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123 CHAPTER

Introduction to Biological Agents and Pandemics

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HISTORICAL PERSPECTIVE

Biological agents have been used as weapons since antiquity. In 600 BC Solon of Athens poisoned the wells of his adversaries with hellebore—a purgative herb—during the siege of Krissa. Similarly the Assyrians contaminated the wells of their enemies with rye ergot.[1–3] In the fourteenth century corpses of plague victims were hurled over walls to infect enemies, and in the seventeenth and eighteenth centuries smallpox-laden blankets were used to target Native Americans. Biological agents played a role in military offenses into the twentieth century and have been used in terrorist actions around the world.

In 1969 President Richard Nixon halted offensive biological and toxin research and production in the United States. Stockpiles of various biological agents and toxins, including *Bacillus anthracis*, botulinum toxin, and *Francisella tularensis*, were subsequently destroyed. In 1972 the United States, the United Kingdom, the USSR, and more than 100 other nations ratified the Biological Weapons Convention (BWC). The BWC prohibits the development, production, and stockpiling of weapons of mass destruction.[1,3] Despite this, during the last 40 years, multiple signatory nations have violated the pact set forth by the BWC. Additionally, there has been a rise in the use of biological agents in terrorist attacks, including the anthrax attacks in 2001, which resulted in few deaths but widespread fear.[2]

The U.S. Centers for Disease Control and Prevention have organized biological weapons into three categories (Table 123-1). Category A, or high-priority agents, include organisms that can be easily disseminated, result in high mortality, and have the potential to cause significant public panic. Anthrax, botulism, smallpox, tularemia, and the viral hemorrhagic fevers are included in category A. Category B agents, including food and water safety threats, are moderately easy to disseminate. Although mortality rates due to these agents are lower they may result in significant morbidity. Finally, category C agents are considered emerging pathogens. These agents may be adapted in the future to take full advantage of their pathogenicity, availability, and lethality.

In general, biological weapons are characterized by low visibility, high potency, and relative ease of delivery and dissemination.[4] The agents must also be easily obtained, cultured, or reproduced and be relatively stable in the environment.

SURVEILLANCE

A good surveillance system is essential to any public health effort and is recognized as the single most important factor in identifying events of global concern.[5] Historically, surveillance systems relied on manual reporting of notifiable diseases or suspicious cases from clinicians, hospitals, and laboratories. There has been a shift to focus more on automated surveillance of readily available data to improve the timeliness, sensitivity, and specificity of the system.[6] The exponential increase in social media use and availability of web-based applications has added another potential surveillance domain, which is being utilized for research and communication.

Syndromic Surveillance

In an effort to better identify and track potential outbreaks related to infectious diseases, both naturally occurring and those related to biowarfare and terrorism, public health practitioners developed surveillance systems designed to analyze routinely collected health information. Syndromic surveillance, as it has come to be known, includes a wide range of surveillance activities, from monitoring over-the-counter medication purchases to tracking discharge diagnoses from emergency departments and analyzing Internet search queries.[1,7] True syndromic surveillance monitors syndromes—or constellations of symptoms—that may represent the prodromes of biological agents or emerging epidemics.[7] It relies on the automated analysis of routinely collected data to detect aberrancies in expected trends in near real-time. This process has been streamlined with the increased availability of electronically collected and exchanged data. It is frequently used in conjunction with alternative surveillance methods and verification techniques to improve outbreak detection.

The goal of syndromic surveillance systems is to enable more timely detection of outbreaks by identifying trends before these patterns are recognized clinically and a formal diagnosis is made.[7] This allows a more rapid response, ultimately decreasing morbidity and mortality.[8] Once an outbreak is suspected public health responders must proceed with a thorough epidemiological investigation to further describe the outbreak and implement control measures.[1]

Although syndromic surveillance complements the more time-consuming and burdensome conventional surveillance systems that rely on physician and laboratory reporting, there are significant limitations, including frequent false alarms.[9] If the system is sensitive enough to detect small outbreaks, it may result in false alarms, which consume resources and make it difficult to separate true outbreaks from daily variation.[6,7,9] Additionally, the ability of a surveillance system to detect an outbreak depends on a variety of factors, including the size of the outbreak, pattern of population dispersion following exposure to the

TABLE 123-1 Bioterrorism Agents, as Categorized by the Centers for Disease Control and Prevention

CATEGORY	DEFINITION	AGENTS/DISEASES
Category A	High-priority agents include organisms that pose a risk to national security because they can be easily disseminated or transmitted from person to person, result in high mortality rates and have the potential for major public health impact, might cause public panic and social disruption, and require special action for public health preparedness.	Anthrax (*Bacillus anthracis*) Botulism (*Clostridium botulinum* toxin) Plague (*Yersinia pestis*) Smallpox (variola major) Tularemia (*Francisella tularensis*) Viral hemorrhagic fevers (e.g., Ebola, Marburg, Lassa, Machupo)
Category B	Second highest priority agents include those that are moderately easy to disseminate, result in moderate morbidity rates and low mortality rates, and require specific enhancements of the CDC's diagnostic capacity and enhanced disease surveillance.	Brucellosis (*Brucella* species) Epsilon toxin of *Clostridium perfringens* Food safety threats (e.g., *Salmonella* species, *Escherichia coli* O157:H7, *Shigella*) Glanders (*Burkholderia mallei*) Melioidosis (*Burkholderia pseudomallei*) Psittacosis (*Chlamydia psittaci*) Q fever (*Coxiella burnetii*) Ricin toxin from *Ricinus communis* (castor beans) Staphylococcal enterotoxin B Typhus fever (*Rickettsia prowazekii*) Viral encephalitis (e.g., Venezuelan equine encephalitis, eastern equine encephalitis, western equine encephalitis) Water safety threats (e.g., *Vibrio cholerae*, *Cryptosporidium parvum*)
Category C	Third highest priority agents include emerging pathogens that could be engineered for mass dissemination in the future because of availability, ease of production and dissemination, and potential for high morbidity and mortality rates and major health impact.	Emerging infectious diseases, such as Nipah virus and hantavirus

