Chapter 3

EPIDEMIOLOGY OF BIOWARFARE AND BIOTERRORISM

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A portion of this chapter has been published as: Dembek ZF, Kortepeter MG, Pavlin JA. Discernment between deliberate and natural infectious disease outbreaks. *Epidemiol Infect*. 2007;135:353-371.

INTRODUCTION

Preparing for and responding to biowarfare (BW) or bioterrorism (BT) falls squarely in the realm of public health and in the purview of public health professionals. Basic epidemiology is needed for management before, during, and after an event to identify populations at risk, target preventive measures such as vaccinations, recognize an outbreak, track and limit disease spread, and provide postexposure treatment or prophylaxis. Many disease-specific management needs such as vaccination and prophylaxis are discussed elsewhere and are not considered here. Also, agricultural terrorism is discussed in chapter 2. This chapter will focus on detection and epidemiological investigation including distinguishing between natural and intentional events. Brief case studies will be presented to demonstrate important indicators and lessons learned from historical outbreaks. Finally, traditional methods of surveillance and ways to improve surveillance for BW/BT will be discussed.

THE EPIDEMIOLOGY OF EPIDEMICS

Definition

The word epidemic comes from the Greek "epi" and "demos," meaning "upon a mass of people assembled in a public place."[1] An epidemic is defined as the occurrence in a community or region of an unusually large or unexpected number of disease cases for the given place and time.[2] Therefore, baseline rates of disease are needed to determine whether an epidemic occurs. This information is obtained at the hospital or community level, or at the state, national, or global level. As an example, thousands of influenza cases in January in the United States may not be unusual; however, thousands of cases in mid-July may be cause for concern. Also, even a single case of a rare disease can be considered an epidemic. With the absence of woolen mill industry in the United States, any inhalational anthrax case should be highly suspect. Many of the diseases considered as classic BW agents, such as smallpox, viral hemorrhagic fevers, and plague (especially pneumonic), are rare, and a single case should be investigated. Determining whether an outbreak occurs depends, therefore, on the disease, the at-risk population, the location, and the time of year.

For an outbreak to occur, three points of the classic epidemiological triangle must be present (Figure 3-1).

There must be a pathogen or agent, typically a virus, bacterium, rickettsia, fungus, or toxin, and a host (in this case, a human) who is susceptible to that pathogen or agent. The two need to be brought together in the right environment to allow infection of the host directly, by a vector, or through another vehicle, such as food, water, or contact with fomites (inanimate objects). The environment must also permit potential transmission to other susceptible hosts. Disruption of any of these three points of the triangle can limit or disrupt the outbreak; therefore, it is important to know the characteristics of the three to control an epidemic. In one scenario, if potential hosts are vaccinated, disease spread would be significantly limited because of herd immunity. However, if the environment is modified, spread may be limited; for example, cleaning up garbage around a home limits rat food and harborage, and thus reduces the likelihood of bringing fleas closer to potential human hosts, limiting a potential bubonic plague outbreak.[3]

Recognition

Immediate effects are evident when an explosion occurs or a chemical weapon is released. However, casualties produced after a BW/BT release may be dispersed in time and space to primary care clinics and hospital emergency departments because of the inherent incubation periods of the pathogens. Therefore, the success in managing a biological event hinges directly on whether and when the event is recognized.

An example of the ramifications of delayed disease outbreak recognition occurred in 1972 in the former Yugoslavia. A single unidentified smallpox case led to 11 secondary cases, also unrecognized. Within a few weeks there was an outbreak of 175 smallpox cases and

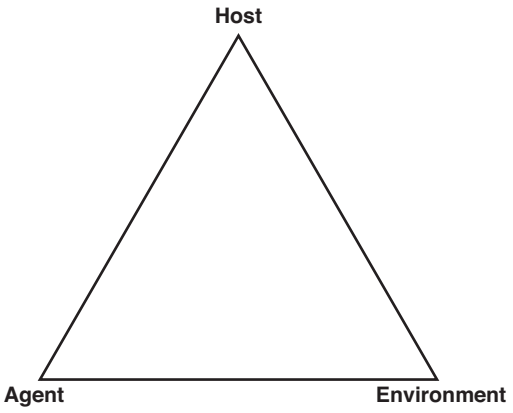

Fig. 3-1. The epidemiological triangle

35 deaths that led to a massive vaccination effort and border closure.[4] Early disease recognition may have significantly modified the outcome. One modeling study of a BT-caused smallpox outbreak showed that the more rapidly a postrelease intervention occurred, including quarantine and vaccination, the greater the chances that intervention would halt the spread of disease.[5] When medical professionals identify a new case, it is unlikely that a BW/BT event would be the first cause suspected, especially if the disease presents similar to other diseases that might occur simultaneously, such as influenza. Physicians are frequently taught to consider common illnesses first and might instead consider the source to be an endemic disease, a new or emerging disease, or a laboratory accident before considering BW/BT.[6] Therefore, care providers should be familiar with the diseases of BW/BT and a maintain a healthy "index of suspicion" to recognize an event early enough to significantly modify the outcome.[7]

Astute clinicians, hospital infection control personnel, school or healthcare facility nursing staff, laboratory personnel, and other public health workers notify public health authorities about disease outbreaks. State and local public health officials regularly examine and review disease surveillance information to detect outbreaks in a timely manner and provide information to policymakers on disease prevention programs. Time constraints are inherent in obtaining case report information because of the elapsed time from patient presentation, lab specimen collection and submission, and laboratory testing time, to final disease or organism identification reporting. Furthermore, the initial BW/BT disease recognition may not come from a traditional reporting partner or surveillance method. Instead, pharmacists and clinical laboratory staff who receive requests or samples from numerous healthcare providers, may be the first to note an increase in purchases or prescriptions of certain medications (eg, doxycycline or ciprofloxacin) or orders for certain laboratory tests (sputum or stool cultures), respectively. Also, because many of the category A high-threat diseases are zoonoses (primarily infecting animals), with humans serving as accidental hosts, veterinarians may be the first to recognize the disease in animals prior to the ensuing human disease. Media and law enforcement personnel and other nontraditional reporters of outbreaks may also provide information on a BT event or potential cases.

Potential Epidemiological Clues to an Unnatural Event

It is not possible to determine the objectives of a bioterrorism perpetrator in advance, whether the intent is to kill, incapacitate, or obtain visibility; or how a biological agent may be dispersed, whether through the air, in contaminated food or water, or by direct inoculation. In a biological attack, the number of casualties may be small and therefore unrecognized as intentionally infected, especially if the agent is a common cause of disease in the community. In addition, given the agent's incubation period, individuals may seek care from different care providers or travel to different parts of the country before they become ill and seek medical care. Despite the potential for these situations to occur, it is useful for healthcare providers to be aware of potential clues that may be tip-offs or "red flags" of something unusual. Although these clues may occur with natural outbreaks and do not necessarily signal a BW/BT attack, they should at least heighten suspicion that an unnatural event has occurred. The following compilation is an illustrative list; however, additional clues may be found elsewhere.[8,9]

Clue 1: A highly unusual event with large numbers of casualties. Although the mention of BW or BT may elicit images of massive casualties, this may not actually occur with a real BW/BT event. Numerous examples of naturally spread illness have caused massive casualties. Nevertheless, the type of large outbreak that should receive particular attention is one in which no plausible natural explanation for the cause of the infection exists.

Clue 2: Higher morbidity or mortality than is expected. If clinicians are seeing illnesses that are causing a higher morbidity or mortality than what is typically seen or reported for a specific disease, this may indicate an unusual event. A perpetrator may have modified an agent to make it more virulent. If the illness is normally sensitive to certain antibiotics but displays resistance, then resistance may have been purposefully engineered. Individuals could also be exposed to a higher inoculum than they would normally receive with natural spread of the agent, thus causing higher morbidity or mortality.

Clue 3: Uncommon disease. Many infectious diseases have predictable population and infectivity distributions based on environment, host, and vector factors; yet unnatural spread may occur if a disease outbreak is uncommon for a certain geographical area. Concern should be heightened if the naturally occurring disease requires a vector for spread and the competent vector is missing. If a case of a disease such as yellow fever, which is endemic to parts of South and Central America and sub-Saharan Africa, occurred in the United States without any known travel, it would be a concern. Natural outbreaks have occurred in new geographical locations including the West Nile virus (WNV) in New York City in 1999.[10] It is important to consider whether the occurrence of these uncommon diseases is natural.

Clue 4: Point source outbreak. For any outbreak, it is useful to develop an outbreak curve demonstrating the timeline of dates when patients developed illness. These timelines can have different morphologies depending on whether individuals are exposed at the same time from a single source or over time, and whether the illness propagates by person-to-person spread. It is thought that with an intentional BT event, a point source outbreak curve would be seen[11] in which individuals would be exposed at a similar point in time. The typical point source outbreak curve has a relatively quick rise in cases, a brief plateau, and then an acute drop, as seen in Figure 3-2. The epidemic curve might be slightly compressed because infected individuals were exposed more closely in time (ie, within seconds to minutes of each other) from an aerosol release, compared with individuals becoming ill after eating a common food over a period of minutes to hours. The inoculum may also be greater than what is typically seen with natural spread, thus yielding a shorter incubation than expected.

Clue 5: Multiple epidemics. If a perpetrator can obtain and release a single agent, why could multiple perpetrators not do so with a single agent at different locations? If simultaneous epidemics occur at the same or different locations with the same or multiple organisms, an unnatural source must be considered. It must also be considered that a mixture of biological organisms with different disease incubation periods could be combined, and would thus cause serial outbreaks of different diseases in the same population.

Clue 6: Lower attack rates in protected individuals. This clue is especially important to military personnel. If certain military units wore military-oriented protective posture (MOPP) gear or respiratory protection (such as high-efficiency particulate air [HEPA]-filtered masks), or stayed in a HEPA-filtered tent, and had lower rates of illness than nearby groups that were unprotected, this may indicate that a biological agent has been released via aerosol.

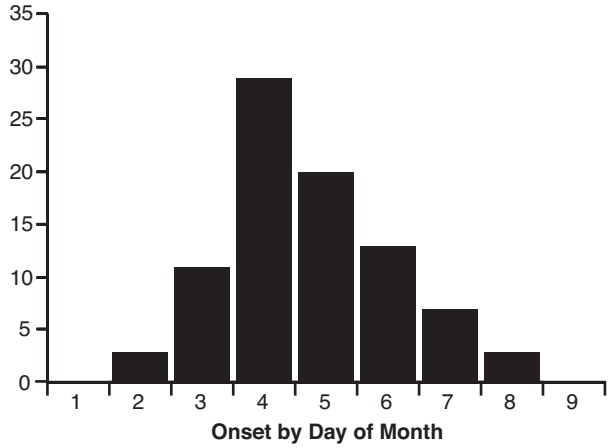

Fig. 3-2. Typical point source outbreak epidemic curve

Clue 7: Dead animals. Historically, animals have been used as sentinels of human disease. The storied use of canaries in coal mines to detect the presence of noxious gases is one example. Because many biological agents that could be used for BW/BT are zoonoses, a local animal die-off may indicate a biological agent release that might also infect humans. This phenomenon was observed during the WNV outbreak in New York City in 1999, when many of the local crows, along with the exotic birds at the Bronx Zoo, developed fatal disease.[12,13]

Clue 8: Reverse or simultaneous spread. Zoonotic illnesses exhibit a typical pattern: an epizootic first occurs among a susceptible animal population, followed by cases of human illness. When Sin Nombre virus initially appeared in the desert southwest of the United States,[14] environmental factors increased food sources and caused the field mouse (*Peromyscus maniculatus*) population to surge. The proliferating field mice encroached upon human habitats. The virus spread among the mice, causing a persistent infection and subsequent excretion in their urine.[15] Humans close to the mice became infected. If human disease precedes animal disease or human and animal disease is simultaneous, then unnatural spread should be considered.

