FOLLOW-UP OF PERSONS IMPACTED BY BIOTERRORISM: RESPONDENTS AND NONRESPONDENTS

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1. Background

Post-exposure antibiotic prophylaxis is effective in preventing inhalation anthrax following an aerosol exposure to *Bacillus anthracis*. attack. The course of antimicrobial use is long, at least 60 days, due to the persistence of anthrax spores. October 4, 2001 identified the first case of intentional inhalation anthrax in the United States. This bioterrorist attack potentially exposed thousands to *B. anthracis* spores and led to 22 cases of anthrax (11 inhalation, 11 cutaneous) in 7 states (Jernigan *et al.*).

This event resulted in the first use of the National Pharmaceutical Stockpile which provided states with the necessary antibiotics for distribution to persons potentially exposed to the anthrax. Approximately 3.75 million tablets were distributed to approximately 10,000 individuals (Perkins *et al.*). The primary antibiotics used in the U.S. as a result of this event were Ciprofloxacin, Doxycycline, and Amoxicillin. At the conclusion of the initial 60-days of antibiotics, the Centers for Disease Control and Prevention (CDC) with FDA approval initiated a program under an Investigational New Drug (IND) protocol to offer all individuals the opportunity to receive additional antibiotics with or without anthrax vaccine.

Antimicrobial prophylaxis campaigns were primarily focused in six sites. Follow-up activities of individuals recommended to receive at least 60 days of antibiotics were contacted at ten days, 30 days, 60 days, and 1 year with an addition follow-up planned for 2-years following receipt of antibiotics.

A 60-day follow-up interview was conducted between January and April 2002 under contract by RTI International (Shepard *et al.*). A standardized questionnaire was developed. All persons recommended to receive antibiotics for at least 60 days were eligible. Potentially impacted persons were identified by investigators and employee lists provided by the United States Postal Service to CDC. Advance letters were sent to persons with an identified mailing address explaining the purpose of the telephone call. Telephone interviews were conducted and up to 20 telephone attempts were made in order to complete the interview. Overall 66% of eligible respondents completed the interview (Table 1) and varied by site. Details of this follow-up are reported by Shepard *et al*.

To understand the characteristics of persons exposed to *B. anthracis* during the anthrax outbreak of 2001 who did not respond to the initial 60-day telephone interview, we conducted a survey among nonresponders to the 60-day program evaluation. The purpose of the nonresponse follow-back survey was to evaluate the possible biases that existed in reported results from the original telephone interview. The two primary issues to be evaluated were (1) the receipt of antibiotics for the National Pharmaceutical Stockpile and (2) the reported adverse events, that is, did the initial interviewed persons disproportionally miss persons with potentially serious adverse events.

Table 1
60 day Follow-back Interview Response Rates*

Site	N	Response Rate
Florida	1,082	78%
New Jersey	1,402	76%
Hart Senate Building	600	82%
Brentwood	2,743	62%
Morgan	2,259	58%
Wallingford	1,217	69%
Total	9,303	66%

*Shepard *et al.*

2. Methods

The 60-day nonresponse follow-back survey was conducted during the one month period from 2 May through 2 June 2002. A brief standardized questionnaire was developed which contained the key elements of the original 60-day follow-up questionnaire, including whether an initial supply of antibiotics was obtained, associated adverse events, and adherence to the antimicrobial regimen. To evaluate the National Pharmaceutical Stockpile, a question was asked "Did you get antibiotics to prevent anthrax, that is, did you or someone you know pick them up?" As with all earlier questionnaires administered to persons recommended for antimicrobial prophylaxis, an adverse event was defined as any self-reported symptom while on antimicrobial prophylaxis. All individuals were

asked to classify the severity of their adverse events. Options included severe, moderate, mild, or none. A question about awareness of the IND and enrollment in the IND were asked of individuals.

Antimicrobial prophylaxis campaigns and follow-up were primarily focused in the following areas: American Media, Inc., Palm Beach County, Florida; Hart Senate Office Building, Washington, DC; Brentwood Postal Facility, Washington, DC; US Postal Service Trenton PD&C, Hamilton Township, New Jersey; Morgan Postal Facility, New York City, New York; and the Wallingford and Seymour Postal Facilities, Connecticut. Interviews were conducted in-person or by telephone. Questionnaires were developed in both a paper and pencil format and computer assisted telephone interview (CATI) format. The three sites with the lowest response rate (RR) from the 60-day interview were selected for this evaluation (i.e., Brentwood [RR 62%]; Morgan [RR 58%]; and Wallingford [RR 69%]).