agent, and data sources and syndrome definitions used in the analysis.[8] Methods have been developed to analyze data using time and time-space relationships to take into account baseline variability; however, these methods have not been standardized across surveillance systems.[6–8] Each community utilizing syndromic surveillance must ultimately set its own threshold level for activation. These thresholds should be set using historical data, hazard vulnerability analysis, and risk-benefit calculations for each syndrome.

Environmental Surveillance

Environmental surveillance systems rely on the remote detection of aerosol clouds or point detection systems to collect and analyze data. Remote detection systems identify and analyze the components of clouds, subsequently transmitting that information to public health personnel on the ground. Point detection systems sample an environmental area using high speed particle concentration methods and rapid diagnostic modalities to detect and identify potential agents.

In 2003 the Department of Homeland Security launched BioWatch, an environmental air sampling program currently under way in more than 30 U.S. cities, with the goal of facilitating detection of specific agents that could be aerosolized and used in a biological attack.[10] BioWatch is intended to complement current surveillance activities at the state and local levels. However, in its current design, it is unlikely that the BioWatch system will result in more timely detection of biological agents unless there is a large-scale aerosol attack in a location monitored by BioWatch using biological agents detectable by the system. The U.S. postal service also instituted point detection systems in high volume mail distribution hubs after the 2001 anthrax incident.

PREPAREDNESS

Since the turn of the century we have faced numerous outbreaks—both naturally occurring and intentional—that have changed the landscape of public health surveillance and preparedness. In 2001 *B. anthracis* spores were sent to various locations around the United States, resulting in 22 cases and 5 deaths.[11] This was followed by the epidemic of severe acute respiratory syndrome (SARS) in 2002, an outbreak of novel influenza A H1N1 in 2009, and in 2012 Middle East respiratory syndrome (MERS-CoV), which continues to spread. Since the anthrax attacks, a significant amount of money and resources has been poured into improving public health infrastructure. However, despite this focus, it is unclear if improvements have actually been achieved. In part this stems from conflicting goals, shifting priorities, and the lack of a clear definition of what it means to be prepared.[12,13] Ultimately reactionary response programs have less impact than hardening all hazards public health infrastructure, which has been neglected for decades.

In 2007 a diverse expert panel convened by the RAND Corporation developed the following definition of public health emergency preparedness (PHEP) in order to strengthen accountability and streamline preparedness efforts. They define PHEP as

> *the capability of the public health and health care systems, communities, and individuals, to prevent, protect against, quickly*

> *respond to, and recover from health emergencies, particularly those whose scale, timing, or unpredictability threatens to overwhelm routine capabilities. Preparedness involves a coordinated and continuous process of planning and implementation that relies on measuring performance and taking corrective action.*[12]

The panel further argued that PHEP must cover a full range of activities, including prevention, mitigation, response, and recovery. Additionally, it must take into account not only capacity (i.e., infrastructure, trained personnel), but also capability—the ability to implement preparedness plans in real time.[12]

Large-scale public health emergencies occur infrequently; as a result, it is difficult to execute, assess, and refine preparedness plans based on experience. Furthermore there is no universally agreed upon standard of preparedness. Federal, state, and local organizations have all established their own conflicting requirements, and there are few data to support one set of standards over another.

Written assessments and exercises have frequently been used to assess preparedness. Although written assessments are easily administered to large groups of people and the data obtained are generally easier to analyze, they frequently focus on the capacity as opposed to the capabilities of a system. Although important, these factors do not ensure an effective emergency response. Exercises, in contrast, may be discussion based or operations based and generally provide a more realistic view of an organization's capability to mobilize resources and infrastructure. However, real-time exercises are rarely evaluated with standard metrics to identify and address performance gaps.[13]

Moving forward it is essential to incorporate evaluations into routine public health functions.[14] In 2009 public health practitioners in both Los Angeles and New York City embedded assessments into influenza A H1N1 vaccination campaigns.[15] As a result, invaluable information was gained about the optimal placement of points of dispensing influenza vaccines within a community and the potential for scaling up electronic immunization information systems to better track immunization progress and manage supply and distribution of vaccines in a pandemic.[16,17] Although it may be difficult to identify questions and develop research protocols in the midst of an emergency, the time between events can serve as an opportunity to engage leaders, develop template protocols, and prioritize areas for investigation.[14]

SUMMARY

Ultimately, leaders must make decisions regarding public health responses with imperfect, limited data. The information provided by surveillance systems, used in conjunction with clinical data, will ultimately help public health practitioners identify an etiologic agent. As preparedness strategies become more standardized and evidence based, our ability to respond to public health emergencies, including biological attacks, will improve. Each chapter in Section 12 will cover a specific biological agent. The authors will outline what is known about the agent currently and, from this, attempt to extrapolate how this agent might be used in a bioterrorism attack.

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