Clue 9: Unusual disease manifestation. Over 95% of worldwide anthrax cases are cutaneous illness. Therefore, a single case of inhalational anthrax may likely be an unnatural event. This logic may be applied to case reports of a disease such as plague, where the majority of naturally occurring cases are the bubonic, and not the pneumonic form. Any inhalational anthrax case may be caused by BW/BT unless proven otherwise. Perhaps the only exception would be an inhalational anthrax case in a woolen mill worker.

Clue 10: Downwind plume pattern. The geographic locations where cases occur can be charted on a geographic grid or map. If the reported cases are found to be clustered in a downwind pattern, an aerosol release may have occurred. During the investigation into the anthrax outbreak in Sverdlovsk in 1979, as examined later in this chapter, mapping out case locations helped to determine that the anthrax cases were caused by an aerosol release rather than by a contaminated food source.[16]

Clue 11: Direct evidence. The final clue may be the most obvious and the most useful. Determining the intentional cause of illnesses is easier if a perpetrator

leaves a signature. The signature could be a letter filled with anthrax spores,[17] a spray device, or another vehicle for agent spread. It would then be useful to compare samples from such a device with the clinical samples obtained from victims to verify that they are the same organism.

Outbreak Investigation

It is important to understand the basic goals of an outbreak investigation, as seen in Exhibit 3-1. Any outbreak should be investigated quickly to find the source of the disease. If an outbreak is ongoing, the source of infection needs to be identified and eliminated quickly. Even if the exposure source has dissipated, all cases should be identified quickly, so that ameliorative care can be offered and case interviews can be conducted. Case identification can assist in preventing additional cases, especially with a transmissible infectious disease.

With notification of any outbreak, whether natural or human-caused, there are standard steps to follow in an outbreak investigation (Exhibit 3-2), although these steps may not always occur in order.[18] The first step is preparation, which involves having the necessary response elements (personnel, equipment, laboratory capabilities) ready, and establishing communications in advance with partners in the investigation. Once an event is ongoing, the second step is to investigate, verify the diagnosis, and decide whether an outbreak exists. Early in an outbreak, its significance and scope are often not known. Therefore, existing surveillance information and heightened targeted surveillance efforts are used to determine whether reported items are cause for concern.

The third step is to define the outbreak and seek a definitive diagnosis based on historical, clinical, epidemiological, and laboratory information. A differential diagnosis can then be established.

The fourth step is to establish a case definition that includes the clinical and laboratory features that the ill individuals have in common. It is preferable to use a broad case definition at first and avoid excluding any potential cases too early. However, a definition should use clinical features that are objectively measured whenever possible, such as temperature exceeding 101.5°F, rash, bloody vomitus, or diarrhea. The case definition enables the investigator to count cases and compare exposures between cases and noncases. To obtain symptom information, it may not be sufficient to look at healthcare facilities only, but it will likely also be necessary to interview the ill persons and their family members, as well as coworkers, classmates, or others with whom they have social contact. It is important to maintain a roster of potential cases while obtaining this information. Commonly during an investigation, there is a risk of double or even triple-counting cases because they may be reported more than once through different means. Key information needed from each ill person includes date of illness onset; signs and symptoms; recent travel; ill contacts at work, home, or school; animal exposures; and treatments received. With this information, an epidemic curve can be constructed (see Figure 3-2) that may provide information as to when a release may have occurred, especially if the disease is known, and an expected exposure date based on the typical incubation period, known ill contacts, or geographic risk factors.

Different modes of disease spread may have typical features that comprise an epidemic curve. If the agent is spread person-to-person, successive waves of illness may be seen as one group of individuals infects a follow-on group, which in turn infects another, and so on

EXHIBIT 3-1

GOALS OF AN OUTBREAK INVESTIGATION

- Find the source of disease
- Rapidly identify cases
- Prevent additional cases

EXHIBIT 3-2

TEN STEPS IN AN OUTBREAK INVESTIGATION

1. Prepare for fieldwork.
2. Verify the diagnosis. Determine an outbreak exists.
3. Define the outbreak and seek a diagnosis.
4. Develop a case definition and identify and count cases.
5. Develop exposure data with respect of person, place, and time.
6. Implement control measures and continually evaluate them.
7. Develop the hypothesis.
8. Test and evaluate the hypothesis with analytical studies and refine the hypothesis.
9. Formulate conclusions.
10. Communicate findings.

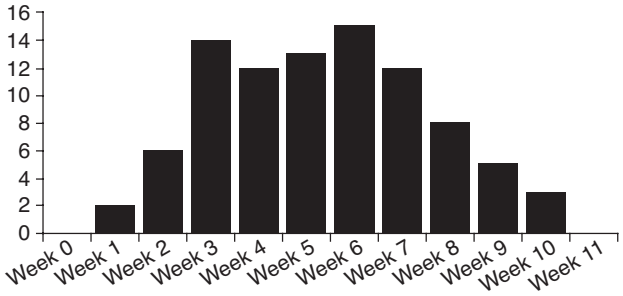

Fig. 3-3. Typical continuous common source outbreak epidemic curve

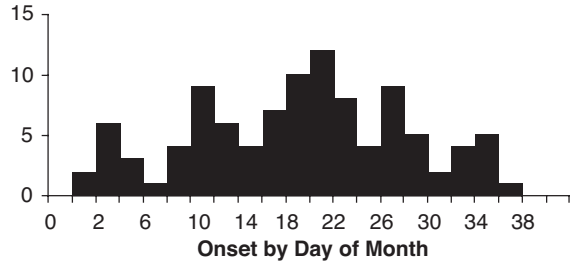

Fig. 3-4. Typical propagated (secondary transmission) outbreak epidemic curve

(Figure 3-3). With time and additional cases, the successive waves of illness may overlap with each other. If there is a common vehicle for disease transmission (such as a food or water source) that remains contaminated, it might be possible to see a longer illness plateau (a continuous common source curve [Figure 3-4]) than is seen with a point source of infection.

The fifth step is to develop exposure data with respect to person, place, and time. Cases need to be identified and counted. Once cases have been identified, exposures based on person, place, and time can be determined. Obtaining information from individuals who would likely have had similar exposures but are not ill can also help determine the potential cause and method of an agent's spread. Information can be obtained either informally or formally with a case control study. A case control study is a type of study where investigators start with individuals with and without disease and compare their potential exposures or risk factors for disease.

The sixth step is to implement control measures and continuously evaluate them. Control measures should be implemented as soon as possible. If necessary, control measures can be quickly implemented and then modified as additional case information becomes available.

The seventh step is to develop a hypothesis. Based on the characteristics of the disease, the ill persons, and environmental factors, it is useful to develop a hypothesis of how the disease occurred, how it is spreading, and the potential risk to the uninfected.

The eighth step is to test and evaluate the hypothesis using analytical studies and refine the hypothesis. Once developed, it is important to test the hypothesis to ensure it fits with the known facts. Does it explain how all the cases were exposed? It is possible that there are some outliers who seem as if they should be ill but are not, or some who are ill but have no known exposure. These outliers can sometimes be the key to determining what happened.

With preliminary control measures implemented, the hypothesis can be tested formally with analytical studies. Further modifications in control measures might be needed and implemented.

The ninth step is to formulate a conclusion about the nature of the disease and exposure route. Findings can then be communicated (step 10) through the media or medical literature, depending on the urgency of notification of the public and medical community. Experience from the anthrax mailings of 2001 indicates that during any BT event, intense pressure will be exerted on public health authorities to provide more information than they can possibly collect, which may interfere with the investigation.[19]

As stated earlier, these different steps may not occur in sequence. It may be necessary to implement control measures with incomplete information, especially if an outbreak is fast-moving or has a high morbidity or mortality rate. Whether the control measures appear to limit the spread of disease or the casualty toll is the ultimate test of whether the original hypothesis was correct.

Early in an investigation, it will probably not be known or suspected that an outbreak was unnaturally spread. Therefore, with a few exceptions, the investigation of an unnaturally spread outbreak will not differ significantly from the investigation of a naturally occurring outbreak. Public health authorities should handle both types of outbreaks. The significant difference is that, with a purposeful outbreak, a potential criminal event may have occurred. An additional goal of this type of investigation, under the purview of law enforcement personnel, is to bring the perpetrator to justice. Therefore, law enforcement personnel need to be involved as early as possible in any suspected case as partners with public health officials in the investigation.[20]

Public health authorities must become familiar with the use of chain of custody, the process used to maintain and document the chronological history of the evidence, so that medical evidence obtained in the investigation will be admissible in court. Public health authorities would need to use chain of custody for

environmental and clinical samples obtained during their investigation of a BT event. Environmental and biological samples can be crucial in determining whether a release has occurred (see the case study in this chapter about the release of anthrax in Tokyo by the Aum Shinrikyo). Although chain of custody is important, public safety should be the primary concern.

Public health authorities must also have an open mind for unusual modes of disease spread, being especially careful to ensure the safety of their personnel if there is a potential exposure risk during the investigation. Public health authorities conducting a field investigation should have personal protective equipment and be trained in its proper use, and have access to occupational health should pre- or postexposure prophylaxis be needed.

EPIDEMIOLOGICAL CASE STUDIES

The following epidemiological case studies are presented to demonstrate the differences between naturally occurring and purposefully created epidemics. Biological attacks and some naturally occurring epidemics of historical significance are considered in the context of BT. Some purposeful BT events have not caused illness; however, some naturally occurring outbreaks have been considered as BT events because of the particular disease or nature of clinical case presentation.

Public health authorities could be held accountable to make a determination quickly as to whether an infectious disease outbreak has been purposefully caused, yet they may lack the necessary information because there may not be clear evidence or responsibility claimed for a BT event. As of the summer of 2007, the perpetrator of the anthrax mailings during the fall of 2001 had still not been apprehended by law enforcement authorities. Public health authorities initially considered the first inhalational anthrax death that occurred in this outbreak to have been naturally occurring. A thorough understanding of how to investigate suspect outbreak occurrences may better enable public health authorities to make difficult public health policy decisions.

Bioterrorism Events

The following section describes BT incidents that occurred in the United States and Japan. None of these events was immediately recognized as having been intentional. The 2001 mail-associated anthrax outbreak and mail-associated ricin attack were recognized within days to weeks. However, for previous BT incidents (anthrax and glanders in 1915, salmonellosis in 1984, and anthrax in 1995), intentionality was not recognized for a year or longer after the initial event.

