SPECIAL SECTION: CONFRONTING BIOLOGICAL WEAPONS

Donald A. Henderson, Thomas V. Inglesby, Jr., and Tara O'Toole, Section Editors

Implications of Pandemic Influenza for Bioterrorism Response

Monica Schoch-Spana

Center for Civilian Biodefense Studies, Johns Hopkins University School of Public Health, Baltimore, Maryland

The 1918–1919 influenza pandemic (Spanish flu) had catastrophic effects upon urban populations in the United States. Large numbers of frightened, critically ill people overwhelmed health care providers. Mortuaries and cemeteries were severely strained by rapid accumulation of corpses of flu victims. Understanding of the outbreak's extent and effectiveness of containment measures was obscured by the swiftness of the disease and an inadequate health reporting system. Epidemic controls such as closing public gathering places elicited both community support and resistance, and fear of contagion incited social and ethnic tensions. Review of this infamous outbreak is intended to advance discussions among health professionals and policymakers about an effective medical and public health response to bioterrorism, an infectious disease crisis of increasing likelihood. Elements of an adequate response include building capacity to care for mass casualties, providing emergency burials that respect social mores, properly characterizing the outbreak, earning public confidence in epidemic containment measures, protecting against social discrimination, and fairly allocating health resources.

At its peak, the 1918–1919 influenza pandemic (Spanish flu) incapacitated American cities and paralyzed the health care system. A 20th century outbreak of disease with calamitous effects in this country, Spanish flu is an apt case to influence current bioterrorism planning efforts. This article presents a set of principles meant to assist medical, public health, and government leaders as they construct a response to the potential mass casualties and social turmoil initiated by a bioterrorist attack.

Influenza: Evolving Pathogens and Profound Health Burden

Throughout human history, global influenza outbreaks have sickened large numbers of people, claimed many lives, and dramatically disrupted social and economic relations [1, 2]. The most infamous episode is the 1918–1919 influenza pandemic, which altered World War I battle plans and peace talks and made almost 1 billion people (one-half the world's population) ill, killing from 21 to 40 million [3, 4]. In interpandemic years, flu still exacts a harsh toll: excess deaths, in the aggregate, approach pandemic levels [2, 5, 6]. Influenza's destructive capacity resides in the pace and unpredictability of the evolution of the virus, which can subvert the body's immune response and outstrip society's efforts at containment [7, 8].

Influenza viruses infect human host cells (typically, epithelial cells that line the respiratory tract) and reproduce [9, 10]. Flu's characteristic structure is a sphere that contains RNA material and is studded with protein surface antigens: hemagglutinin that binds the virus to the host cell, initiating replication, and neuraminidase that frees up newly manufactured virions from the host cell, facilitating virus spread. Three types of influenza virus exist: type A, isolated from humans, birds, pigs, horses, and sea mammals; and types B and C, found only in humans. Influenza A viruses are subtyped according to the unique surface antigens that they manifest (e.g., H1N1 and H3N2). Fifteen different types of hemagglutinin and 9 types of neuraminidase have been observed.

Influenza A and B viruses are genetically and structurally more similar to each other than either are to influenza C viruses, and they contribute to a greater proportion of human disease than does influenza C virus [10, 11]. Epidemics of influenza A tend to affect all age groups but especially children and the elderly, spread widely across regions and continents, and exhibit significant excess mortality rates. About 1% of all US deaths from 1972 through 1992 could be attributed to influenza (9.1 deaths per 100,000 population per season), most occurring when influenza A (H3N2) viruses were prevalent [5]. Charac-

Received 17 July 2000; revised 7 August 2000; electronically published 17 November 2000.

Reprints or correspondence: Dr. Monica Schoch-Spana, Johns Hopkins Center for Civilian Biodefense Studies, Candler Building, Ste. 850, 111 Market Pl., Baltimore, MD 21202 (mschoch@jhsph.edu).

Clinical Infectious Diseases 2000; 31:1409–13

1058-4838/2000/3106-0015$03.00

teristic of influenza B outbreaks are mild respiratory disease that tends to target children, potentially high attack rates among concentrated groups (e.g., schools), regional distribution of cases, and limited excess mortality despite high incidence. Influenza C infrequently causes mild respiratory disease, mainly in young children.