The sample was stratified within each location by an individual's final status at the conclusion of the initial interview. The three strata were (1) unlocatable, (2) no telephone but a confirmed address, and (3) refused to participate. An individual was defined as unlocatable if the telephone number and address provided from the initial list were incorrect and after extensive work at RTI International's tracing facility failed to identify a valid telephone number and/or address. RTI International specializes in tracing hard-to-find individuals by using a variety of databases and other interactive locating procedures. Those who were considered "hard" refusals, that is individuals who expressed they did not want to be contacted ever again regarding their exposure to *B. anthracis*, were excluded from the sample frame.

The names of sampled individuals from the unlocatable strata were sent to RTI International's telephone tracing facility for identification through the many available databases . If a working telephone number was identified, these individuals were contacted by telephone to participate. Sampled individuals with no telephone, but a confirmed address were contacted by a field interviewer for an in-person interview. Lastly, sampled individuals who initially refused were randomly assigned to a telephone interview (50%) or an in-person interview (50%). The total number eligible and the number sampled from each strata within each site are show in Table 2.

Data management was conducted in SAS Version 8.2 (SAS Institute Inc., Cary, NC). All statistical analyses were conducted using SUDAAN Version 8.0 (Research Triangle Institute).

3. Results

Response rates from the nonresponse follow back survey were 16% (38/231) at Morgan, 27% (66/245) at Brentwood, and 34% (67/196) at Wallingford (Table 2). A total of 171 interviews were completed across the three sites with 104 in-person interviews and 67 telephone interviews. Morgan had a total of 38 completed interview (12 in-person, 26 telephone); Brentwood had 66 completed interviews (37 in-person, 29 telephone); Wallingford had 67 completed interviews (55 in-person, 12 telephone). Persons identified as ineligible, i.e., persons who reported that they had not be recommended to receive at least 60 days of antimicrobials because of exposure to anthrax, were excluded from response rate calculations (Morgan, n=3; Brentwood, n=8; Wallingford, n=9).

Table 2
Nonresponse Followback Survey Sample Frame

Site	Nonresponse Type	N	Samp #	# Comp
Brentwood	Unlocatable	254	63	20
Brentwood	Conf.Address & No Phone	435	79	19
Brentwood	Refusal	320	111	27
Total		1009	253	66
Morgan	Unlocatable	251	64	18
Morgan	Conf.Address & No Phone	437	82	16
Morgan	Refusal	248	88	4
Total		936	234	38
Wallingford	Unlocatable	82	43	8
Wallingford	Conf.Address & No Phone	131	50	17
Wallingford	Refusal	154	112	42
Total		367	205	67

Note: "Hard" refusals were excluded.

Demographics between respondents (i.e., those that responded to the initial 60-day interview) and nonrespondents (i.e., those that responded to the nonresponse followback survey) varied across sites. The median age in years was similar in Morgan and Wallingford, but was statistically different in Brentwood (respondents 40.3 versus nonrespondents 48.2, $p<0.05$). The percent black race was similar in

Brentwood and Wallingford. Morgan reported 45.5% black respondents initially, but in the nonreponse followback survey, 57.9% reported being black (p=0.018). The percent male responding was statistically different in all sites (NY Morgan: 54.7% initial interview versus 37.1% nonresponse followback survey, p=0.016; Brentwood: 57.6% versus 54.6%, p=0.008; Wallingford 57.5% versus 50.3%, p=0.026).

Regarding receipt of antibiotics, no differences were reported between respondents and nonrespondents across all sites. Each site showed over 90% reporting receipt of antibiotics (Table 3).

Table 3
Results - Receipt of Antibiotics

Sample Site	Respondent	Nonresp	p-value
Morgan	94.7	94.3	NS*
Brentwood	98.6	98.5	NS
Wallingford	92.6	94.1	NS

*NS denotes not statistically significant

The percent of individuals told to stop taking the antibiotics by a doctor for any reason were not different between respondents and nonrespondents at any site (Table 4).

Table 4
Results - Percent told to Stop Antibiotics by Doctor

Sample Site	Respondent	Nonresp	p-value
Morgan	8.8	7.4	NS*
Brentwood	7.5	9.3	NS
Wallingford	10.1	12.8	NS

*NS denotes not statistically significant

Also, the percent of individuals told to stop taking the antibiotics by a doctor because of adverse events did not differ between respondents and nonrespondents at any site (Table 5).

Table 5
Results - Percent told to Stop Antibiotics by Doctor because of Adverse events

Sample Site	Respondent	Nonresp	p-value
Morgan	5.5	7.4	NS*
Brentwood	5.6	6.3	NS
Wallingford	7.6	7.7	NS

*NS denotes not statistically significant

The percent that classified their adverse events as moderate or severe were similar at Brentwood and Wallingford (Table 6).