Anthrax and Glanders—Maryland; New York, New York; and Virginia, 1915–1916

From 1915 through 1918, Germany had a state-sponsored offensive BW program to sabotage suppliers to the Allies directed at draft, cavalry, and military livestock. Human disease was neither intended nor recorded from these events, although the program could have been expanded to spread zoonotic illness among a target population. Unintended human disease may have occurred but was never recorded. Countries targeted by Germany included the United States, Argentina, Romania, Russia, Norway, and Spain. The biological sabotage program was directed by the German army general staff and implemented despite official German army doctrine prohibiting such activities. Germany's plans to spread a wheat fungus and contaminate food produced at "meat factories" were dropped.[21] One 1916 German plan never carried out proposed to drop vats of plague cultures from Zeppelins over England.[22]

In April 1915, German-American physician Anton Dilger returned to the United States from Germany with cultures of *Burkholderia mallei* and *Bacillus anthracis*. His intent was to infect horses and mules then being shipped from the United States to France and England for use in cavalry and transport. These cultures were propagated and tested for virulence using guinea pigs in the basement of a house (known as "Tony's Lab") rented by Anton and his brother Carl, in Chevy Chase, Maryland, near Washington, DC.[23] From the summer of 1915 through the fall of 1916, the cultures were used on horses and mules in holding pens in the docks at the ports of Baltimore, Maryland; Newport News, Virginia; Norfolk, Virginia; and New York, New York. Stevedores working for German steamships were recruited and given 2-inch, cork-stoppered glass vials containing the cultures, in which a hollow steel needle had been placed. These stevedores were instructed to wear rubber gloves while jabbing the animals with the needle. These cultures were also spread to the animals by pouring them into the animal feed and drinking water.[24]

Case Review of 1915–1916 Anthrax and Glanders Incidents

Biological Agents: *B anthracis*, gram-positive bacillus; *B mallei*, gram-negative bacillus

Potential Epidemiological Clues: 2, 7, 8

Review: A full assessment of the success of this BW

program 90 years later is not possible. German agents claimed that epidemics occurred among the animals shipped from the US ports. A claim of effect upon the 1917 British advance on Baghdad during the Mesopotamian campaign is dubious. However, disease observed among animals might have originated naturally or from stressful holding and shipment conditions. One writer suspected that nonviable cultures may have originated from Tony's Lab because of the lack of illness among the saboteurs.[22] However, using rubber gloves may have protected the plotters from acquiring cutaneous anthrax or glanders from the bacterial cultures.

If a similar incident occurred now, would current biological detection capabilities alert health officials? Glanders produces disease in horses, mules, and donkeys and is poorly transmitted directly to humans. The examining clinician should be suspicious when seeing persons exhibiting this disease without previous exposure to these animal vectors.

Few syndromic surveillance systems incorporate comprehensive veterinary surveillance. This is an important disease detection vulnerability because many of the BW agents (ie, *B anthracis*, *Brucella suis*, *B mallei*, *B pseudomallei*, *Coxiella burnetii*, *Francisella tularensis*, *Yersinia pestis*, encephalitis, and hemorrhagic fever viruses) can cause zoonotic illness. Furthermore, US industrial agricultural practices are vulnerable to the threat of antianimal agents.[25,26] Few geographic areas have an established infrastructure that permits accurate and comprehensive animal disease reporting. A comprehensive animal surveillance network would include reports from veterinary examinations of farm and companion animals, and from wildlife examinations by state environmental officials and animal rehabilitators. Current animal disease surveillance networks that address these deficiencies include the National Animal Health Laboratory Network[27]and the Centers for Epidemiology and Animal Health,[28] both part of the US Department of Agriculture (USDA).

Depending on exposures and timing, a purposeful use of anthrax (*B anthracis*) or glanders (*B mallei*), such as the occurrence in 1915–1916, would likely be detected initially by hospital emergency department clinicians or physicians in private practice through their examination of affected persons, or by veterinarians inspecting animals for transport. If such an incident with large numbers of glanders or anthrax cases in animals about to be shipped overseas occurred now, detection might occur through the USDA Animal and Plant Health Inspection Service's inspection or record-keeping processes. Case-specific information for human cases would be reported to state health authorities, and ultimately the Centers for Disease Control and Prevention (CDC) would be notified.

Disease outbreak information exchange between federal partners such as CDC and USDA may eventually lead to a "one medicine approach" linking human and animal health reporting. A viable hospital emergency department syndromic surveillance network monitored by state health authorities could detect a cluster of patients with similar etiologies indicating anthrax. Law enforcement authorities might also interview sentinel cases from a suspect outbreak to investigate whether they could be outbreak perpetrators who had inadvertently become infected.

Lessons Learned: Veterinarians familiar with glanders or anthrax in livestock and USDA select agricultural agents should report these diseases to state health and federal authorities as possible indicators of BT. Until recently, glanders had not occurred in the United States since 1945, when it was reported in military laboratory workers.[29] In 2000, 55 years later, a Maryland laboratory worker contracted glanders, demonstrating the continuing potential for risk of occupational exposure to this disease in biodefense laboratory workers,[30] as well as the paramount importance of adhering to biosafety level 3 standards. Endemic anthrax also occasionally occurs in the United States, along with zoonotic[31] or laboratory transmission.[32,33]

Salmonellosis—The Dalles, Oregon, 1984

A large outbreak of Salmonella cases occurred in and around The Dalles, Oregon, in 1984. This farming community, with a 1984 population of 10,500, is near the Columbia River on the border of Oregon and Washington. Salmonellosis is the second most common bacterial foodborne illness and is underreported by a factor of about 38-fold.[34,35] The average onset period for salmonellosis is about 12 to 36 hours, and the disease manifests as acute gastroenteritis. Fever occurs, anorexia and diarrhea persist for several days, and more severe manifestations may at times occur, especially in very young or elderly persons. Contaminated food (most often poultry) is the principal route of disease transmission.[36]

At the time (and now), public health authorities would not consider a foodborne salmonellosis outbreak initially as having been caused purposefully. It has been estimated that 1.4 million salmonellosis infections occur annually in the United States, resulting in 15,000 hospitalizations and 400 deaths.[37] Therefore, the index of suspicion for an intentional Salmonella outbreak was—and remains today—low. However, atypical events associated with this outbreak eventually led officials to realize that this particular disease occurrence was historically different.

Two cohorts of cases occurred: (1) from September 9 through 18, 1984, and (2) from September 19 through October 10, 1984. Public health authorities received initial reports of illness on September 17, and local and state health officials interviewed the ill persons. Patronizing two restaurants in the city of The Dalles and eating salad bar food items were commonly cited in these interviews. *Salmonella typhimurium* isolates were then obtained from clinical specimens of the ill persons.[38]

The source for this outbreak was puzzling. Epidemiological analysis revealed multiple items rather than a single suspect item as the cause of the restaurant patrons' illness. This finding is not uncommon either during the initial stages of an investigation of

a foodborne disease outbreak (until a suspected food item is identified), or when an infected food handler is identified as the source of the outbreak. Although dozens of food handlers became ill, their time of symptom onset did not precede those of their customers. As gastroenteritis cases occurred in increasing numbers, health officials imposed a closure of all salad bars in The Dalles on September 25. By the end of the outbreak, 751 salmonellosis cases were identified, with those affected ranging in age from newborns to 87 years, and most were associated with dining in 10 area restaurants. At least 45 persons were hospitalized, but no fatalities occurred.

Bhagwan Shree Rajneesh, a charismatic guru, had established a community for his followers in 1981 at a ranch near The Dalles. These cult members, or "Rajneeshees," attempted to use Oregon's liberal voter registration laws to control zoning and land use restrictions to their advantage. Conflict between the commune and the neighboring traditional community had escalated. To gain political control of the area, the Rajneeshees attempted to influence an election by making voters too ill to vote.[21] Approximately 12 individuals were involved in the plot, and up to 8 individuals distributed *S typhimurium* cultures to the salad bars. After considering the use of several biological agents, including *S typhi* (the causative agent of typhoid fever) and the human immunodeficiency virus, the Rajneeshees legally obtained cultures of *S typhimurium* (ATCC strain 14028) from a commercial supplier and used them to grow bacterial stock cultures. The Rajneeshees first spread Salmonella by contaminating the commune members' hands to greet outsiders, as well as the county courthouse's doorknobs and urinal handles; these efforts did not cause illness. Then the cult spread Salmonella cultures on salad bars in area restaurants.

Public health authorities conducted an extensive investigation in response to the salmonellosis outbreak. Authorities identified confirmed cases microbiologically by stool culture of *S typhimurium*, or with the clinical criteria of diarrheal illness and at least three of the following symptoms: fever, chills, headache, nausea, vomiting, abdominal pain, or bloody stools. *S typhimurium* was isolated from 388 patients. In the 4 years before the outbreak, the local health department had collected 16 isolates of Salmonella, 8 of which were *S typhimurium*. No local cases of salmonellosis had been reported in 1984 before August.[38]

The 38 restaurants in The Dalles were grouped according to the number of culture-confirmed customer cases with a single restaurant exposure in the week before symptom onset. Additional ill customers were located through laboratory reporting of clinical specimens or clinician reporting to public health authorities (passive disease surveillance). Press releases were issued to encourage disease reporting by patients and clinicians.[38] Public health officials interviewed ill persons to obtain their symptoms, risk factors, and comprehensive food histories, as well as the names of all persons who had eaten with them at the restaurant. Employees of restaurants with the greatest number of cases were interviewed twice and required to submit a stool sample as a condition of continued employment. The state public health laboratory serotyped the Salmonella isolates and performed antibiotic-susceptibility testing on a subset. A representative sample of outbreak isolates was sent to CDC for further characterization, during which the outbreak strain was compared with national surveys of human and veterinary isolates. Sanitarians inspected the restaurants, and tap water was collected and analyzed. The local health department and USDA also investigated the distributors and suppliers of foods used in these restaurants. None was found to have contaminated food, nor was a common supplier found for all of the implicated restaurants.

Many food items served at the salad bars of the restaurants were associated with illness and differed among the restaurants. Illness was associated with eating blue cheese dressing at one of the restaurants. The consumption of potato salad had the greatest association with illness, followed by lettuce. *S typhimurium* was isolated from the blue cheese dressing collected at one restaurant, but not from the dry mix used to prepare the dressing.

The size and nature of the outbreak helped to initiate a criminal investigation. The source and cause of the outbreak only became known when the Federal Bureau of Investigation (FBI) investigated the cult for other criminal violations.[39] An Oregon public health laboratory official accompanying the FBI discovered an open vial containing the original culture strain of *S typhimurium* in the Rajneeshee clinic laboratory in October 1985.[21,38] This strain was indistinguishable from the outbreak strain as isolated from food items and clinical specimens, and records were found documenting its purchase before the outbreak.[38]

Intentional contamination of the salad bars is consistent with the retrospective epidemiology.[38] Eventually, two cult members were arrested and served federal prison terms. Despite the Rajneeshees' success of the restaurant-associated BT, the publicity and subsequent legal pressure caused them to abandon subsequent efforts.[21]

Case Review of 1984 Salmonellosis Outbreak
Biological Agents: *S typhimurium*, gram-negative bacillus
Potential Epidemiological Clues: 1, 4, 5, 11

Review: Only one commune member admitted to contamination of a salad dressing with a bacterial culture, and it is unknown what other food items the other perpetrators contaminated. Public health authorities found no statistical association with any single food item.[21] The isolation of *S typhimurium* from the blue cheese dressing, but not from the dry mix used in dressing preparation, should have indicated to authorities the contamination of the prepared dressing that was then served at a salad bar.

