Epidemiologic Clues to Bioterrorism

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SYNOPSIS

Public health investigators have successfully carried out epidemiologic investigations of outbreaks of disease for many years. By far the majority of these outbreaks have occurred naturally. With the recent illnesses resulting from deliberate dissemination of *B. anthracis* on an unsuspecting population, public health investigation of diseases must now include consideration of bioterrorism as a potential cause of outbreaks of disease.

The features of naturally occurring outbreaks have a certain amount of predictability in terms of consistency with previous occurrences, or at least biological plausibility. However, with a deliberately introduced outbreak or infection among a population, this predictability is minimized. In this paper, the authors propose some epidemiologic clues that highlight features of outbreaks that may be suggestive of bioterrorism. They also describe briefly the general process of involvement of agencies at various levels of government, public health and non-public health, depending on the extent of an outbreak or level of suspicion.

I would rather live in a world where my life is surrounded by mystery than live in a world so small that my mind could comprehend it.

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Beginning in 1996, the United States embarked on a new civilian biodefense program targeted at chemical and biological terrorism.[1,2] The impetus for this program stemmed from a combination of high profile terrorist events in the United States, revelation of the extent of chemical and biological weapons development programs in Iraq and the former Soviet Union, and fictional and non-fictional accounts describing this threat to our civilian population.[3–7] Recent events, including those of September 11 and the cases of anthrax resulting from the intentional release of *Bacillus anthracis,* have accentuated the need for concerted efforts to counter chemical and biological terrorism.[8–12]

The first documented deliberate use of a biological agent on a population in the United States occurred in 1984, when members of the Rajneesh sect contaminated food with *Salmonella* serotype typhimurium to test their ability to influence voter turnout at an upcoming election, causing illness in 751 people.[13] It is noteworthy that, despite suspicions of the community, a rigorous epidemiologic investigation failed to demonstrate that the outbreak was deliberately caused. More than one year later, the criminal investigation provided essential evidence that linked the religious commune with the outbreak. More recently, the first documented case of intentionally induced infection with *B. anthracis* was identified in October 2001. Subsequent cases of both cutaneous and inhalational anthrax have been identified that appear to be associated.[8] These events, and the likely occurrence of additional events, demonstrate the necessity of understanding the epidemiology of biological and chemical terrorism. While the focus last fall was on *B. anthracis,* and currently is on the possibility of introduced smallpox, we need to remain vigilant for cases of any unusual illness as well as illness due to other critical biological agents.[14,15]

Epidemiologists have routinely investigated outbreaks of infectious and non-infectious diseases among both human and animal populations for decades.[16–18] Such investigations have frequently identified known or at least biologically plausible risk factors or vehicles of transmission for illness, whether the outbreak was caused by a familiar, unfamiliar, or emerging agent.[19–24] The possibility of deliberate contamination or dispersion of agents among populations raises questions about possible risk factors, vehicles, and agents, most of which are very difficult to answer. However, by evaluating the list of agents thought to be weaponizable[14] and considering the usual epidemiologic patterns of illness caused by those or other agents causing similar conditions, we have derived a list of epidemiologic clues that identify atypical features of an outbreak that might be suggestive of bioterrorism. We also describe briefly the general process of involvement of agencies at various levels of government, public health and non-public health, depending on the extent of an outbreak or level of suspicion.

Epidemiologic clues

There are many ways to describe the clinical, epidemiologic, and laboratory clues suggestive of deliberate dissemination of a biologic or chemical agent.[25–29] A version of the clues in this paper was first presented during the satellite broadcast, "Biological Warfare and Terrorism: The Military and Public Health Response," on September 21–23, 1999, and was adapted for use by others immediately after the September 11, 2001 attacks on the World Trade Center. It was also adapted for use in surveillance and epidemiology guidance available to states for emergency bioterrorism funding.[29–31] To generate these clues, we started with the list of biologic agents with potential to be used as weapons.[14] From the biologic and epidemiologic features of illness caused by these agents, we derived epidemiologic clues of unusual illness (rare agent/rare disease) or unusual patterns of person, place, and time, taking into consideration routine illnesses that these agents cause or that infection with these agents might resemble. For example, a case of community-acquired smallpox must be rigorously investigated as a case of bioterrorism, while a case of inhalational anthrax is a clue to a possible case of bioterrorism. However, outbreaks of chickenpox among adults or influenza-like illness during the summer are also clues because they include individuals or a seasonality that is unexpected.