Recurrent human influenza virus infection and potential for severe outbreaks are a result of the virus' penchant for change [9–11]. In antigenic "drift," simple genetic mutations gradually transform the surface proteins (primarily hemagglutinin) to which the host produces antibodies. Vulnerability to infection arises with the increasing "mismatch" between antibodies and surface antigens: immunity developed during one flu season to a particular strain may have no or limited future value. In antigenic "shift," a profound change in surface proteins occurs, rendering the virus unrecognizable to the circulating antibodies in most people. Influenza B viruses evolve slowly through antigenic drift. Influenza A viruses transform more quickly, through both antigenic drift and shift.

A new influenza A virus subtype, produced through antigenic shift, sets the stage for a possible pandemic. Two forms of genetic reassortment have been hypothesized to generate pandemic virus. First, a commingling of gene segments from the prevailing human influenza virus and an avian influenza virus may occur, as is thought to have produced the 1957 Asian flu and the 1968 Hong Kong flu [10]. In some parts of Asia, pigs serve as animal intermediaries facilitating the exchange of viruses between bird and human hosts [10, 12]. A second mechanism involves reassortment of subtypes from prior human outbreaks within a human host [10, 13]. An alternate theory of emergence is that an avian or mammalian virus becomes infectious for humans and capable of person-to-person transmission, a possible scenario for Spanish flu [10].

A typical case of influenza causes high-grade fever, cough, sore throat, rhinitis, muscle ache, headache, and extreme fatigue with a 2-week recovery unless pneumonia or a secondary medical condition develops; complications are potentially fatal [14]. The collective burden of influenza in a community can be substantial, depending upon seasonal prevalence of infections, proportions and virulence of circulating strains, and population resistance [15]. Excess hospitalizations averaged 50 per 100,000 Americans per season in the early 1970s to mid-1990s [5, 16]. The number of deaths beyond what is typically expected during an outbreak of influenza-like illness (i.e., "excess death") have been substantial during pandemics: 1918 Spanish flu, 218.4 deaths per 100,000 Americans; 1957 Asian flu, 22 deaths per 100,000 population; 1968 Hong Kong flu, 13.9 deaths per 100,000 population [2]. Flu's direct costs (hospitalizations, medical fees, drugs, tests, and equipment) were estimated in 1986 at $1 billion annually; indirect costs were estimated from $2 to $4 billion (lost productivity and wages) [17]. Without a mass vaccination campaign, the cost of the next pandemic is projected at $71.3 to $166.5 billion in 1995 US dollars (inpatient and outpatient care, self-treatment, and lost work days and wages) [18].

Spanish Flu: Unparalleled Lethality and Social Distress

In early spring 1918, an influenza A (H1N1) virus began a global campaign, producing a moderate outbreak among US military recruits in the Midwest and Southeast before moving into the civilian population and then by troopships to Europe and beyond [3, 4, 19, 20]. By summer's end, this first wave had circled the world and earned the name Spanish flu after receiving much publicity in Spain, a neutral country without news censorship. This outbreak caused disproportionately high mortality rates among young adults, presaging the disastrous autumn when a related, more virulent form of the virus began to circulate. By late August, epidemics of unprecedented lethality had broken out in ports in France (Brest), the United States (Boston), and Sierra Leone (Freetown), after which the pathogen blanketed the globe, aided by ship, railroad, and by war-induced migrations of civilians and military personnel. Dispersed episodic outbreaks during winter and spring (1918–1919) comprised a third wave.

The course of disease during fall 1918 was often swift. Convalescence in survivors was protracted, with fatigue, weakness, and depression frequently lasting for weeks [3, 20–23]. Symptoms presented suddenly: high-grade fever and rigors, severe headache and myalgias, cough, pharyngitis, coryza, and in some cases epistaxis. Some patients had mild illness and recuperated without incident. Other patients were stricken quickly and severely, with symptoms and signs consistent with hemorrhagic pneumonia, and died within days and sometimes hours. Autopsies revealed inflamed hemorrhagic lungs. Still other patients with more typical flu developed severe superinfection with bacterial pneumonia, resulting in death or a laborious recovery. Unusually lethal, Spanish flu was also distinct in killing what was typically the cohort least vulnerable to influenza, 20- to 40-year-olds.