The ongoing law enforcement investigation eventually revealed purposeful restaurant food contamination by the Rajneshees more than a year after the outbreak occurred. Public health and law enforcement authorities lacked cooperative protocols in 1984, yet the public health and law enforcement teams in Oregon worked well together, as demonstrated by a public health laboratory official accompanying the FBI investigation. This official noticed the *S typhimurium* culture, which may have gone unnoticed by the FBI. An outbreak of this magnitude would today initiate a joint inquiry and investigation by public health and law enforcement, increasing chances that the outbreak cause would be identified in a more timely manner.

Lessons Learned: These events illustrate the need to have joint public health and law enforcement investigations and mutual cooperation. Additionally, this outbreak shows the importance of the mode of disease spread in discerning whether it occurred naturally. An unlikely vehicle may be responsible for a deliberate foodborne disease outbreak. Although not occurring in this case, when different locations are involved, there could be a central supplier of a contaminated product shipped to all the locations.

Anthrax—Tokyo, Japan, 1995

The notorious sarin (a chemical nerve agent) attacks in a Tokyo suburb, Kameido, in 1994 and 1995, culminated with a sarin release in the Tokyo subway system.[40,41] Less well known is that before their efforts with chemical weapons the apocalyptic cult Aum Shinrikyo appears to have first invested efforts into the production of biological agents and had tried to use them.[21]

Shoko Asahara, a charismatic guru, built the Aum Shinrikyo cult into a membership of 10,000 with financial assets exceeding $300 million. Aum Shinrikyo's organization mimicked a government entity, with various ministries and departments, including a ministry of science and technology that included graduate-level researchers within modern laboratories interested in developing biological and chemical weapons. *B anthracis* cultures were also obtained and grown into a slurry for use as a biological weapon. This cult may have investigated the use of *C burnetii* (the bacteria that causes Q fever) and toxic mushrooms. In 1992 a team of 40 cult members, including Asahara, traveled to Zaire to attempt to acquire Ebola virus; the success of these efforts is unknown.

The Aum Shinrikyo experimented with the release of aerosolized biological agents. In June 1993 the cult sprayed *B anthracis* from the roof of one of its buildings in downtown Tokyo. In July 1993 the cult sprayed *B anthracis* from a moving truck onto the Diet (Japan's parliament) and also around the Imperial Palace in Tokyo.

Information about the anthrax release became public when, during the arraignment of Asahara on May 23, 1996, for the Kameido sarin attack, cult members testified about their efforts to aerosolize a liquid suspension of *B anthracis* to cause an inhalational anthrax epidemic. Their goal was to have an epidemic trigger a world war that would permit Asahara to rule the world.[42] In 1999 a retrospective case-detection survey was conducted to assess the possibility that some anthrax cases may have been unreported. Complaints of odors from neighborhood residents were associated with the anthrax releases. These complaints were retrospectively mapped to provide the geographic areas of the greatest anthrax exposure risk. Physicians at 39 medical facilities serving this area were surveyed. None reported having seen cases of anthrax or relevant syndromes.[42] It is not known whether a similar retrospective examination of anthrax-caused animal deaths was or could have been performed.

Case Review of 1995 Anthrax Releases
Biological Agents: *B anthracis*, gram-positive bacillus
Potential Epidemiological Clues: 11

Review: None of the biological attacks carried out by the Aum Shinrikyo cult were successful. In contrast, there were 12 deaths and about 1,000 hospitalizations from the sarin releases by the Aum Shinrikyo.[40] Technical errors in either the biological agent production or dissemination rendered the attacks harmless. The anthrax strain that the cult was using was likely a harmless strain used in animal vaccines.

In 2001 specimens from the exterior of the Tokyo building where the cult released anthrax spores were cultured to analyze the strain's genetic material. Molecular analysis revealed that the *B anthracis* isolates were similar to the Sterne 34F2 strain, the strain of anthrax used in animal vaccines. Dispersal of this type of anthrax (regarded as nonpathogenic for immunocompetent individuals) had little possibility to cause harm.[42]

Even if the strain used was pathogenic, the concentration of spores in the liquid suspension is significantly less (10^4 bacteria/mL) than that considered optimal for a biological weapon (10^9–10^{10} bacteria/mL). The viscosity of the suspension was also problematic for successful aerosolization. Area residents described a gelatinous substance, suggesting poor dispersion. Also, the Aum Shinrikyo spray system's

effectiveness is doubtful; reports indicate it repeatedly broke down. Finally, the weather on the day of dispersal may have helped prevent infection: spore inactivation resulting from solar radiation could have further reduced the anthrax mix's potency.[42] These experiences show that it is difficult to both create a pathogenic biological weapon and to use it. However, if the Aum Shinrikyo had obtained a different strain of *B anthracis*, the intended effects may have been more successful, which may have led the cult to use a biological agent in the Tokyo subway system. Its failures with biological agents led the group to use sarin, a chemical nerve agent.

Lessons Learned: Both health and law enforcement officials should be aware of the possibility for use of more than one biological agent or a combination of agents. The Aum Shinrikyo knew that it could effectively use sarin from experience with an earlier release in the Matsumoto area of Tokyo in 1994.[40] If the cult had not failed to culture and develop biological agents, it may have used a combination biological and chemical weapon in 1995. Another lesson learned is the importance of environmental sample collection and proper storage. The emerging discipline of forensic molecular biology proved the occurrence of an anthrax release by analysis of archived samples 8 years after the incident.[43]

Shigellosis—Dallas, Texas, 1996

From October 29 through November 1, 1996, 12 clinical laboratory workers at the St Paul Medical Center in Dallas developed severe acute diarrheal illness.[21] *Shigella dysenteriae* type 2 was cultured from the stool of eight of these cases. This strain of shigella is uncommon and, before this outbreak, had last been reported as the source of an outbreak in the United States in 1983. A 13th individual became ill from eating pastries brought home by one of the laboratory workers; this individual also had stool cultures positive for *S dysenteriae* type 2. Five patients were treated in hospital emergency departments and released, four were hospitalized, but no deaths resulted.[44]

During the subsequent epidemiological investigation, 45 laboratory employees who had worked during the first or third shifts, when the ill employees had worked, were interviewed. The employees stated that an unsigned email sent from a supervisor's computer invited recipients to take pastries available in the laboratory break room. The supervisor was away from the office when the email was sent, and the break room could only be accessed using a numeric security code. The muffins and pastries had been commercially prepared, yet there were no other cases in the community outside the hospital laboratory. The ill persons reported eating a pastry between 7:15 AM and 1:30 PM on October 29. Diarrhea onset for the ill laboratory workers occurred between 9:00 PM that day and 4:00 AM on November 1. The mean incubation period until diarrhea onset was 25 hours and was preceded by nausea, abdominal discomfort, and bloating. All who ate a muffin or doughnut became ill (ie, 100% attack rate). No increased risk for illness was found from eating food from the break room refrigerator or drinking any beverage, eating in the hospital cafeteria, or attending social gatherings during the time of exposure to the pathogen.

An examination of the hospital laboratory storage freezer revealed tampering of reference cultures of *S dysenteriae* type 2. The stored reference cultures had each contained 25 porous beads that were impregnated with microorganisms. The *S dysenteriae* type 2 vial contained at that time only 19 beads, and laboratory records indicated that the vial had not been used. *S dysenteriae* type 2 was isolated in virtually pure culture from the muffin specimen, and the same organism was isolated from the stools of eight laboratory worker patients. Pulsed-field gel electrophoresis revealed that the reference culture isolates were indistinguishable from those obtained from a contaminated muffin and the collected stool cultures, but differed from two non-outbreak *S dysenteriae* type 2 isolates obtained from other Texas counties during that time.

Case Review of 1996 Shigellosis Food Poisonings

Biological Agents: *S dysenteriae* type 2, gram-negative bacillus

Potential Epidemiological Clues: 3, 4, 11

Review: There was a strong epidemiological link among those ill persons, the uneaten muffin, and the laboratory's stock culture of *S dysenteriae* type 2. This specific pathogen was known to be uncommon. No research with this microorganism had been conducted at the hospital; therefore, laboratory technicians were not at risk of infection through laboratory error. No concurrent outbreaks of *S dysenteriae* type 2 were reported nationally at the time. Contamination of pastries during commercial production was unlikely. Shigella contamination by a food service worker during food preparation would have had to occur subsequent to baking because Shigella bacteria would not have survived the heat. Therefore, health authorities did not order a food recall. When the epidemiological report was published,[44] it was hypothesized that someone had removed the laboratory culture of *S dysenteriae* type 2 from the freezer, cultured the microorganism and inoculated the pastries, and had access to the supervisor's computer and the locked break room. On August 28, 1997, a laboratory technician who had access to the laboratory culture stocks and a history of purposeful use of biological agents against a boyfriend, was indicted on three charges of tampering with a food product, and accused of infecting 12 coworkers with *S dysenteriae* type 2. She was subsequently sentenced to 20 years in prison.[45]

Lessons Learned: A match of clinical, food, and laboratory isolates helped to prove an epidemiological link among them. In this case, only an individual with direct access to the laboratory culture could have committed this "biocrime," and one such person was eventually apprehended. In addition,

the epidemiological investigation was helped by the knowledge that only postproduction tampering of the baked goods could have resulted in their successful contamination.

Anthrax—USA, 2001

On October 4, 2001, an inhalational anthrax case was reported in a 63-year-old male in Florida.[46] Public health and government authorities initially misunderstood the nature of inhalational anthrax exposure and assumed that this individual had contracted the illness by outdoor hunting activities.[47] Two other cases were subsequently identified in Florida, and a fourth case of anthrax, via cutaneous exposure, was identified in a female employee at NBC News in New York City.[48] Investigators then realized that the exposures resulted from anthrax-containing letters placed in the mail. On October 15, a letter was received at Senate Majority Leader Tom Daschle's office that threatened an anthrax attack and also contained anthrax spores. The Hart Senate Office Building in Washington, DC, was subsequently closed.[49] By the end of the year, anthrax-laden letters placed in the mail had caused 22 cases of anthrax-related illness (11 inhalational [all confirmed], and 11 cutaneous anthrax [seven confirmed, four suspected]) and five deaths. Almost all anthrax cases were among postal workers and those who had handled mail.[50,51] A 12th cutaneous anthrax case related to these mailings occurred in March 2002 in a Texas laboratory where anthrax samples had been processed.[52]

Case Review of 2001 Anthrax Mailings
Biological Agents: *B anthracis*, gram-positive bacillus
Potential Epidemiological Clues: 3, 5, 9, 11
Review: An unprecedented national response occurred because of these events. Massive public health and law enforcement investigations occurred, involving thousands of investigators from federal, state, and local agencies. Close collaboration was required of all agencies, and the CDC and FBI formed partnerships to conduct public health and criminal investigations.[53] Public health surveillance to both detect previously unreported anthrax cases and to determine that no new cases were taking place severely strained public health capacity.[54,55] Even states that did not have anthrax cases were inundated with requests from the public to test various pieces of mail and powder-containing articles. This outbreak highlighted the importance of containing not only the disease but also public panic.