We then listed these clues generally, from the "most specific" (i.e., highly unusual agents) to "least specific" for bioterrorism (i.e., large numbers of ill with unexplained illness, which resembles a more common outbreak) (Figure 1). The more specific clues will automatically cause the public health investigator to suspect bioterrorism, much as certain clinical data point toward specific diagnoses. For example, just as erythema migrans is pathognomonic for Lyme disease, a case of smallpox cannot be anything other than bioterrorism. Other examples that are more "specific" for bioterrorism include a case of Lassa fever without history of travel or laboratory exposure, or anthrax and tularemia simultaneously affecting a single person. Other less specific clues could describe the early stages of any routine outbreak, much like the initial stages of clinical information gathering (e.g., for a complaint of

Figure 1. Epidemiologic clues that may signal a biologic or chemical terrorist attack

1. Single case of disease caused by an uncommon agent (e.g., glanders, smallpox, viral hemorrhagic fever, inhalational or cutaneous anthrax) without adequate epidemiologic explanation
2. Unusual, atypical, genetically engineered, or antiquated strain of an agent (or antibiotic- resistance pattern)
3. Higher morbidity and mortality in association with a common disease or syndrome or failure of such patients to respond to usual therapy
4. Unusual disease presentation (e.g., inhalational anthrax or pneumonic plague)
5. Disease with an unusual geographic or seasonal distribution (e.g., tularemia in a non-endemic area, influenza in the summer)
6. Stable endemic disease with an unexplained increase in incidence (e.g., tularemia, plague)
7. Atypical disease transmission through aerosols, food, or water, in a mode suggesting deliberate sabotage (i.e., no other possible physical explanation)
8. No illness in persons who are not exposed to common ventilation systems (have separate closed ventilation systems) when illness is seen in persons in close proximity who have a common ventilation system
9. Several unusual or unexplained diseases coexisting in the same patient without any other explanation
10. Unusual illness that affects a large, disparate population (e.g., respiratory disease in a large population may suggest exposure to an inhalational pathogen or chemical agent)
11. Illness that is unusual (or atypical) for a given population or age group (e.g., outbreak of measles-like rash in adults)
12. Unusual pattern of death or illness among animals, (which may be unexplained or attributed to an agent of bioterrorism) that precedes or accompanies illness or death in humans
13. Unusual pattern of death or illness among humans, (which may be unexplained or attributed to an agent of bioterrorism) that precedes or accompanies illness or death in animals
14. Ill persons who seek treatment at about the same time (point source with compressed epidemic curve)
15. Similar genetic type among agents isolated from temporally or spatially distinct sources
16. Simultaneous clusters of similar illness in noncontiguous areas, domestic or foreign
17. Large numbers of cases of unexplained diseases or deaths

chest pain one must consider gastrointestinal and muscular causes, as well as cardiac disease), but should at least ensure that bioterrorism is considered as a possible cause. The specificity of any of these clues also depends on the examples used and the context; for example, one could argue that chickenpox-like illness among adults, an example of clue #11, should have bioterrorism included as a potential cause of an otherwise unusual occurrence.

Thus, the clues are meaningful only in the context of a complete epidemiologic investigation. Regardless of presumed specificity for bioterrorism, the clues listed here suggest only that a cluster of cases is unusual from a public health perspective. It is critical to recognize that no one of these clues may be sufficient in itself to suggest bioterrorism and that most of these clues, individually, were actually found at least once in the investigation of naturally occurring outbreaks such as Legionnaire's disease, toxic-shock syndrome, eosinophila myalgia syndrome, hantavirus pulmonary syndrome, Lyme disease, and hypoglycemic shock syndrome, to name just a few recently recognized diseases. Combinations of clues—especially those that link clinical information with epidemiologic features, such as an uncommon agent isolated from large numbers of patients across the country, or an unexplained increase in the incidence of pneumonic plague—should increase the index of suspicion that an event may be due to bioterrorism. Epidemiologic judgment,[16] like clinical judgment, will be important for determining what is unusual enough to warrant a concern regarding bioterrorism.