The disease's incidence, severity, and pattern of spread baffled laypeople and experts alike [3, 4, 20, 21]. Doctors debated possible pathogens, with no final consensus: Pfeiffer's bacillus (presumed cause of influenza since the 1889–1990 pandemic but rarely isolated from 1918 victims); *Yersinia pestis* (because of migrating laborers from China, the site of pneumonic plague outbreaks in 1910–1917); *Streptococcus* species, *Streptococcus pneumoniae,* and *Staphylococcus* species (cultured from specimens from patients with Spanish flu); and a hypothesized "filtrable virus" (based on experiments that produced an infectious filtrate after removing known microorganisms) were all suggested as possible etiologies. Popular explanations included the foul atmosphere conjured by the war's rotting corpses, mustard gas, and explosions; a covert German biological weapon; spiritual malaise due to the sins of war and materialism; and con-

ditions fostered by the European conflict and overall impoverishment.

During the fall, the disease moved swiftly through US cities. Acute absenteeism among critical personnel strained industrial production, government services (e.g., sanitation, law enforcement, fire fighting, postal delivery), and maintenance of basic infrastructure (e.g., transportation, communications, health care, food supply) [3, 22, 24]. Given the incomplete disease reporting, inaccurate diagnoses, and circumscribed census practices of the day, morbidity and mortality figures are conservative estimates [3, 19]. Twenty-eight percent of Americans became ill, and there were 550,000 deaths in excess of what is normally expected during influenza season [3]. The case-fatality rate associated with Spanish flu has been estimated at 2.5% [20], but this rate more likely represents the experience of the developed world. Africa and Asia had fall death rates an order of magnitude higher than those of Europe and North America (e.g., India, 4200–6700 deaths per 100,000 population; England, 490 deaths per 100,000 population) [19].

Bioterrorism Response: Lessons from the 1918–1919 Influenza Pandemic

A catastrophic epidemic that would severely tax society's ability to care for the sick and dying and to contain disease is the scenario of greatest concern to medical, public health, and political leaders charged with developing a response to bioterrorism [25]. Surveying the prominent issues that arose during Spanish flu's fall peak in 1918 provides a number of lessons on how the suffering and social disruption caused by a large-scale lethal epidemic might be reduced. The following recommendations are meant to advance conversations among health professionals and policymakers about what constitutes an effective medical and public health reaction to a bioterrorist act and to inform planning for any large-scale infectious disease emergency (e.g., pandemic flu).

Build capacity to care for mass casualties. US cities sustained most influenza cases and deaths over 3–4 weeks in autumn 1918, crippling the health care system. Baltimore incurred 2 of every 3 pandemic-related deaths (3110 people or 0.5% of its population) in October alone [3]. Acute demand for medical, nursing, hospital, and pharmacy services exceeded supply. Over one-third of physicians and even more nurses were serving overseas [4], and hospitals found it difficult to fill every position (e.g., orderlies, custodians, and cooks) [3]. Influenza further reduced the pool of health care workers by infecting caregivers, pharmacists, and laboratory workers and other personnel [3, 21, 24] and by creating fear of contagion among some [23]. Community doctors faced tremendous caseloads, and public health nurses were frequently surrounded by throngs of tenement dwellers requesting help [22, 26]. Druggists struggled to fill demands for prescription medications, and customers, desperate for protection or relief, emptied pharmacy shelves of over-the-counter remedies (author's unpublished data).

Few in number, nurses were critical in alleviating the distress of Spanish flu: they provided comfort measures and reassurance, instructed families in basic care, and assisted with daily needs (e.g., laundry and cooking) [3, 22, 26]. Appealing to retired, private, and student nurses and women with any nursing experience, the Red Cross readied a network of professionals and volunteers for deployment in collaboration with the US Public Health Service and state health chiefs [3, 27]. To ameliorate the physician shortage, the US Public Health Service dispatched its Volunteer Medical Service Corps, a reserve of civilian doctors unable to serve overseas [3, 27]. States compensated for the lack of doctors by authorizing dentists as physicians, graduating medical students early, and expediting medical board examinations [4]. Without antibiotics or medical treatments for flu, however, physicians had very little to offer patients [3, 4], and conflicting reports about the effectiveness of different vaccines made most practitioners hesitant to use them [28].