The Laboratory Response Network, a multilevel network connecting local and state public health laboratories[56] with national public health and military laboratories, served as a lead resource for both identifying and ruling out a potential biological attack.[57] Molecular subtyping of *B anthracis* strains played an important role in the differentiation and identification of anthrax. High-resolution molecular subtyping determined that the anthrax mail-related isolates were indistinguishable and likely came from a single source.[58] Postal workers and others handling mail were shown to be at risk from the anthrax-containing letters[59] and contaminated postal machinery[60]; therefore, environmental sampling,[61] cleaning,[62] and protective measures as well as antibiotic prophylaxis, were instituted by federal and state health officials.[63] Similar protective actions were taken after discovery of the anthrax spore-laden envelope opened in the Senate Office Building.[49] The continued monitoring of this population will provide invaluable information concerning anthrax exposures and the efficacy of prophylaxis.[64]

Anthrax has been known to be an occupational hazard to industrial workers in the United States even before the causative organism *B anthracis* was isolated by Robert Koch in 1877.[65] As previously mentioned, German agents used anthrax as an agent for materiel sabotage in the United States during 1915 and 1916. As of the summer of 2007, the perpetrator of the anthrax mailings has still not been apprehended by law enforcement authorities. The anthrax mailings have irreversibly changed much of US society and greatly influenced the public's perception of vulnerability to an attack from a biological agent. In the month after public notification of confirmed cases, the CDC responded to over 11,000 phone calls.[66] A "crisis mode" prevailed at many state and local health departments, who also managed similar phone triage from the public. These agencies also received queries around the clock from healthcare providers presenting patient details and requesting clinical information to rule out anthrax, media queries, and reports of untold numbers of "white powder" incidents demanding instant identification of the substance.[67] In states where anthrax cases occurred, these demands were exacerbated by the need for anthrax exposure assessments for postal workers, patients, and workplace and home environments; distribution of pharmaceuticals; and exhaustive statewide prospective and retrospective anthrax-syndromic surveillance case review and reporting.[68] According to Casani, Matuszak, and Benjamin, government authorities sent conflicting messages on policies and priorities based on scientific knowledge that changed hourly, daily, and weekly.[67]

As a direct result of the anthrax mailings, on January 31, 2002, the federal government made $1.1 billion available to the states for BT preparedness.[69] Disease detection and notification efforts, a cornerstone of BT preparedness, have changed dramatically since the incident with the implementation of automated laboratory reporting via the National Electronic Disease Surveillance System[70] and automated hospital syndromic surveillance reporting[71] by public health agencies in many states and large cities. Continuing efforts to strengthen the public health workforce should help to better detect, respond, and manage a future BT crisis.[72]

Lessons Learned: An enhanced index of suspicion is necessary for unusual manifestations of BT diseases. Healthcare providers can learn to heighten their index of suspicion and diagnosis early if information is available and they are aware of a disease in a community. No one can anticipate how an initial case will present. The most important lesson learned in this outbreak is that fine particles of a biological agent can become airborne, thereby contaminating areas and placing persons at risk without direct exposure to the

contaminated vehicle. An exposure can occur anywhere along the path of the contaminant, and increased medical surveillance and possibly prophylaxis should be instituted for anyone with potential exposure.

Ricin—South Carolina and Washington, DC, 2003–2004

After a terrorist plot to use ricin in England in January 2003,[73] this toxin was found in a South Carolina postal facility in October 2003.[74] Ricin was also discovered in the office of Senator Bill Frist at the Dirksen Senate Office Building in Washington, DC, on February 3, 2004.[75]

On October 15, 2003, an envelope containing a note threatening to poison water supplies with ricin and a sealed container were processed at a mail-processing plant and distribution facility in Greenville, South Carolina. Laboratory testing at the CDC on October 21 confirmed the presence of ricin in the container. All postal workers at the facility were then interviewed by state health authorities, and statewide surveillance for illness consistent with ricin exposure was initiated. The postal facility was closed on October 22, and epidemiological and environmental investigations were conducted. Hospital emergency departments, clinicians, health departments, and the postal facility were asked to report any cases consistent with ricin exposure. State poison control center and intensive care unit charts at seven hospitals near the postal facility were reviewed daily. A medical toxicologist and epidemiologists interviewed all 36 workers at the postal facility to determine whether any were ill, and no postal employees had illness indicating ricin exposure. CDC also conducted environmental testing at the postal facility; all tests were subsequently found negative for ricin.[74]

Case Review of 2003–2004 Ricin Events
Biological Agents: *Ricin communis* toxin
Potential Epidemiological Clues: 3, 11

Review: Ricin is a potent cytotoxin derived from the beans of the castor plant (*R communis*). Ricin will likely continue to be a threat agent because castor beans are grown and used commercially worldwide, and the toxin can be readily extracted. Ricin is considered to be a more potent toxin when it is ingested or inhaled than when injected. Treatment for ricin toxicity is supportive care because no antidote exists, and the toxin cannot be removed by dialysis.

Difficulties inherent in responding to a threat of ricin use include the lack of a detection method for the presence of ricin in clinical samples. A mild ricin poisoning may resemble gastroenteritis or respiratory illness. Ingestion of higher ricin doses leads to severe gastrointestinal symptoms followed by vascular collapse and death; inhalation of a small particle aerosol may produce severe respiratory symptoms followed by acute hypoxic respiratory failure.[76]

Any ricin threat should be investigated. Healthcare providers and public health officials must be vigilant for illness consistent with ricin exposure. However, in the above incidents, no cases resulted from exposure. It is likely that the material used in these incidents was not processed, purified, or dispersed in a manner that would cause human illness.

Accidental Release of Biological Agents

The following case studies document the events that transpired after what is understood to be the accidental release of two biological warfare agents, *B anthracis* and *Variola major*, in the former Soviet Union during the 1970s. The former Soviet Union had a massive state-sponsored biological weapons program, as documented by its former deputy director Ken Alibek in his book *Biohazard*.[77] These accounts place frightening emphasis on the dangers to innocent populations from purposeful biological weapon development.

Smallpox—Aralsk, Kazakhstan, 1971

An outbreak of smallpox occurred as a result of a field test at a Soviet biological weapons facility in 1971, largely unknown to the outside world until 2002.[78] Vozrozhdeniya (Renaissance) Island lies in the Aral Sea, and belongs jointly to the post-Soviet republics of Kazakhstan and Uzbekistan. In 1954 a biological weapons test site (Aralsk-7) was built on this island and on neighboring Komsomolskiy Island. The Soviet Ministry of Defense also established a field scientific research laboratory to conduct biological experiments on Renaissance Island.[79] BW agents tested here included *B anthracis*, *C burnetii*, *F tularensis*, *B suis*, *Rickettsia prowazekii*, *V major*, *Y pestis*, botulinum toxin, and Venezuelan equine encephalitis virus.[80]

According to Soviet General Pyotr Burgasov, field testing of 400 g of smallpox caused this outbreak at Renaissance Island on July 30, 1971.[78] Ten persons contracted smallpox, and three unvaccinated individuals (a woman and two children) died from the hemorrhagic form of the disease. One crew member on the research ship the Lev Berg contracted smallpox as the ship passed within 9 miles of the island. This crew member became ill on August 6 with fever, headache, and myalgia. The ship then landed in the port city of Aralsk on August 11. The ill crew member returned to her home, and she developed a cough and temperature exceeding 102°F. Her physician prescribed antibiotics and aspirin. Although she was previously vaccinated for smallpox, a rash subsequently appeared on her back, face, and scalp; her fever subsided; and she recovered by August 15. On August 27 this patient's 9-year-old brother developed a rash and fever, his pediatrician prescribed tetracycline and aspirin, and he recovered.[79]

During the following 3 weeks, eight additional cases of fever and rash occurred in Aralsk. Five adults ranging in age from 23 to 60, and three children (4 and 9 months old, and a 5-year-old) were diagnosed with smallpox both clinically and by laboratory testing. These children and the 23-year-old were previously unvaccinated. The two youngest children and the 23-year-old subsequently developed the hemorrhagic form of smallpox and died. The remaining individuals had previously been vaccinated, and all recovered after having an attenuated form of the disease.[79]

A massive public health response to the smallpox cases in Aralsk ensued once the disease was recognized. In less than 2 weeks, approximately 50,000 residents of Aralsk were vaccinated. Household quarantine of potentially exposed individuals was enacted, and hundreds were isolated in a makeshift facility at the edge of the city. All traffic in and out of the city was stopped, and approximately 54,000 square feet of living space and 18 metric tons of household goods were decontaminated by health officials.[79]

Case Review of 1971 Smallpox Outbreak
Biological Agents: *V major* virus
Potential Epidemiological Clues: 3, 4, 6, 10, 11
Review: The high ratio of hemorrhagic smallpox cases in this outbreak, combined with the rate of infectivity and the testimony of General Pyotr Burgasov (former Soviet vice-minister of health), has led to the understanding that an enhanced weaponized strain of smallpox virus was released from Aralsk-7 in 1971.[79] It may never be known whether the release was purposeful, but the Lev Berg inadvertently traveled into the plume of this bioweapons release, initiating the smallpox outbreak in Aralsk.
Lessons Learned: The Aralsk-7 BW facility had a history of association with mass deaths of fish, various regional plague outbreaks, a saiga antelope die-off, and individual cases of infectious disease among visitors to Renaissance Island.[80] These events present a timely warning for BW defense researchers working with biological agents that have the potential for infecting not only the laboratory workers, but also their family members and the surrounding community. Recent laboratory-acquired infections with tularemia,[81] Sabia virus,[82] and glanders[83] underscore the potential for risk of disease transmission in this manner. Considering that Lake and Francis reported six cases of laboratory-acquired tularemia in 1921,[84] this is not a new phenomenon. The epidemiological lesson learned is that when unusual BT-related illnesses occur, a laboratory accident or open air testing of a BW program may have occurred.