In addition, this is merely a template for consideration of potential public health presentations of bioterrorism, and not an exhaustive list of every possibility. There is no list or algorithm that can replace intelligent, sound epidemiology. The generality of this list takes into account that we cannot truly predict what agent will be used in a bioterrorist attack, the route of exposure, or the number of people exposed, as we have learned in recent *B. anthracis* investigations. Thus, whether or not a cluster of illness is even-

tually determined to be due to bioterrorism, these clues are intended to spur rapid investigations and early implementation of control measures for any unusual outbreak, a goal that is consistent with that of the routine public health response to an outbreak.[16–18]

INVESTIGATION AND NOTIFICATION CRITERIA

While heightened awareness exists that clusters or even unusual single cases of illness could represent biological or chemical terrorism, without the discovery of a dissemination device such as a letter or other definitive clue, the criteria for notification of law enforcement authorities are not well defined. No one would argue with immediate notification of the Federal Bureau of Investigation upon notification from an individual or a group that a terrorist attack has occurred or will occur, or upon discovery of a suspicious dispersal/delivery device. However, for anything less blatant, an initial public health evaluation of illness or injury in the community is crucial to assess the possibility of bioterrorism and the need to notify law enforcement authorities.

We grouped the epidemiologic clues from Figure 1 into two additional lists to suggest criteria for graded levels of public health involvement (Figure 2), and considerations for when to notify the Federal Bureau of Investigation, which has the lead responsibility for operational response to terrorist events (Figure 3). The general schema for the preliminary public health evaluation (Figure 2) will not look new to most practicing public health professionals. A preliminary investigation by local health officials will generally take place if any of the clues suggest that such an outbreak is underway in the community. Any outbreak that has more unusual features based on the epidemiologic clues will likely be further investigated with notification and/or involvement of state health officials and the Centers for Disease Control and Prevention (CDC). For certain events or investigations where suspicion for terrorism is high and no natural cause for the outbreak is found, law enforcement should be involved (Figure 3).

DISCUSSION

The events of September 11 and the recent cases of anthrax have underscored the susceptibility of the U.S. population to bioterrorism. While the vast majority of cases and outbreaks of infectious disease will be natu-

Figure 2. Recommendations for level of public health involvement for investigation of potential biologic or chemical terrorist attack

Initial investigation at the local level

a. Higher morbidity and mortality than expected, associated with a common disease or syndrome
b. Disease with an unusual geographic or seasonal distribution
c. Multiple unusual or unexplained disease entities coexisting in the same patient.
d. Unusual illness in a population (e.g., renal disease in a large population which may be suggestive of toxic exposure to agent such as mercury)
e. Ill persons seeking treatment at about the same time
f. Illness in persons suggesting a common exposure (e.g., same office building, meal, sporting event, or social event)

Continued investigation with involvement of the State Health Department and/or Centers for Disease Control and Prevention

a. At least a single, definitively diagnosed case(s) with one of the following:
   —Uncommon agent or disease
   —Illness due to a genetically altered organism.
b. Unusual, atypical, or antiquated strain of agent
c. Disease with an unusual geographic, seasonal or "typical patient" distribution
d. Endemic disease with unexplained increase in incidence
e. No illness in persons not exposed to common ventilation systems
f. Simultaneous clusters of similar illness in non-contiguous areas, domestic or foreign
g. Cluster of patients presenting with similar genetic type among agents isolated from temporally or spatially distinct sources

Figure 3. Considerations for notifying law enforcement of a possible biologic or chemical terrorist attack

Immediate notification of the Federal Bureau of Investigation:

a. Receive notification from individual or group that a terrorist attack has occurred or will occur.
b. Find potential dispersal/delivery device such as a munition or sprayer or a questionable letter with a powder.

Notification of the FBI as soon as an investigation suggests:

a. Illness due to unexplained aerosol, food or water transmission
b. At least a single, definitively diagnosed case(s) with one or the following:
   —Uncommon agent or disease occurring in a person with no other explanation
   —Illness due to a genetically altered organism

Notification of the FBI after an investigation confirms the following (with no plausible explanation):

a. Disease with an unusual geographic, seasonal, or "typical patient" distribution
b. Unusual, atypical, or antiquated strain of agent
c. Simultaneous clusters of similar illness in non-contiguous areas, domestic or foreign
d. Cluster of patients presenting with similar genetic type among agents isolated from temporally or spatially distinct sources

rally occurring, clinicians and public health officials must maintain a heightened suspicion of possible bioterrorism. Just as the clinician's ability to recognize a suspected case of anthrax and to report it to the local health department is critical to our recognition of current bioterrorist events, local and state public health agencies need to suspect certain outbreaks may be due to bioterrorism, investigate them, and report them to the appropriate authorities. This list provides a mechanism to evaluate clues accumulated during the course of an investigation, and should serve as a reminder to at least consider bioterrorism as a cause.