Already inundated with patients, hospitals frequently turned people away for want of space and personnel. Facing extraordinary demand, hospitals lengthened staff hours, tasked student doctors and nurses with professional duties, discharged the least ill, accepted only urgent admissions, and prepared makeshift accommodations in halls, offices, porches, and tents [3, 26]. Basic supplies (e.g., linens, mattresses, bedpans, and gowns) were sometimes difficult to obtain [23]. Gymnasiums, state armories, parish halls, and other spaces served as emergency hospitals [3, 4, 26]. Many people languished at home, having neither strength nor opportunity to go to the hospital; social workers, visiting nurses, and Red Cross volunteers provided home health care as well as food, child care, and burial assistance to these patients and their families [26, 29].

Extrapolating from 1918, we can identify several elements that are likely to be critical to the capacity to handle mass casualties from a bioweapon among civilians. Health care workers, from least to most technically expert, would be a critical asset that should be protected, at minimum, by preventing secondary infection and by educating and reassuring them about the infectious disease outbreak. Hospitals, actual and symbolic loci of care, should have contingency plans in place and receive government support to endure a period of crisis as people converge on them. Decentralized delivery of aid (e.g., home care) would be indispensable in the context of overburdened health facilities or a contagious disease whose management dictates home isolation. In the context of a disease outbreak for which limited or no curative or preventive therapies were available, compassionate supportive care of the sick would be one of the few and most essential measures provided by the health care system.

Respect social mores relating to burial practices. At the climax of the Spanish flu pandemic, the numerous and rapid

deaths overwhelmed undertakers and gravediggers (many of whom were ill) and exhausted supplies of caskets and burial plots (author's unpublished data; [3, 4, 23]). Corpses remained unburied at home as relatives searched for the virtually unobtainable: a willing mortician, an affordable yet "decent" coffin, and a prepared grave. Some funeral homes and cemeteries were accused of price gouging, and local leaders were accused of not doing enough to help the bereaved. With body disposal interrupted, city and hospital morgues exceeded capacity, in some cases 10-fold, prompting a search for auxiliary space. Cities took desperate measures: Philadelphia commissioned coffins from local woodworkers, Buffalo produced its own, and Washington, DC, seized railroad cars with coffins en route to Pittsburgh, where the demand was equally desperate. Emergency internment measures such as mass graves and families digging graves themselves undermined the prevailing sense of propriety. Bodies stranded at home and coffins accumulating at cemeteries provided powerful symbols of the country's inability to function normally during the fall of 1918. Proper treatment of the dead during an infectious disease emergency would require expeditious handling of corpses to prevent public health threats while avoiding mortuary practices seen to be dehumanizing.

Characterize outbreak accurately and promptly. Poor disease reporting systems seriously hampered the ability of public health officials to keep the public informed and to manage the outbreak. Influenza was not a reportable condition before the outbreak, and no well-developed system existed through which federal, state, and local health entities could sketch the course of the disease [3]. With a crisis evident, the US Surgeon General urged weekly reports from state and municipal health departments [27]. Preoccupied with vast patient loads, doctors did not register cases quickly [3, 19], and public health officers recognized their own inability to evaluate efforts to prevent influenza's spread (author's unpublished data). Death certificates poorly reflected flu's impact: physicians frequently cited preexisting conditions (e.g., heart disease) as the cause of death [3, 19], and overworked health departments could not analyze the multitude of death reports at the outbreak's peak (author's unpublished data). Despite the uncertainty of official counts, some newspapers relentlessly reported new cases and deaths, fueling public speculation as to whether the epidemic was retreating or advancing (author's unpublished data).

Faced with the uncertainties that accompany an epidemic (e.g., whom will it claim and when and how will it end), people need a way to measure and describe it. Health officials and clinicians need the means to judge the efficacy of interventions. Communities must have a way to make sense of individual and collective losses. An effective medical and public health response to bioterrorism would include the capacity to count cases and deaths accurately and promptly, measure the success of epidemic controls, and communicate with the public as the epidemic unfolds.