Anthrax—Sverdlovsk, Soviet Union, 1979

In April and May 1979, the largest documented outbreak of human inhalational anthrax occurred in Sverdlovsk in the Soviet Union (now Ekaterinburg, Russia), with at least 77 cases of disease and 66 deaths. Soviet authorities initially reported the occurrence of a gastrointestinal anthrax outbreak. Gastrointestinal anthrax is an uncharacteristic clinical manifestation from ingestion of *B anthracis* spores, although it occasionally occurs in the republics of the former Soviet Union.[16,85] When case history and autopsy results were reexamined by a joint team of Soviet and Western physicians and scientists, it became apparent that the Sverdlovsk outbreak and subsequent deaths had been caused by inhalational anthrax.[16] The geographic distribution of human cases coupled with the location of animal cases indicated that all anthrax disease occurred within a very narrow geographic zone (4 km for the humans, 40 km for the animals) from a point of origin in Sverdlovsk. Historical meteorological data, when combined with this case distribution, demonstrated a point of origin at a military microbiological facility, Compound 19.[16] This data also indicated that the most likely day on which this event occurred was April 2, 1979.[16]

Public health authorities established an emergency commission that directed public health response measures on April 10, 1979, which did not include the Soviet military. A triage response was established at Sverdlovsk city hospital by April 12. Separate areas were designated for screening suspected cases and for treating nonsystemic cutaneous anthrax cases, for intensive care, and for autopsy. Anthrax illness was understood not to be transmitted from person-to-person. Those who had died were placed in coffins containing chlorinated lime and buried in a separate part of the city cemetery. Hospital and factory workers were recruited into teams that visited homes of both suspected and confirmed cases throughout the city to conduct medical interviews, dispense tetracycline as a prophylactic antibiotic, disinfect kitchens and patient sickrooms, and collect meat and environmental samples for microbiological testing. Local fire brigades washed trees and building exteriors in the section of the city where most cases were located. Some of the control measures put into place by authorities likely had little value. Stray dogs were shot, and some unpaved streets were paved. Newspaper articles were published and posters were displayed that warned residents of the anthrax risk from eating uninspected meat or having contact with sick animals. Meat shipments entering the city were examined, and uninspected meat was embargoed and burned. In mid-April a voluntary anthrax vaccination program for healthy individuals ages 18 to 55 years was begun in the part of the city where most of the infected persons lived. Of the 59,000 people eligible to receive anthrax vaccine, about 80% received at least a single dose of the vaccine.[16,86]

Case Review of 1979 Sverdlovsk Anthrax Release
Biological Agents: *B anthracis* gram-positive bacillus
Potential Epidemiological Clues: 1, 2, 3, 4, 7, 9, 10
Review: In the absence of confirmatory information of an aerosol anthrax release, the public health response was spectacular. Research has estimated that about 14% more deaths would have occurred in Sverdlovsk in the absence of the public health intervention that included distribution of antibiotics and vaccination.[86] The Soviet military's secrecy hid many facts that would have helped physicians to diagnose and treat inhalational anthrax exposure. It is possible that many more individuals than existing medical records indicate may have become ill and recovered, or died.[87] Ambulance personnel often made an initial case diagnosis of pneumonia.[88]

Government authorities confiscated patient records and autopsy reports from the hospital. Some of these records could have provided invaluable inhalational anthrax medical intervention information from those patients that survived. Along with the absence of an epidemiological investigation at Sverdlovsk, this was a stunning loss of vital information for BW defense purposes.[89]

Former Soviet physicians released important information about anthrax prophylaxis and treatment, some of whom took tissue samples and records home at their own risk. This information indicated that the incubation period for inhalational anthrax may be as long as 2 months, and that an antibiotic course of 5 days likely prolonged the incubation period for illness.[89] Molecular analysis of tissue samples collected from 11 victims, and retained by Sverdlovsk physicians, indicate that these cases had been exposed to a number of different *B anthracis* strains,[90] which belies the claim for a single-source, naturally occurring anthrax outbreak, and points toward the release of a BW anthrax formulation from Compound 19.

Lessons Learned: Retrospective pathology findings from victims, weather patterns, and geographic mapping can help to determine the outbreak source and also whether an outbreak was spread intentionally. Most importantly, the public health personnel in Sverdlovsk instituted effective preventive measures before they knew exactly what the exposure was or the cause of the illnesses, and they used information from cases to determine possible exposure routes. Once the disease agent was determined, they provided prophylactic antibiotics and vaccination and undertook protective environmental measures.

Studies of Natural Outbreaks for Potential Bioweapon Use

Although the following accounts are examples of naturally occurring outbreaks, they have components that raise suspicion that they were intentionally caused. Subsequent to the 1999 WNV outbreak in New York City, suggestions were made that Iraqi operatives covertly released a biological weapon. These allegations are based on documentation showing that CDC had provided Iraq with various biological agents from 1984 through 1993, including *Y pestis*, dengue and WNV,[91] and the government of Iraq was known to have had a covert biological weapons program.[92] Similar allegations of the covert use of a biological weapon could have been made with the 2000 Martha's Vineyard, Massachusetts, tularemia outbreak and were made during the 1999 through 2000 Kosovo tularemia outbreak, which occurred during wartime.

West Nile Virus, New York, New York, 1999

An outbreak of an unusual encephalitis was first recognized in New York City in late August 1999. On August 23 an infectious disease physician from a Queens hospital contacted the New York City Department of Hygiene and Mental Health to report two patients with encephalitis. The health department then conducted a citywide investigation that revealed a cluster of six patients with encephalitis, five of whom had profound muscle weakness, and four of whom required respiratory support. CDC's initial clinical tests of these patients' cerebrospinal fluid and serum samples indicated positive results for Saint Louis encephalitis on September 3. More cases of encephalitis in New York City ensued, and because eight of the earliest cases were residents of a 2-square-mile area in Queens, aerial and ground applications of mosquito pesticides began in northern Queens and South Bronx on September 3.[93]

Active encephalitis surveillance began in New York City on August 30, and in nearby Nassau and Westchester counties on September 3. A clinical case was defined as a presumptive diagnosis of viral encephalitis with or without muscle weakness or acute flaccid paralysis, Guillain-Barre syndrome, aseptic meningitis, or presence of the clinical syndrome as identified in earlier cases.[93] Before and during this outbreak, an observed increase in bird deaths (especially crows) was noted in New York City.[12] The USDA National Veterinary Services Laboratory in Ames, Iowa, analyzed tissue specimens taken from dead birds in the Bronx Zoo for common avian pathogens and equine encephalitis. When these test results were negative, the samples were forwarded to CDC, which revealed on September 23 that the virus was similar to WNV in genetic composition.[94] At that time WNV had never been isolated in the Western hemisphere.

Concurrently, brain tissue from three New York City encephalitis case deaths tested positive for WNV at the University of California at Irvine. As of September 28, 17 confirmed and 20 probable cases had occurred in New York City and Nassau and Westchester counties, resulting in four deaths. Onset dates were from August 5 through September 16. The median age of the patients was 71 years (range 15–87 years). By October 5 the number of laboratory-positive cases had increased to 50 (27 confirmed and 23 probable). Emergency

telephone hotlines were established in New York City on September 3, and 130,000 calls were received by September 28. About 300,000 cans of N, N-diethyl-meta-toluamide (DEET)-based mosquito repellant were distributed citywide through local firehouses, and 750,000 public health leaflets were distributed with information on protection from mosquito bites. Radio, television, and the Internet provided public health messages.[93] A seroprevalence survey later determined that approximately 100 asymptomatic infections and 30 WNV fever cases occurred for each WNV encephalitis case in the New York City area.[95]

Case Review of 1999 West Nile Virus Outbreak
Biological Agents: West Nile virus, a flavivirus
Potential Epidemiological Clues: 1, 2, 3, 7

Review: After this outbreak had occurred, author Richard Preston claimed in a magazine article that Cuba and Iraq had developed WNV as a bioweapon.[96] Although it may not be possible to disprove such a claim, it is even more difficult to substantiate. The appearance of WNV in New York City in 1999 and its subsequent spread to the rest of the United States was most likely a natural occurrence.

Saint Louis encephalitis and WNV are antigenically related, and cross reactions can occur with some serologic testing.[93] Limitations of serologic testing underscore the importance of isolation and identification of virus.[93] Within its normal geographic area of distribution in Africa, West Asia, and the Middle East, birds do not normally show symptoms when infected with WNV.[97] WNV from this part of the world occasionally causes epidemics in Europe that may be initiated by migrant birds.[98,99] An epizootic that results in the deaths of large numbers of crows may be a clue that either a new population is susceptible to the virus or a new, more virulent strain of a virus has been introduced.[93]

WNV is transmitted primarily by *Culex pipiens* mosquitoes,[100] which contributed to its spread in the United States after the 1999 outbreak.[101] Therefore, nationwide public health mosquito surveillance was subsequently instituted. Genetic testing revealed that the virus was 99% identical to a virus isolated in 1999 from a goose in Israel.[102] Potential routes for WNV introduction include importation of WNV-infected birds, mosquitoes, or ill persons. The New York City area where WNV was prevalent includes two large international airports.[103] Before this outbreak, death was rarely associated with WNV infection.[104] In patients with WNV encephalitis, computer-assisted tomography often revealed preexisting lesions and chronic changes in brain tissue,[105] perhaps suggestive of the potential for a greater susceptibility to deleterious outcome in elderly persons.

Lessons Learned: This outbreak emphasizes the important relationship among veterinarians, physicians, and public health authorities in disease surveillance, and the importance of considering uncommon pathogens.[104] The incident is an example of a typical zoonotic disease epidemic pattern—a natural epidemic occurred first among birds, followed by disease in humans. Once WNV became established within the indigenous North American mosquito vectors, it spread and has become endemic to the continent. The origin of outbreaks fitting some of the clues for a biological attack (a new disease for a geographic region) cannot be immediately determined without further investigation. Emerging diseases, whether new for a particular geographic area, like WNV, or a totally new disease (eg, severe acute respiratory syndrome), are not uncommon. Regardless of origin, outbreak investigation steps remain the same, as does the need for a robust public health surveillance, investigation, and response system.

Tularemia, Martha's Vineyard, Massachusetts, 2000

During the summer of 2000, an outbreak of primary pneumonic tularemia occurred on Martha's Vineyard, Massachusetts.[106] In July five cases of primary pneumonic tularemia were reported, with onset dates between May 30 and June 22. The Massachusetts Department of Public Health and CDC initiated active surveillance, and 15 confirmed tularemia cases were subsequently identified. A confirmed case was defined as occurring in a visitor or resident to Martha's Vineyard who had symptoms suggesting primary pneumonic tularemia; was ill between May 15 and October 31, 2000; and had test results showing a serum titer of anti-*F tularensis* antibody of at least 1:128 on an agglutination assay. Of these cases, 11 had the pneumonic form of the disease, 2 had ulceroglandular disease, and 2 had fever and malaise. Fourteen of the patients were male, and the median age was 43 years (range 13–59). One 43-year-old man died of primary pneumonic tularemia.

Control subjects for a case-control study were obtained by random-digit dialing to Martha's Vineyard residents, enrolling 100 control subjects at least 18 years old who had spent at least 15 days on the island between May 15 and their September interviews. Both ill persons and control subjects were questioned about occupation, landscaping activities, animal and arthropod exposures, recreational and outdoor activities, and general health history and status. Information was obtained about exposure to risk factors between May 15 and the interview, and for 2 weeks before illness for ill persons and 2 weeks before interview for control subjects.

The suspected site of exposure for each patient was visited. Activities that may have led to exposure (eg, lawn mowing and "weed whacking") were reproduced, and environmental and personal air samples were taken. Samples from soil, water, grass, wild mammals, and dogs were also taken. Epidemiological analysis revealed that in the 2 weeks before illness, using a lawn mower or brush cutter was significantly associated with illness. Of all the environmental and animal tissue samples taken, only two were positive for *F tularensis*: (1) a striped skunk and (2) a Norway rat.