Table 6
Results - Percent who Classified Adverse events as Moderate or Severe

Sample Site	Respondent	Nonresp	p-value
Morgan	66.6	52.0	0.028
Brentwood	49.1	43.8	NS*
Wallingford	66.6	64.1	NS

*NS denotes not statistically significant

Initial respondents from Morgan reported more problems (66.6%) than those who responded to the nonresponse followback survey (52.0%), a statistically significant result (p=0.028).

The percent of individuals who reported IND enrollment was similar for respondents and nonrespondents at the Morgan Postal Facility, but was different in the other two locations with the higher percent seen among initial respondents (Brentwood: 39.4% initial interview versus 18.5% nonresponse followback survey, p<0.001; Wallingford 11.4% versus 5.9%, p=0.002).

4. Conclusion

The nonresponse followback survey assisted in our understanding that potentially serious adverse events were not missed. This provides greater assurance that our report of adverse events are representative of adverse events that do occur.(Shepard *et al)*. We do not believe that we have missed individuals with the most serious adverse events. However, refining approaches at initial contact with individuals following a bioterrorism event need to be improved to ensure high response rates and representativeness of all impacted individuals.

Nonresponders are an important group to understand, especially in an unprecedented event such as the 2001 anthrax outbreak and the potentially serious threat posed by an exposure to *B. anthracis*. We devoted a great deal of effort in trying to understand the similarities and differences between those that initially responded to the 60-day telephone interview and those that did not. We feel important insights were learned.

Groves and Couper have defined four areas that influence interviewer cooperation. Two are dependent of the survey design and two are independent upon the survey design. Factors dependent of the survey design include the protocol and quality of the interviewers. Factors independent of the survey design include "social environmental influences" and "knowledge and social psychological attributes of the sample persons," such as civic duty. A bioterrorist event will impact social environment influences as these individuals will be reminded constantly about their situation through the news media and workplace. Fear and panic may tend to override positive contributors such as civic duty or improving the services available given a bioterrorist event. Better understanding and knowledge about the social environmental influences and the knowledge and social psychological attributes can help interviewers better communicate with individuals and gain their cooperation to participate in the interview.

The nonresponse followback survey had very low response rates. The low response rates may be attributable to the high level of stress felt in this population following their exposure to anthrax in combination with the hysteria and media coverage (Jefferds *et al.*). With such low response rates it is difficult to assume that those responding to the nonresponse followback survey and those not responding are similar, or to assume the group of respondents adequately represent all nonrespondents. However, the small group of individuals responding to the nonresponse followback survey allowed us the opportunity to evaluate our primary objectives regarding receipt of antibiotics from the National Pharmaceutical Stockpile and reported adverse events.

It was reassuring to see the similarities between the initial respondents and those from the nonresponse followback survey in their ability to obtain antibiotics from the National Pharmaceutical Stockpile and the stopping of antibiotics because of medical advise or due to adverse events. Morgan reported fewer persons from the nonresponse followback survey who had moderate or severe adverse events than initial reported. The other sites had no differences. This suggests that we have not systematically missed those with potentially serious adverse events from our initial interview, and n actuality, we may be over reporting the rates of adverse events from our initial interview.

Demographics characteristics differed somewhat among initial respondents and those from the nonresponse followback survey although it is not clear that these differences impact results. A higher proportion of males responded to the initial interview than the nonresponse followback survey in all sites. Morgan yielded a higher proportion of blacks responding to the nonresponse followback survey than initially responded. Brentwood had younger respondents for the nonresponse followback survey than the initial interview, but the medians differed by only 2 years of age. Although these differences may be real, the small sample size from the nonresponse followback survey casts doubts about the representativeness of these individuals.

It was not surprising to learn that those individuals who enrolled in the IND, which may be a surrogate for those who perceived themselves at risk for inhalation anthrax, were more likely to respond to the initial interview. These individuals were contacted during the time of their participation in the IND and may have felt it was their civic duty to respond, one of the areas Grove and Couper discuss as an area of influence when gaining respondent cooperation. Information about enrollment in the IND was self reported. The individuals we contacted and attempted to contact were the first persons in the U.S. to be impacted by a bioterrorist event (Perkins *et al.*). Besides having co-workers fall ill because of an anthrax exposure and/or identifying occupational anthrax exposures, these individuals were operating day-to-day under great stress. Stress can also contribute to medical problems or other adverse events. The adverse events reported were self-reported by individuals and does not imply a causal relationship with a particular brand of antibiotics. But given another bioterrorist event, stress will once again play a role in reported adverse events.

Given our low response rates for the nonresponse followback survey and the great amount of time, effort, energy, and cost, we do not believe that nonresponse followback surveys should become a routine part of follow-up in a bioterrorism related event. However, methods need to be explored to improve response rates at the initial contact following a bioterrorism event so that we have the best data available in order to properly assess the impact on affected individuals.

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