Identifying the cause of outbreaks as due to bioterrorism is now as important as excluding bioterrorism as the cause of an outbreak of unknown etiology. The outbreak of West Nile-like virus-associated encephalitis in New York highlighted the impact of concerns about bioterrorism even with naturally occurring disease.[32] Media reports suggesting that West Nile virus was deliberately released spawned public panic that the outbreak was intentional.[33] Fear, whether substantiated or not, can lead to many forms of hysteria[34] and may in fact hinder public health response. Of recent note are the community fears about possible bioterrorism immediately after the attack on the World Trade Center, even before the detection of cases of anthrax.[35] Private physicians and hospitals were deluged with requests for inappropriate use of antibiotics, depleting the supply of antibiotics for those who eventually needed them.[36] In these incidents, effective public health response was hampered by public perception and fear. These incidents underscore the need for a strong epidemiologic response, especially when there is any suspicion of bioterrorism, to rule it in or out as causally related. Stronger epidemiologic methods must be developed to determine the likelihood of chemical or biological terrorist attack.

Public health officials must work closely with law enforcement and emergency management when bioterrorism is suspected. The appropriate officials in all of these chains, from the local to federal levels, must be identified before an event occurs to facilitate rapid, efficient dissemination and sharing of appropriate information. As the investigation ensues, each of these entities will have bits of information that will contribute to the whole picture. For an effective public health response to bioterrorism to occur, many agencies must work together in a coordinated fashion.[36]

To reiterate, the most noteworthy aspect of these guidelines is that nature has been much more imaginative than any known terrorist. Therefore, except for the most blatant violations of natural principles, bioterrorism will continue to remain difficult to differentiate from naturally occurring outbreaks. It is hoped that these clues will help in the evaluation and provide some guidelines to prioritize investigations of outbreaks that are potentially due to bioterrorism, and will help to quickly assess the level of resources necessary to complete an investigation. Fortunately, attribution of the cause of an outbreak does not change our requi-

site public health response. This response does not differentiate between naturally occurring and deliberate illness. Evaluation of unusual outbreaks will also force us to rely more heavily on and expand the limits of our epidemiologic and laboratory methods, and to consider deploying new and innovative technology. Such evaluations will also lead to a greater understanding of the natural history of current diseases and disease agents. The biggest reward for these efforts will be the early detection and identification of numerous new or evolving biological agents, and, most importantly, the improved health of the public.