Case Review of 2000 Martha's Vineyard Tularemia Outbreak

Biological Agents: *F tularensis*, a gram-negative bacillus

Potential Epidemiological Clues: 1, 2, 3, 9

Review: Caused by a gram-negative bacillus, *F tularensis* tularemia is a rare infection in the United States. Between 1990 and 2000, an average of 124 cases per year was reported.[107] Over half of all cases reported during these 11 years came from Arkansas, Missouri, South Dakota, and Oklahoma, and most cases were acquired from tick bites or contact with infected rabbits. Higher incidences of the disease have been noted in persons ages 5 to 9 and older than 75 years, and incidence was greatest among American Indians and Alaska natives.[107]

The only other previously reported pneumonic tularemia outbreak in the United States had occurred on Martha's Vineyard during the summer of 1978.[106] During a single week (July 30–August 6) seven persons stayed in a vacation cottage. By August 12, six of them had a fever, headache, and myalgia; and the seventh had a low-grade fever by August 19. A search for additional cases on the island uncovered six other tularemia cases, five of which were pneumonic, and one was ulceroglandular. No source for the disease exposure was discovered, although two rabbits later found dead were culture-positive for *F tularensis*. Tularemia had been reported sporadically since rabbits had been introduced to Martha's Vineyard in the 1930s,[106] and pneumonic tularemia was first reported in Massachusetts in 1947.[108] Classic research on human tularemia rates showed that very high rabbit populations increase the tularemia hazard.[109] Hospital clinicians on Martha's Vineyard initially detected this outbreak and recognized tularemia-caused pneumonic summer illness,[110] in part based on the experiences with the previous outbreak.[106]

In the 2000 outbreak of tularemia, Feldman et al proposed that on Martha's Vineyard, *F tularensis* was shed in animal excreta, persisted in the environment, and infected persons after mechanical aerosolization and inhalation. This is a likely exposure scenario given the principal form of primary pneumonic tularemia seen in these cases and strong epidemiological association with grass cutting.[111] A seroprevalence survey conducted in 2001 in Martha's Vineyard demonstrated that landscapers were more likely to have an antibody titer to *F tularensis* than nonlandscapers, revealing an occupational risk for tularemia.[112]

Lessons Learned: Naturally occurring disease can present in the pneumonic form. However, if tularemia were used as a biological weapon, an aerosolized release would probably result in multiple simultaneous cases presenting with the pneumonic form of the disease.[110] There may also be disease transmission mechanisms (in this example, grass cutting) that are unknown or poorly understood.

Tularemia, Kosovo, 1999–2000

After a decade of political crises and warfare, a large outbreak of tularemia occurred in Kosovo from 1999 through 2000. Tularemia had not been reported in Kosovo since 1974.[113] By April 2000, 250 suspected cases had been identified and spread nationwide, but with most cases in the western area where ethnic Albanians resided.[114]

Unusual outbreaks of zoonoses or vectorborne disease may readily occur in war-torn or crisis-afflicted regions that have previously been free of these diseases. Historically, typhus, plague, cholera, dysentery, typhoid fever, and smallpox have long been observed in war-torn regions.[115] Among early examples is the plague of Athens that arose during the second year of the Peloponnesian War, as described by Thucydides.[116] Speculation may arise that these epidemics were purposefully caused. Many biological agents are zoonotic pathogens,[113] including tularemia, a category A BW pathogen. Purposeful use of this pathogen merits consideration when such an outbreak occurs with a potential BW pathogen.[117] Remarks made by the head epidemiologist at the Kosovo Institute of Public Health about unidentifiable ampoules and white powders discovered near various wells could not be verified and added to a perception of use of a BW by Serbian forces.[113]

F tularensis biovar tularensis (type A) is highly pathogenic for humans. It is found mostly in North America and has been developed for use as a biological weapon. Disease progression often follows an acute and severe course, with prominent pneumonitis. *F tularensis biovar holarctica* (type B) is less pathogenic and is found throughout the northern hemisphere.[118] To further complicate matters, a 1998 report documented that type A tularemia had been introduced into arthropod populations in the nearby Slovak Republic.[119]

The United Nations mission in Kosovo requested that the World Health Organization assist Kosovar health authorities in an epidemiological investigation of the tularemia outbreak. Teams of international and Kosovar public health personnel collaborated in epidemiological, environmental, and microbiological field and laboratory investigations.[120] Tularemia cases were discovered by both prospective surveillance and retrospective hospital review of a pharyngitis and cervical lymphadenitis syndrome. Ill persons were clinically examined and interviewed, blood samples were taken from suspected cases, and antibiotics were prescribed as appropriate. Rural villagers reported an increase in mice and rats in the summer of 1999. A causal association was suspected between the increased population density of rodents and human tularemia cases. Tularemia is naturally transmitted to humans via small lesions in the skin of persons handling diseased rabbits, ingestion of contaminated water or food, bites of infectious arthropods, or inhalation of infective dusts.[113]

A matched case-control study was conducted with paired households in villages in regions with the greatest number of reported cases. Case households

had one or more family members with a laboratory-confirmed case of tularemia as of November 1, 1999. Control households were the two households closest to a suspected case household, having no individuals with the disease, and the person who prepared the family's food was serologically negative for tularemia. Blood specimens were also drawn from all suspected cases. Questionnaires were completed on household food consumption, water supply, presence of rodents, and condition of wells and food preparation and storage areas. The study period began a month before symptom onset of the first case in the suspected case household. Well water sampling and rodent collection and analysis were performed.

By June 30, 2000, over 900 suspected tularemia cases had been discovered. From these, 327 were confirmed as serologically positive. The earliest onset of reported symptoms in the confirmed cases was October 1999, with an epidemic peak in January 2000. Confirmed cases were identified in 21 of 29 Kosovo municipalities. Cases were equally distributed by sex, and all age groups were equally affected. Case households were more likely to have nonrodent-proof water sources, and members in these households were less likely to have eaten fresh vegetables. Risk factors for case households included rodent feces in food preparation and storage areas and large numbers of field mice observed outside the house. Of the field samples collected, positive antigen for *F tularensis* was detected in striped field mouse and black rat fecal specimens.

Case Review of 2000 Kosovo Tularemia Outbreak
Biological Agents: *F tularensis*, a gram-negative bacillus
Potential Epidemiological Clues: 1, 3, 5, 9
Review: Clinical and serologic evidence indicate that a tularemia outbreak occurred in Kosovo from October 1999 through May 2000. The case-control study indicated that transmission of tularemia was foodborne, based on the associations of illness and large numbers of rodents in the household environment, rodent contamination of food storage and preparation areas, and consumption of certain uncooked foods. Unprotected water that was not boiled likely contributed to the outbreak. The protective value of eating fresh vegetables may be related to a minimal storage life and lessened opportunity for contamination.

Purposeful use of tularemia was considered. Initial field investigations rapidly demonstrated that a widespread natural event was occurring and likely resulted from the unusual environmental conditions existing in war-torn Kosovo. The principal populations affected by the tularemia outbreak were ethnic Albanians in rural farming villages with limited economic resources. These people had fled during North Atlantic Treaty Organization bombing and Serbian reprisals during the spring of 1999. Upon return to their villages, refugees discovered bombed and ransacked homes, unprotected food storage areas, unharvested crops, damaged wells, and a rodent population explosion. Both ignorance of infection and lack of hygienic measures contributed to a foodborne infection in the population.[113] These factors likely resulted in conditions favorable for epizootic tularemia spread in rodents and widespread environmental contamination with *F tularensis* because this organism can survive for prolonged periods in cold, moist conditions. A natural decrease in rodent population resulting from the cold winter, food shortages, and the disease itself likely all helped to end the zoonoses.[113]

Although tularemia was not recognized endemically or enzootically in Kosovo before the 1999 through 2000 outbreak, it became well established in a host reservoir. A second outbreak occurred there in 2003, causing over 300 cases of oropharyngeal tularemia.[121] Historically, war in Europe caused tularemia outbreaks. During World War II, an outbreak of over 100,000 cases of tularemia occurred in the Soviet Union,[122] and outbreaks with hundreds of cases following the war occurred in Austria and France.[121]

Lessons Learned: War provides a fertile ground for the reemergence of diseases and potential cover for BW agent use that is plausible, and may go unrecognized as a BW event. An extensive investigation must be conducted to conclude or disprove that a BW event has occurred.

EPIDEMIOLOGICAL ASSESSMENT TOOL

It is especially useful for public health authorities to quickly determine whether an infectious disease outbreak is intentional or naturally occurring. Grunow and Finke developed an epidemiological assessment tool to rule out biological agent use during infectious disease outbreaks. This assessment tool's relevance was demonstrated by analysis of the 1999 through 2000 Kosovo tularemia outbreak.[113] In their evaluation scheme, each assessment criterion can be given a varying number of points dependent on its presence and characteristics. There are two types of evaluation criteria: (1) nonconclusive and (2) conclusive. The most significant nonconclusive criteria include a biological threat or risk, special aspects of a biological agent, a high concentration of biological agent in the environment, and epidemic characteristics. Conclusive criteria include the unquestionable identification of the cause of illness as a BW agent or proof of the release of an agent as a biological weapon. Neither of these conclusive proofs occurred in Kosovo. With conclusive criteria, additional confirmatory information is unnecessary.[113]

According to Grunow and Finke's nonconclusive criteria, a biological risk may be considered if a political or terrorist environment exists from which a biological attack could originate:

- Biorisk. Are BW agents available, with the means for distribution, and the will to use them? Or can an outbreak be explained by natural biological hazards, or the changes incurred by military conflict? Natural occurrence of tularemia in Kosovo, even in the absence of a previous outbreak, needed to be considered.
- Biothreat. Does a biological threat exist by virtue of a group having a BW agent and credibly threatening to use it? In Kosovo there was no evidence of a biological threat.
- Special aspects. Is there plausible evidence of purposeful manipulation of a pathogen? In Kosovo, bacterial cultures were not created because of a lack of resources and fear of laboratory transmission, so purposeful manipulation could not be determined.
- Geographic distribution. Is the disease's geographic distribution likely given its locale? With the advent of a nonendemic pathogen, a thorough evaluation should include epidemiological, epizootic, ecological, microbiological, and forensic analysis. A 25-year absence of reported tularemia did not eliminate the potential occurrence of an epidemic.
- Environmental concentration. Is there a high environmental concentration of the pathogen? The almost exclusive occurrence of oropharyngeal tularemia in Kosovo likely indicated ingestion of a high number of bacteria that could occur through food or water contamination. *F tularensis* was not found in drinking water and soil, but was discovered in rodent vectors.
- Epidemic intensity. Is the course of illness relative to disease intensity and spread in the population expected in naturally occurring illness? Because tularemia was absent in Kosovo before the epidemic, the 2000 outbreak was considered to be unusually intensive.
- Transmission mode. Was the path of disease transmission considered naturally occurring? A naturally occurring epidemic in itself does not rule out the purposeful use of a BW agent.
- Time. Was the calendar time of the epidemic unusual? The Kosovo epidemic began in October 1999, peaked in January 2000, and ended in May, which is a typical seasonal pattern for a naturally occurring European tularemia epidemic.
- Unusually rapid spread. Was the spread of the epidemic unusually rapid? The Kosovo epidemic was unusual in that within a brief time period tularemia appeared throughout almost the entire Albanian territory.
- Population limitation. Was the epidemic limited to a specific (target) population? If certain persons were given prior warning of a BW attack, then they may protect themselves, as compared to naïve target populations. In the Kosovo epidemic, the Serbian population was not found to have been purposefully spared from a BW attack, and poor hygiene and living conditions probably facilitated the disease spread in the ethnic Albanian population.
- Clinical. Were the clinical manifestations of the disease to be expected? During the Kosovo outbreak, clinical diagnosis was made more difficult by the simultaneous appearance of mumps and tuberculosis in the population.[113]

The Grunow-Finke epidemiological assessment procedure (Table 3-1) was used to evaluate the case studies presented in this chapter. To use the assessment tool uniformly for all the events described in this chapter, some artificial constraints were placed upon the analysis. For this exercise, only nonconclusive criteria were used because the use of conclusive criteria may have excluded many of the case studies with a retrospective assessment. During an outbreak investigation, however, epidemiological investigators would also initially use the nonconclusive evaluation criteria. With the exception of the 2001 anthrax and 2003 ricin events, none of the outbreaks described had been positively identified as having been caused by a biological agent until some time after the events had occurred.

