersey postal workers, and Washington, D.C. postal workers (normalized to 1 at maximum).

References and Notes

1. See www.cdc.gov/mmwr/indexbt.html.
2. T. V. Inglesby *et al.*, *J. Am. Med. Assoc.* **281**, 1735 (1999).
3. J. A. Jernigan *et al.*, *Emerg. Infect. Dis.* **7**, 933 (2001).
4. The likelihood function is the product of factors from three groups. For the *i*th group, x_i is observed number of cases, and n_i is number of cases that would have occurred had AP not been used. Factors for clusters with known exposure date are binomial likelihoods $\binom{n_i}{x_i}$, $[F(T_i)]^{x_i}\,[1-F(T_i)]^{n_i-x_i}$, where T_i is the time interval between exposure and AP. The likelihood factor for the group with unknown exposure date (E) is
$$\binom{n_i}{x_i}\,[1 - F(P - E)]^{n_i - x_i} \prod_{j=1}^{x_i} f(t_j - E),$$
where P is the date of AP, t_j is the onset date of symptoms for the *j*th case, and f is the incubation density. The profile likelihood for total $N = n_1 + n_2 + n_3$ is obtained by maximizing over E, n_1, and n_2.
5. M. Meselson *et al.*, *Science* **266**, 1202 (1994).
6. R. Brookmeyer *et al.*, *Biostatistics* **2**, 233 (2001).

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