Earn public confidence in emergency measures. Some community members embraced public health measures to control Spanish flu; others resisted orders seen as inconsistent, burdensome, or contrary to common sense or deeply held values. At the US Surgeon General's October behest, state and local health officials suspended public gatherings: entertainment centers, schools, and churches were closed, meetings were postponed, funerals were banned, and retail hours were curtailed [3, 4, 27]. Gauze masks and sanitation ordinances (e.g., hosing of walkways and prohibition of spitting) complemented closures [4, 27]. Health department directives evoked strong criticism in Baltimore. The public argued that the order to keep streetcar windows open in the cold fall weather was promoting disease and not preventing it. Closed churches and open saloons revealed the arbitrariness of closures. Lay and religious observers loudly protested church closures, arguing that an exclusively medical perspective of human suffering ignored a more spiritual one, depriving residents of solace (author's unpublished data). Most San Franciscans ignored a mandate to redon masks during the winter/spring wave: civil libertarians railed against the tyranny of compulsory behavior; business owners, about a veiled public afraid to shop; and Christian Scientists, about trampled personal liberties [3].

Neither support nor resistance to public health recommendations by the community, a critical ally, should be taken for granted. A successful plan for managing an epidemic would convey consistent and meaningful messages, serve audiences with diverse beliefs and languages, and acknowledge citizen concerns and grievances.

Guard against discrimination and allocate resources fairly. Spanish flu fostered both social cohesion and distance. Through a common enemy and shared sacrifices of war, many Americans had a well-developed sense of fellowship when the epidemic struck [3]. At risk to themselves, neighbors nursed one another, fed the sick, helped with daily tasks, and joined the volunteer ranks [4]. Nonetheless, fear of contagion interrupted normal displays of intimacy (e.g., kissing, shaking hands, and huddling to gossip) [4] and pitted groups against one another in an effort to assign blame or to protect access to limited resources. Rumors circulated in the United States that German spies, some disguised as doctors and nurses, were spreading flu and that Bayer aspirin, a German product, was infected with flu germs [3, 27]. Baltimore hospitals, during Jim Crow segregation, were closed to blacks at their moment of dire need, and once the epidemic passed, an official defended the city's poor public health record by attributing high mortality rates to the number of black residents (author's unpublished data).

As evident during Spanish flu and other historic outbreaks, explanations of disease often convey prejudice and serve to reinforce existing social schisms and inequalities. In a bioterrorist scenario, medical, public health, and political leaders should protect against social discrimination and assure fair allocation of resources.

Conclusion: Signs of Unpreparedness in 2000

Influenza's lessons for bioterrorism planners do not end with an 80-year-old crisis. The 1999–2000 flu season, which the Centers for Disease Control and Prevention did not consider unusually severe, stymied US hospitals in ways that parallel 1918. At the season's peak, hospitals faced acute shortages of staff, beds, and equipment; patients confronted long delays in care. The disruption was the result, not of an especially virulent virus, but a health care system unable to cope with a nominal upswing in demand [30]. Hospitals have had to employ strategies (e.g., fewer staffed acute beds) to assure survival in a harsh fiscal climate (e.g., slim profit margins, managed care demands for cost reduction, and mandated yet uncompensated care for the uninsured), leaving the country ill-prepared to deal with a mass casualty scenario [31, 32].

Research and development needs in the control of influenza virus, a familiar if elusive pathogen, are substantial (e.g., accelerated manufacturing processes and development of alternate vaccines and antivirals) [6, 8], raising the question as to the vast research and development challenges posed by the more unusual pathogens identified as likely bioterrorist agents [33]. The logistics and time frame for manufacture and administration of the conventional killed influenza virus vaccine (6 months from identification of a strain to vaccine production and distribution and 1–2 months for delivery en masse) would inhibit the availability of vaccine before the first wave of a pandemic [2, 6, 8]. A comparably long production timetable characterizes the new live attenuated virus vaccines, which nonetheless promise broader immune response as well as easier administration and social acceptance through intranasal delivery [9]. Antiviral compounds may have limited value amidst pandemic conditions due to costs associated with prolonged use, the potential for drug resistance, and the short time in which demand would exceed supply [6, 8].

Medical, public health, and policy communities should attend to the warnings of influenza, in its pandemic form and during interpandemic years, about the potential frailty of populations and institutions in the face of an infectious disease emergency, particularly one initiated by a deliberately released pathogen.