Grunow and Finke provide the following cut-off scores for nonconclusive criteria with respect to the likelihood of biological weapon use:

- unlikely (0%–33% confidence): 0 to 17 points;
- doubtful (18%–35% confidence): 18 to 35 points;
- likely (67%–94% confidence): 36 to 50 points; and
- highly likely (95%–100% confidence): 51 to 54 points.

Based on this scoring, only the 2001 anthrax mailings would be considered as highly likely to have been caused by a BW agent. The 1915 and 1979 anthrax events qualify as likely to have been caused by a BW agent. All other case study scenarios are either doubtful or unlikely to have been caused by a BW agent.

The authors conducted this evaluative exercise by consensus of opinion. Although subjective, the

TABLE 3-1

EPIDEMIOLOGICAL ASSESSMENT AND EVALUATION OF CASE STUDY OUTBREAKS

Nonconclusive Criteria	Assessment (possible points)	Weighting Factor	Maximum No. of Points	1915 Anthrax Eastern USA	1971 Smallpox Aralsk	1979 Anthrax Sverdlovsk	1984 Salmonella Oregon	1995 Anthrax Tokyo	1996 Shigella Texas
Biorisk	0–3	2	6	4	4	4	6	6	0
Biothreat	0–3	3	9	0	0	0	0	6	0
Special aspects	0–3	3	9	6	6	6	3	0	6
Geographic distribution	0–3	1	3	3	3	3	2	3	2
Environmental concentration	0–3	2	6	6	0	6	0	6	0
Epidemic intensity	0–3	1	3	3	3	3	3	0	3
Transmission mode	0–3	2	6	6	2	6	4	0	0
Time	0–3	1	3	3	3	3	1	0	1
Unusually rapid spread	0–3	1	3	3	1	3	3	0	3
Population limitation	0–3	1	3	1	0	1	0	0	3
Clinical	0–3	1	3	3	3	3	0	0	1
Score			**54**	**38**	**25**	**38**	**22**	**21**	**19**

Nonconclusive Criteria	1999 WNV NYC	1999 Tularemia Kosovo	2000 Tularemia Martha's Vineyard	2001 Anthrax USA	2003 Ricin USA
Biorisk	6	2	0	6	6
Biothreat	6	3	0	6	9
Special aspects	0	0	0	9	0
Geographic distribution	3	3	3	3	3
Environmental concentration	4	4	4	6	6
Epidemic intensity	3	3	3	3	0
Transmission mode	2	2	6	6	0
Time	1	0	3	3	0
Unusually rapid spread	3	1	3	3	0
Population limitation	0	0	2	3	0
Clinical	1	1	3	3	0
Score	**29**	**19**	**27**	**51**	**24**

NYC: New York City
USA: United States of America
WNV: West Nile Virus

exercise underscores the challenges facing epidemiologists in determining whether a BT/BW event has occurred, unless evidence indicates a purposeful event or someone credibly claims responsibility. The basic epidemiological principles described earlier in this chapter (including those needed for disease recognition) to determine the occurrence of an unnatural event, and for basic outbreak investigation, are the foundation of infectious disease response and control. Public health authorities must remain vigilant to quickly and appropriately respond to any infectious disease event.

IMPROVING RECOGNITION AND SURVEILLANCE OF BIOTERRORISM

Existing disease surveillance systems may not be sensitive enough to detect a few cases of illness. Disease reporting can be initiated throughout the illness exposure and the incubation period; the healthcare provider presentation; and the initial diagnoses, laboratory testing, and patient hospital visit. Clinicians, laboratories, hospitals, ancillary healthcare professionals, veterinarians, medical examiners, morticians, and others may be partners in reporting the disease to public health authorities.

If a medical surveillance system first detects a biological attack, there may be a significant number of cases, and the available time to prevent further illness is short or already over. The point of release is the earliest detection point of a biological event. Some disease could be prevented at the point of release through publicized avoidance of the area, prophylactic medication use or vaccination of those exposed, and immediate disease recognition and patient treatment. The Department of Homeland Security's BioWatch program has deployed biological detectors in major urban centers nationwide to detect trace amounts of airborne biological materials[123] and help determine the presence and geographic extent of a biological release to focus emergency public health response and consequence management.

Although deployed sensors may detect an agent's release, the infinite number of venues and limited resources to deploy sensors and analyze air samples minimize the chances that an agent release will occur within range of an environmental monitor. In this case, the earliest opportunity to detect an attack will be recognizing ill patients.

Depending on the agent, the mode of dissemination, and the number exposed, initial cases will present in different ways. If the disease is severe, such as with the category A biological agents, one case will launch an investigation, as seen during the 2001 anthrax attacks.[50] Even if the cause is initially unknown, extremely severe or rapidly fatal cases of illness in previously healthy individuals should be reported to public health authorities. If many people are exposed, as would be expected with a large aerosol release, an overwhelming number of people may visit hospital emergency departments and outpatient clinics. Even with less severe disease, such cases should be recognized and quickly reported.

However, in the absence of confirmed laboratory diagnoses or high attack rates, infectious disease outbreaks are often not reported. If the disease is not rapidly fatal or cases are distributed among a variety of practitioners, it may not be readily apparent that a disease outbreak is under way. Therefore, there is a need for better awareness of the health of communities—a way to quickly detect shifts in potentially infectious diseases, whether of bioterrorist origin or not. This need has been recognized and has resulted in the proliferation of what is commonly known as syndromic surveillance systems.

Syndromic surveillance has been defined as the ongoing, systematic collection, analysis, and interpretation of data that precede diagnosis and can indicate a potential disease outbreak earlier than when public health authorities would usually be notified.[124] The data used in syndromic surveillance systems are usually nonspecific potential signs and symptoms of an illness spectrum indicating that disease may be higher than expected in a community. This data can be from new or existing sources.[125] For syndrome surveillance of BT, the emphasis is on timeliness, with automated analysis and visualization tools such as Web-based graphs and maps. These tools provide information that initiates a public health investigation as soon as possible.[126]

Numerous regional and national syndromic surveillance systems have recently been developed, including programs that rely on data collected specifically for the surveillance system and those that use existing medical data (eg, diagnostic codes, chief complaints, nurse advice calls) and other information (eg, pharmacy sales, absenteeism) to detect changes in population health. Systems that use active data collection can be "drop-in" (those instituted for a specific high-threat time) such as those performed immediately after September 11, 2001,[127-129] or during large gatherings for sports or other events[130]; or they can be sustained systems for continuous surveillance.[131,132] Systems that require new data entry benefit from greater specificity in the type of syndromes and illnesses reported, but they require extra work and are difficult to maintain. Systems that use existing data can be less specific, especially with information taken from behaviors early in the disease, such as over-the-counter pharmacy sales and absenteeism. However, these programs have the large advantage of continuous data streams that are not dependent on provider input or influenced by news reports of disease rates. Such systems, examples of which are described below, have become standard in many health departments, the military, and the CDC.

In the US Department of Defense, the Electronic Surveillance System for the Early Notification of Community-based Epidemics (ESSENCE) uses outpatient diagnostic *International Classification of Diseases, Ninth Revision* codes and pharmacy prescriptions to track disease groups in military beneficiaries. The system has been expanded in some locations to include civilian data such as hospital emergency department chief complaints, over-the-counter pharmacy sales, outpatient billing codes, school absenteeism, and laboratory test orders.[133,134] Temporal and spatial data are presented through a web-based interface, and statistical algorithms are run to detect any aberrations that could indicate a disease outbreak.[135] This system is available for all permanent US military treatment facilities worldwide and also for some deployed forces in the Middle East. Civilian versions of ESSENCE are also deployed to select cities through the Department of Homeland Security's BioWatch program.

Public health departments such as the New York City Department of Hygiene and Mental Health have also developed surveillance systems based on data already collected for other purposes. New York City uses coded 911 calls, hospital emergency department chief complaints, retail pharmacy sales, and work absenteeism data.[136] The department has detected communitywide increases in gastrointestinal and respiratory illnesses and reassured the public during high-profile public events that no evidence of outbreaks had been found.[137]

The University of Pittsburgh's Realtime Outbreak Detection System (RODS) uses the National Retail Data Monitor and hospital emergency department chief complaints to detect and track disease outbreaks.[138,139] Nearly 20,000 retail pharmacy, grocery, and mass merchandise stores participate in the National Retail Data Monitor, which monitors sales of over-the-counter healthcare products.[140] In addition, to integrate health data for earlier outbreak detection program, the RODS laboratory provides assistance to some health departments that participate in the BioWatch biosensor.[141] As of 2004, RODS has been deployed in 10 US sites and one international site.[142]

CDC has developed the BioSense program using national data sources such as the Department of Defense and Department of Veterans Affairs outpatient diagnostic codes, as well as laboratory test orders from a commercial vendor, to track disease patterns nationwide. The information is provided in a web-based format to health departments.[143] Algorithms are run on the data and send out an alert when levels of outpatient visits or laboratory test orders exceed those expected. The information is presented in temporal and spatial format, allowing the health department to track disease based on the patient's home zip code. BioSense is one part of the Public Health Information Network, an organization whose goal is to facilitate sharing of automated detection and visualization algorithms and promote national standards.

Despite the proliferation of systems, there are definite limitations in the ability to detect bioterrorist attacks using syndromic surveillance. Some have argued that even if syndromic surveillance could detect an outbreak faster than traditional methods, the advanced warning may not assist with disease mitigation.[71] The warning may not be early enough or effective countermeasures may not be available. In addition, although nonspecific data such as absenteeism may provide some early warning, it is very difficult to institute preventive measures without more specific information. However, nonspecific data can still serve as an early indicator, prompting authorities to monitor specific data sources more carefully.

Most importantly, because a BT attack can present in a variety of ways depending on the agent, population, and environment, it is impossible to predict how any individual surveillance system will perform. It is generally agreed that most syndromic surveillance systems will not detect a few cases of disease, but they can assist in detecting more widespread disease increases and assessing the population impact, an outbreak's spread, and the success of mitigation efforts. The coverage area of the surveillance system is crucial in determining outbreak detection sensitivity in any part of a community.

In the future, syndromic surveillance will probably be based on national models such as BioSense and use readily available electronic databases. Local health departments could then build on a national system using local data that can improve population coverage. Future disease monitoring and reporting systems need to be seamlessly integrated with other traditional disease surveillance systems. Ideally, these systems should also help to educate clinicians on the importance of maintaining a high index of suspicion and to promptly report unusual diseases or disease clusters to public health authorities.

SUMMARY

Because management of BT and BW events depends on the disease surveillance, laboratory, and outbreak investigation capabilities of public health authorities, the science of epidemiology will always be the foundation for a response to these events. An enhanced index of suspicion, awareness of potential red flags, open lines of communication between local healthcare providers and law enforcement authorities, knowledge of historical outbreak investigation information, and robust disease surveillance systems will improve our ability to respond to any future BT or BW event.

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