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REFERENCES

1. The Defense Against Weapons of Mass Destruction Act, contained in the National Defense Authorization Act for Fiscal Year 1997, Pub. L. No. 104-201 (Sep. 23, 1996).
2. Khan AS, Levitt AM, Sage MJ. Biological and chemical terrorism: strategic plan for preparedness and response. Recommendations of the CDC Strategic Planning Workgroup. MMWR Morb Mortal Wkly Rep 2000;49(RR-4).
3. Okumura T, Suzuki K, Fukuda A, Kohama A, Takasu N, Ishimatsu S, Hinohara S. Tokyo subway sarin attack; disaster management, part 1: community emergency response. Acad Emerg Med 1998;5:613-7.
4. Outbreak. 1995. VHS/DVD, 130 min. Burbank (CA): Warner Brothers, Inc.
5. Preston R. The cobra event. New York: Random House; 1997.
6. Mallonee S, Shariat S, Stennies G, Waxweiler R, Hogan D, Jordan F. Physical injuries and fatalities resulting from the Oklahoma City bombing. JAMA 1996;276:382-7.
7. Christopher GW, Cieslak TJ, Pavlin JA, Eitzen EM Jr. Biological warfare. A historical perspective. JAMA 1997; 278:412-7.
8. Jernigan JA, Stephens DS, Ashford DA, Omenaca C, Topiel MS, Galbraith M, et al. Bioterrorism-related anthrax: the first 10 cases reported in the United States. Emerg Infect Dis 2001;7:933-44.
9. Update: investigation of bioterrorism-related anthrax. MMWR Morb Mortal Wkly Rep 2000;50:1008-10.
10. Update: investigation of bioterrorism-related inhalational anthrax—Connecticut, 2001. MMWR Morb Mortal Wkly Rep 2000;50:1049-51.
11. Update: Investigation of bioterrorism-related anthrax—Connecticut, 2001. MMWR Morb Mortal Wkly Rep 2000; 50:1077-9.
12. Evaluation of Bacillus anthracis contamination inside the Brentwood Mail Processing and Distribution Center—District of Columbia, October 2001. MMWR Morb Mortal Wkly Rep 2000;50:1129-33.
13. Torok TJ, Tauxe RV, Wise RP, Livengood JR, Sokolow R, Mauvais S, et al. A large community outbreak of salmonellosis caused by intentional contamination of restaurant salad bars. JAMA 1997;278:389-95.
14. Biological and chemical terrorism : strategic plan for preparedness and response. MMWR Morb Mortal Wkly Rep 2000;49(RR-4):5-6.
15. CDC Public Health Emergency Preparedness and Response website [cited 2002 Oct]. Available from: URL: http://www.bt.cdc.gov
16. Goodman RA, Buehler JW, Koplan JP. The epidemiologic field investigation: science and judgement in public health practive. Am J Epidemiol 1990;132:9-16.
17. Mackenzie WR, Goodman RA. The public health response to an outbreak. Current Issues in Public Health 1996;2:1-4.
18. Reingold AL. Outbreak investigations—a perspective. Emerging Infect Dis 1998;4:21-7.
19. Hennessy TW, Hedberg CW, Slutsker L, White KE, Besser-Wiek JM, Moen ME, et al. A national outbreak of Salmonella enteritidis infections from ice cream. N Engl J Med 1996;334:1281-6.
20. Kaposi's sarcoma and Pneumocystis pneumonia among homosexual men—New York City and California. MMWR Morb Mortal Wkly Rep 1981;30:305-8.
21. Epidemiologic notes and reports hepatitis B associated with jet gun injection—California. MMWR Morb Mortal Wkly Rep 1986;35:373-6.
22. Katz D, Kumar S, Malecki J, Lowdermilk M, Koumans EH, Hopkins R. Cyclosporiasis associated with imported raspberries, Florida 1996. Public Health Rep 1999;114:427-38.
23. Swygert LA, Maes EF, Sewell LE, Miller L, Falk H, Kilbourne EM. Eosinophilia-myalgia syndrome. Results of national surveillance. JAMA 1990;264:1698-703.
24. Fatalities associated with ingestion of diethylene glycol-contaminated glycerin used to manufacture acetaminophen syrup—Haiti, November 1995–June 1996. MMWR 1996;45:649-50.
25. Noah DL, Sobel AL, Ostroff SM, Kildew JA. Biological warfare training: infectious disease outbreak differentiation criteria. Mil Med 1998;163:198-201.
26. Pavlin J. Epidemiology of bioterrorism. Emerg Infect Dis 1999;5:528-30.
27. Kadlec RP, Zelicoff AP, Vrtis AM. Biological weapons control. Prospects and implications for the future. JAMA 1997;278:351-6.
28. Wiener SL, Barrett J. Trauma management for civilian and military physicians. Philadelphia: W.B. Saunders; 1986. p. 507-28.
29. Recognition of illness associated with the intentional release of a biologic agent. MMWR Morb Mortal Wkly Rep 2001;50:893-7.
30. New York City Department of Health. Update #4: terrorist attack at the World Trade Center in New York City: medical and public health issues 2001 Sep 24. Available from: URL: http://NYC.gov/html/doh/html/cd/wtce.html

31. Guidance for CDC bioterrorism funding for states [cited 2002 Apr 8]. Available from: URL: http://www.bt.cdc.gov/Planning/CoopAgreementAward/index.asp32
32. Outbreak of West Nile-like viral encephalitis—New York, 1999. MMWR Morb Mortal Wkly Rep 1999;48:845-9.
33. Engelberg S, Altman LK. A nation challenged: news analysis; fighting a new health threat, on the fly. New York Times 2001 Oct 24.
34. Jones TF, Craig AS, Hoy D, Gunter EW, Ashley DL, Barr DB, et al. Mass psychogenic illness attributed to toxic exposure at a high school. New Engl J Med 2000; 342:96-100.
35. Stolberg SG. A nation challenged: the biological threat; some experts say U.S. is vulnerable to a germ attack. New York Times 2001 Sep 30.
36. Altman L, Kolata G. A nation challenged: anthrax; anthrax missteps offer guide to fight next bioterror battle. New York Times 2002 Jan 6.