References

1. Ghendon Y. Introduction to pandemic influenza through history. Eur J Epidemiol **1994**; 10:451–3.
2. Glezen WP. Emerging infections: pandemic influenza. Epidemiol Rev **1996**; 18:64–76.
3. Crosby A. America's forgotten pandemic: the influenza of 1918. New York: Cambridge University Press, **1989**.
4. Iezzoni I. Influenza 1918: the worst epidemic in American history. New York: TV Books, **1999**.
5. Simonsen L. The global impact of influenza on morbidity and mortality. Vaccine **1999**; 17(Suppl 1):3–10.
6. Gross PA. Preparing for the next influenza pandemic: a re-emerging infection. Ann Intern Med **1996**; 124:682–5.
7. Cox NJ. Prevention and control of influenza. Lancet **1999**; 354:30.
8. Patriarca PA, Cox NJ. Influenza pandemic preparedness plan for the United States. J Infect Dis **1997**; 176(Suppl 1):4–7.
9. Laver WG, Bischofberger N, Webster RG. Disarming flu viruses. Sci Am **1999**; 280:78–87.
10. Webster RG, Bean WJ, Gorman OT, et al. Evolution and ecology of influenza A viruses. Microbiol Rev **1992**; 56:152–79.
11. Langmuir AD, Schoenbaum SC. The epidemiology of influenza. Hosp Pract **1976**; 11:49–56.
12. Webster RG. Predictions for future human influenza pandemics. J Infect Dis **1997**; 176(Suppl 1):14–9.
13. Oxford JS. Influenza A pandemics of the 20th century with special reference to 1918: virology, pathology and epidemiology. Rev Med Virol **2000**; 10: 119–33.
14. Centers for Disease Control and Prevention. Influenza fact sheet. Available at: www.cdc.gov/ncidod/diseases/flu/fluinfo.htm. Accessed 14 January **2000**.
15. Izurieta HS, Thompson WW, Kramarz P, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. N Engl J Med **2000**; 342:232–9.
16. Simonsen L, Fukuda K, Schonberger LB, et al. The impact of influenza epidemics on hospitalizations. J Infect Dis **2000**; 181:831–7.
17. Schoenbaum SC. Economic impact of influenza: the individual's perspective. Am J Med **1987**; 82:26–30.
18. Meltzer MI, Cox NJ, Fukuda K. The economic impact of pandemic influenza in the United States: priorities for intervention. Emerg Infect Dis **1999**; 5:659–71.
19. Patterson KD, Pyle GF. The geography and mortality of the 1918 influenza pandemic. Bull Hist Med **1991**; 65:4–21.
20. Kolata G. Flu: the story of the great influenza pandemic of 1918 and the search for the virus that caused it. New York: Farrar, Straus, & Giroux, **1999**.
21. Nuzum JW, Pilot I, Stangl FH, et al. 1918 pandemic influenza and pneumonia in a large civil hospital. IMJ Ill Med J **1976**; 150:612–6.
22. Keen-Payne R. We must have nurses: Spanish influenza in America 1918–1919. Nurs Hist Rev **2000**; 8:143–56.
23. McCord CP. The purple death: some things remembered about the influenza epidemic of 1918 at one army camp. J Occup Med **1966**; 8:593–8.
24. Straight WM. Florida and the Spanish flu. J Fla Med Assoc **1981**; 68:644 –54.
25. Inglesby TV, O'Toole T, Henderson, DA. Addressing the challenge of biological weapons. Clin Infect Dis **2000**; 30:926–9.
26. Robinson KR. The role of nursing in the influenza epidemic of 1918–1919. Nurs Forum **1990**; 25:19–26.
27. Gernhart G. A forgotten enemy: PHS's fight against the 1918 influenza pandemic. Public Health Rep **1999**; 114:559–61.
28. Heagerty JJ. Influenza and vaccination. CMAJ **1991**; 145:481–2.
29. Kerson TS. Sixty years ago: hospital social work in 1918. Soc Work Health Care **1979**; 4:331–43.
30. Schoch-Spana M. Hospitals buckle during normal flu season: implications for bioterrorism response. Biodefense Quarterly **2000**; 1:1–2, 8.
31. Espinal D. California health care 1999–2005: view of the future, the turn of the millennium. Sacramento, CA: California Healthcare Association, **1999**.
32. Moore Jr JD. Understaffed in California: state report urges added ER capacity for flu season. Mod Healthc **1998**; 28:64, 6.
33. Committee on R&D Needs for Improving Civilian Medical Response to Chemical and Biological Terrorism Incidents, Health Science Policy Program, Institute of Medicine, and Board on Environmental Studies and Toxicology, Commission on Life Sciences, National Research Council. Chemical and biological terrorism: research and development to improve civilian medical response. Washington, DC: National Academy Press, **1999**.